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PHARMACOPEIAL FORUM VOL. 32 NO. 1 JAN.–FEB. 2006

* The *USP–NF* (*USP30–NF25*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

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

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

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

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

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Fax: (301) 816-8148.

STANDARDS DEVELOPMENT

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

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

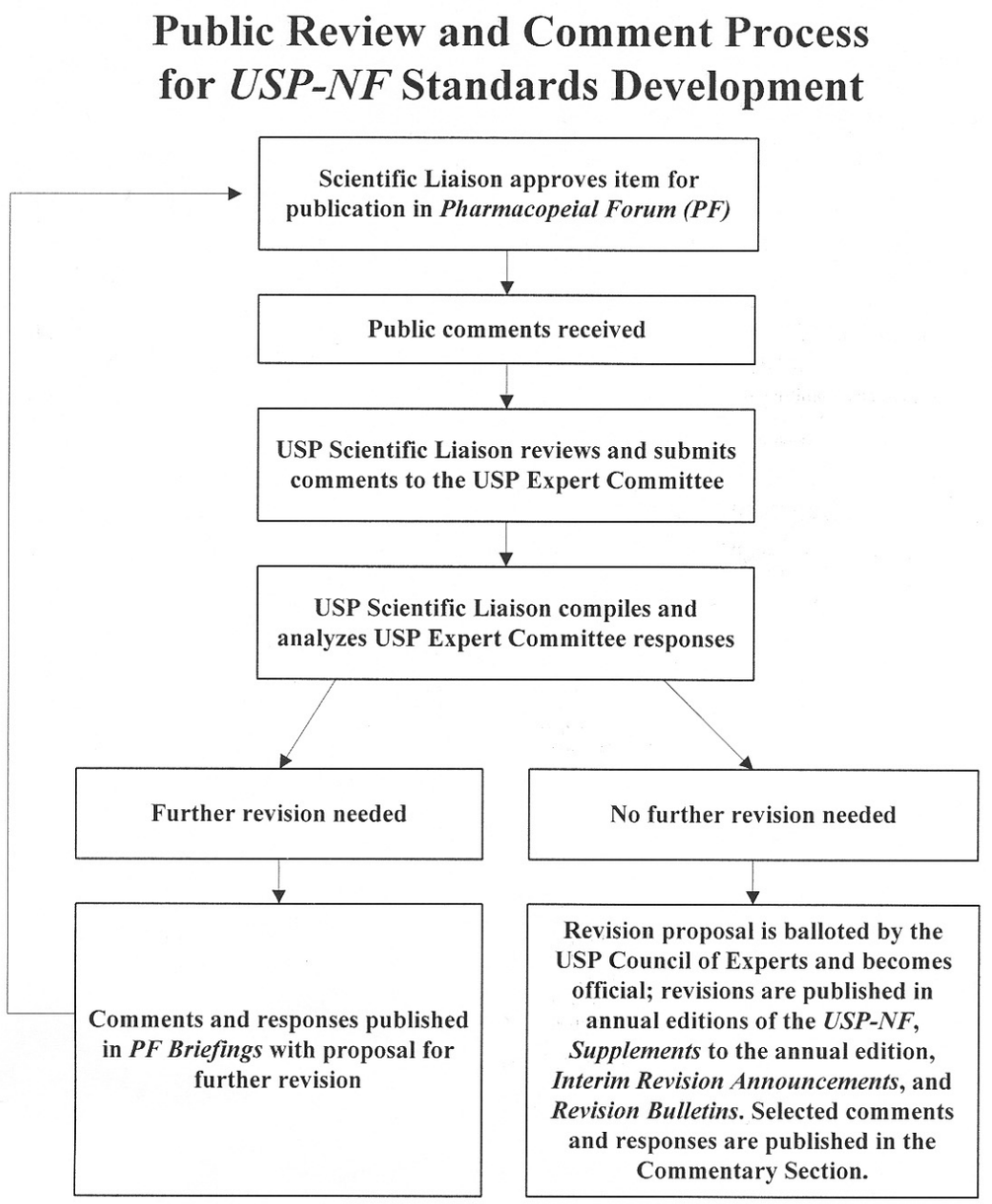
PF includes the following:

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

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

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

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



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@usp.org).

HOW TO USE *PF*

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

The content of the different sections of *PF* are briefly described below. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a *Request for Revision* is available in the *Guideline for Submitting Requests for Revision to the USP–NF* on the USP website (www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP–NF*

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

Other Sections

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

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

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

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

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

Index
Cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

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

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

EXPERT COMMITTEE DESIGNATIONS*

2005–2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell, Gene, and Tissue Therapies
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding
RMI	Radiopharmaceuticals and Medical Imaging Agents

2005–2010 (*Continued*)

RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics
VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005–2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

STAFF	E-MAIL	PHONE	ASSIGNMENT
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Antonio Hernandez-Cardoso Scientist, Latin American Specialist	ahc@usp.org	(301) 816-8308	USP Spanish Edition; General Chapters (GC)
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Shawn F. Dressman, Ph.D., Director, Reference Standards Evaluation	sfd@usp.org	(301) 816-8261	Reference Standards (RS)
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STAFF DIRECTORY *(continued)*

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STAFF DIRECTORY *(continued)*

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Hong Wang, Ph.D., Senior Scientific Associate	hw@usp.org	(301) 816-8351	Excipient Monographs 2 (EM2); Excipient General Chapters (EGC)
Beryl Voigt, Director, Executive Secretariat	bev@usp.org	(301) 816-8155	
Andrzej Wilk, Ph.D., Scientist	aw@usp.org	(301) 816-8305	Radiopharmaceuticals and Medical Imaging Agents (RMI); Radiopharmaceutical Information (RI)
Kahkashan Zaidi, Ph.D., Scientist	kxz@usp.org	(301) 816-8269	Aerosols (AER); General Chapters (GC)

POLICIES AND ANNOUNCEMENTS

This section includes information about general scientific and policy issues that may have an impact on *USP–NF* standards and processes and announcements about issues being considered by USP. This section also includes publication and comment schedules.

GENERAL CHAPTERS ⟨1⟩ AND ⟨905⟩ POSTPONEMENTS—CLARIFICATION. Two postponements that appeared in the *Fifth IRA* and *Sixth IRA* respectively for ⟨1⟩ *Injections,* and ⟨905⟩ *Uniformity of Dosage Units,* do not appear as postponed in the *USP 29–NF 24*. This is due to USP's publication schedule, which slates the *Fifth IRA* and *Sixth IRA* for the *First Supplement* to *USP 29–NF 24*, rather than to the book. The *First Supplement* is scheduled to be published February 15 and official April 1, 2006. The complete publication schedule is available on page 30.

For general chapter ⟨1⟩ *Injections,* USP has postponed the text for *Printing on Ferrules and Cap Overseals* that was to become official on October 1, 2005 as stated in *USP 28–NF 23*. The reason for the postponement is that the Parenteral Products-Industrial, Nomenclature, and Safe Medication Use Expert Committees have approved a revision of this section that also appears in *Pharmacopeial Forum* 31(5) with an implementation date of February 1, 2009.

For general chapter ⟨905⟩ *Uniformity of Dosage Units,* USP has postponed the official date from April 1, 2006 to January 1, 2007, to provide additional time for the Pharmacopeial Discussion Group to evaluate comments received concerning this revision.

Further information about these postponements is available on USP's website (www.usp.org). If you have any questions, please contact Beryl Voigt, Director, Executive Secretariat (301-816-8155 or bev@usp.org).

USP ISSUES NOTICE OF RETRACTION FOR RESIDUAL SOLVENTS. Please note the following retraction notice that has been included on page 14 of the *USP 29–NF 24*.

"*Residual Solvents ⟨467⟩: meet the requirements." is hereby withdrawn from all monographs in the USP and the NF. This retraction is made to allow the USP Council of Experts further time to evaluate the most appropriate manner to implement the Residual Solvents test. The General Notices statement concerning the application of Residual Solvents to all monographs is unaffected by this retraction.*

This notice also serves as an additional request for comments on this issue from all users of the USP. Please forward your comments to:

Todd Cecil, Ph.D.
Vice President
Department of Standards Development
USP
12601 Twinbrook Parkway
Rockville, MD 20852

Comments must be received by June 1, 2006 to ensure consideration.

REVISIONS TO GOLDENSEAL MONOGRAPHS. It is proposed to use Hydrastine free base as the USP Reference Standard because the water sorption analysis showed greater stability than the currently official hydrochloride form. Correction factors are accordingly removed from the procedures. These revisions are proposed to bring the procedures in the monographs in agreement with the free base form of Reference Standard materials already released by USP. Since these revisions do not change the essence of the procedures, they are intended to become official via immediate *Interim Revision Announcement.*

USP DIRECTOR OF EXECUTIVE SECRETARIAT NAMED. Beryl E. Voigt has been named the new Director, Executive Secretariat. Ms. Voigt joined USP in 1994 and worked her way up in the Research and Development Laboratory from Senior Chemist II to Senior Group Leader, where she was responsible for the administration of many RDL responsibilities. Prior to joining USP, she served in various chemist positions for pharmaceutical companies in Maryland, Pennsylvania, and New Jersey. Ms. Voigt earned her B.S. in Chemistry with a management option from Carnegie-Mellon University. Ms. Voigt will be responsible for many of the procedural responsibilities for USP Expert Committees and the standards-setting process.

EXPERT COMMITTEE SUMMARIES AVAILABLE ON THE USP WEBSITE. Summaries of the first meetings of the cycle for the 2005–2010 Standards Expert Committees are now posted and available at http://www.usp.org/USPNF/meetingSummaries/.

USP ANNOUNCES THE CHAIRS OF THE INFORMATION EXPERT COMMITTEES. USP is pleased to announce the following individuals who were elected to the USP Council of Experts in September as chairs of Information Expert Committees. Two individuals declined their appointments, resulting in vacancies for the Clinical Toxicology and Nephrology and Urology Expert Committees. Another election to fill these vacancies will take place in the future. Expert Committee members for these Expert Committees will be elected in the Spring of 2006.

Cardiology: Sarah A. Spinler, Pharm.D.; Clinical: Toxicology Vacant; Dermatology: Dennis P. West, Ph.D.; Endocrinology: Karim A. Calis, Pharm.D., M.P.H.; Gastroenterology: Bruce Bacon, M.D.; Hematology: Patrick A. McKee, M.D.; Immunology: John D. Grabenstein,

Ph.D.; Infectious Diseases: Douglas W. MacPherson, M.D.; Nephrology and Urology: Vacant; Neurology/Otorhinolaryngology/Ophthalmology: Mitchell F. Brin, M.D.; Oncology: Barbara A. Burtness, M.D.; Psychiatry: Amy H. Schwartz, Pharm.D., B.C.P.S.; Pulmonary: Elliott Israel, M.D.; Rheumatology: David H. Campen, M.D.; Special Populations/Clinical Pharmacology: Joseph T. Hanlon, Pharm.D.; Therapeutic Decision Making: Nancy Jo Braden, M.D.

USP SEEKS SUBMISSION OF PROPOSALS FOR STABILITY INDICATING ASSAY PROCEDURES FOR STEROIDS. The assay procedures for steroids in many *USP–NF* monographs are not stability indicating. In an effort to update the monographs, the Monograph Development—Pulmonary and Steroids Expert Committee is seeking submission of proposals of stability indicating assay procedures for steroids, preferably HPLC- or GC-based, for inclusion in the following *USP–NF* monographs to replace the current procedures that are not stability indicating. The submissions should include data and other information recommended in the *USP Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/pdf/EN/USPNF/revisionGuide.pdf. Each submission should include analytical validation data, data demonstrating that the procedure is stability indicating, and results of analysis from three commercial batches. Please submit proposals for steroid assay procedures for the following *USP–NF* monographs to Daniel Bempong, Ph.D., or contact him for the details at 301-816-8143 or dkb@usp.org.

Drug Substance:

Clocortolone Pivalate
Danazol
Desoxycorticosterone Acetate
Estriol
Fludrocortisone Acetate
Flumethasone Pivalate
Hydrocortisone Sodium Phosphate
Hydrocortisone Sodium Succinate
Hydroxyprogesterone Caproate
Levonorgestrel
Meprednisone
Mestranol
Methylprednisolone Sodium Succinate
Nandrolone Phenpropionate
Norethindrone
Norethindrone Acetate
Norethynodrel
Norgestrel
Oxandrolone
Oxymetholone
Paramethasone Acetate
Prednisolone Hemisuccinate
Prednisolone Sodium Phosphate
Testosterone
Testosterone Enanthate
Testosterone Propionate

Dosage Form:

Betamethasone Oral Solution
Clocortolone Pivalate Cream
Desoxycorticosterone Acetate Injection
Desoxycorticosterone Acetate Pellets
Dexamethasone Gel
Dexamethasone Sodium Inhalation Aerosol
Dexamethasone Tablets
Dexamethasone Topical Aerosol
Estradiol Injectable Suspension
Estradiol Tablets
Estrone Injection
Flumethasone Pivalate Cream
Hydrocortisone Acetate Injectable Suspension
Hydrocortisone Acetate Ophthalmic Ointment
Hydrocortisone Acetate Ophthalmic Suspension
Hydrocortisone Injectable Suspension
Hydrocortisone Sodium Phosphate Injection
Hydroxyprogesterone Caproate Injection
Methylprednisolone Acetate Cream
Methyltestosterone Capsules
Methyltestosterone Tablets
Nandrolone Phenpropionate Injection
Norethindrone Acetate Tablets
Norethindrone Acetate and Ethinyl Estradiol Tablets (assay for both steroids)
Norethindrone Tablets
Norgestrel Tablets
Oxymetholone Tablets
Paramethasone Acetate Tablets
Penicillin G Procaine, Dihydrostreptomycin Sulfate, and Prednisolone Injectable Suspension (assay for Prednisolone)
Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment (assay for Prednisolone Acetate)
Prednisolone Sodium Phosphate Injection
Prednisolone Sodium Phosphate Ophthalmic Solution
Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment (assay for Prednisolone Sodium Phosphate)

Prednisolone Sodium Succinate for Injection
Prednisolone Cream
Progesterone Intrauterine Contraceptive System
Testosterone Enanthate Injection
Testosterone Injectable Suspension
Testosterone Propionate Injection

CALL FOR HIGH PRIORITY MONOGRAPHS FOR DRUG SUBSTANCES AND PRODUCTS AND EXCIPIENTS. USP is seeking monographs for the following drug substances and drug products that are, or soon will be, off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below (updated as of September 1, 2005). Monograph sponsors should consult the *USP Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/pdf/EN/USPNF/revisionGuide.pdf.

For further information, contact Karen Russo, Ph.D., kar@usp.org.

Noncomplex Actives (Drug Substances)

Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Amlodipine	Anagrelide Hydrochloride ***(Received)***	Arsenic Trioxide
Azelaic Acid	Balsalazide Disodium	Bentoquatam
Bepridil Hydrochloride	Bicalutamide ***(Received)***	Bivalirudin
Budesonide ***(Received)***	Cabergoline	Calcipotriene
Calcium Trisodium Pentetate	Calfactant	Candesartan Cilexetil
Carmustine	Carvedilol	Cefdinir
Cefditoren Pivoxil	Ceftibuten	Cetirizine Hydrochloride ***(Received)***
Cetrorelix	Cevimeline	Chloroxine
Cilostazol ***(Received)***	Citalopram Hydrobromide ***(Received)***	Colfosceril
Cytarabine Liposome	Dalfopristin	Dantrolene Sodium ***(Received)***
Dapirazole Hydrochloride	Desirudin	Dexrazoxane
Didanosine ***(Received)***	Difloxacin Hydrochloride	Divalproex Sodium ***(Received)***
Docosanol	Entacapone	Epoprostenol
Erythromycin Phosphate	Erythromycin Thiocyanate	Esomeprazole Magnesium
Esmolol	Estazolam	Estramustine Phosphate Sodium
Estradiol Benzoate	Ethanolamine Oleate	Etomidate
Etoposide Phosphate	Exemestane	Felbamate
Fentanyl ***(Received)***	Fluoromethane F 18	Foscarnet Sodium
Fosfomycin Tromethamine	Gadobenate Dimeglumine	Galantamine Hydrobromide
Gadopentetic Acid	Gallium Nitrate	Ganirelix
Glyceryl Aminobenzoate	Granisetron	Halobetasol Propionate
Haloperidol Decanoate ***(Received)***	Hydrocodone Polistirex	Hydrocortisone ***(Received)***
Ibandronate Sodium	Imipramine Pamoate	Imiquimod
Irinotecan	Isosulfan Blue	Itraconazole
Lamotrigine ***(Received)***	Latanoprost	Lawsone
Levetriacepam	Levobetaxolol	Levocabastine Hydrochloride ***(Received)***
Levofloxacin ***(Received)***	Levomethadyl Acetate	Lomustine
Lopinavir	Metipranolol Hydrochloride	Midazolam Hydrochloride
Miglitol	Mifepristone	Misoprostol ***(Received)***
Mivacurium	Moexipril	Nalbuphine Hydrochloride
Nalmefene Hydrochloride	Nateglinide	Nedocromil
Nicardipine Hydrochloride	Nilutamide	Nisoldipine
Olopatadine	Olsalazine Sodium	Orbifloxacin
Orlistat ***(Received)***	Oxcarbazepine ***(Received)***	Pancuronium Bromide ***(Received)***
Pantoprazole Sodium	Pemoline	Pentamidine Isethionate
Piperonyl Butoxide	Pirbuterol Acetate	Poractant Alpha
Prednicarbate ***(Received)***	Proguanil	Quetiapine Fumarate

Noncomplex Actives (Drug Substances) *(Continued)*

Risperidone ***(Received)***	Rose Bengal	Salmeterol Xinafoate
Sodium Phenylbutyrate	Simethicone Powder	Sterile Methotrexate Sodium
Streptozocin	Sulfacytine	Tacrolimus
Terbinafine Hydrochloride	Terconazole	Tiludronate Disodium
Tiopronin	Tranexamic Acid	Trimipramine Maleate
Trovafloxacin Mesylate	Voriconazole	Zinc Tridosium Pentetate

Noncomplex Actives (Drug Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol For Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Supository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Amlodipine and Benazepril Hydrochloride Capsules	Aminopterin Sodium Tablets
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Metered-Dose Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Brompheniramine Maleate, Dextromethorphan Hydrobromide and Pseudoephedrine Hydrochloride Oral Solution
Bivalirudin Injection	Budesonide Metered-Dose Inhalation Aerosol	Budesonide Inhalation Aerosol
Bupivacaine and Lidocaine Hydrochlorides Injection	Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules
Butalbital and Acetaminophen Tablets	Butorphanol Tartrate Nasal Solution ***(Received)***	Calcipotriene Topical Solution Cabergoline Tablets
Calcipotriene Cream	Calcipotriene Ointment	Calcitriol Capsules
Calcitriol Oral Solution	Calcium Acetate Capsules	Calfactant Intratracheal Suspension
Calcium Trisodium Pentetate Injection	Carbidopa and Levodopa Extended-Release Tablets	Carbidopa and Levodopa Tablets for Oral Suspension
Carbidopa, Levidopa, and Entacapone Tablets	Carmustine Implant	Carmustine for Injection
Carvedilol Tablets	Cefditoren Pivoxil Tablets	Cefdinir Tablets
Ceftibuten Capsules	Ceftibuten for Oral Suspension	Cetirizine Hydrochloride Oral Solution
Ceftiofur Hydrochloride Oral Suspension	Cetrorelix Injection	Cetirizine Hydrochloride Tablets
Cevimeline Hydrochloride Capsules	Choline and Magnesium Salicylates Oral Solution	Chloroxine Cream
Chlorpromazine Hydrochloride Extended-Release Capsules	Ciclopirox Shampoo	Choline and Magnesium Salicylates Tablets
Choline Salicylate Oral Solution	Ciclopirox Topical Gel	Ciclopirox Topical Solution
Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	Cilostazol Tablets	Cimetidine Oral Solution

Noncomplex Actives (Drug Products) *(Continued)*		
Citalopram Hydrobromide Oral Solution	Citalopram Hydrobromide Tablets ***(Received)***	Ciprofloxacin Otic Solution
Cladribine Injection	Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation	Clonazepam Orally-Disintegrating Tablets
Clemastine Fumarate Syrup	Clobetasol Propionate Gel	Clotrimazole and Betamethasone Dipropionate Lotion
Clorazepate Dipotassium Capsules	Clorazepate Dipotassium Extended-Release Tablets	Colfosceril and Tyloxapol Suspension
Colestipol Hydrochloride Tablets	Conjugated Estrogens and Medroxyprogesterone Acetate Tablets	Compound Undecylenic Acid Cream
Compound Undecylenic Acid Topical Powder	Cyclosporine Modified Oral Solution	Cromolyn Sodium Metered-Dose Nasal Solution
Cyclosporine Modified Capsules	Cysteamine Bitartrate Capsules	Cyclosporine Ointment
Cyclosporine Topical Solution	Cytarabine Liposome Injection	Dantrolene Sodium Capsules ***(Received)***
Dalfopristin and Quinupristin Injection	Dapiprazole for Ophthalmic Solution	Dantrolene Sodium for Injection ***(Received)***
Dantrolene Sodium Oral Suspension	Desirudin for Injection	Desonide ***(Received)***
Desonide Cream	Dexrazoxane for Injection	Dextroamphetamine Sulfate Extended-Release Capsules
Dextromethorphan Polistirex Extended-Release Oral Suspension	Diazepam Injectable	Diclofenac Sodium Ophthalmic Solution
Didanosine Chewable Tablets ***(Received)***	Didanosine for Oral Solution ***(Received)***	Diethylpropion Hydrochloride Extended-Release Tablets
Difenoxin and Atropine Tablets	Difloxacin Hydrochloride Tablets	Dihydroergotamine Mesylate Metered Spray
Diltiazem Malate Extended-Release Tablets	Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets
Divalproex Sodium Delayed-Release Capsules	Dorzolamide and Timolol Ophthalmic Solution	Dorzolamide Ophthalmic Solution
Doxacurium Chloride Injection	Doxepin Hydrochloride Cream	Doxycycline Oral Gel
Econazole Nitrate Cream	Edrophonium Chloride and Atropine Sulfate Injection	Emulsion
Enalaprilat Injection	Enalapril Maleate and Diltiazem Malate Extended-Release Tablets	Enalapril Maleate and Felodipine Extended-Release Tablets
Entacapone Tablets	Ephedrine Sulfate and Guaifenesin Tablets	Epoprostenol for Injection
Epoprostenol Injection	Esmolol Hydrochloride Injection	Esomeprazole Magnesium Capsules
Estazolam Tablets	Estramustine Phosphate Sodium Capsules	Ethanolamine Oleate Injection
Etomidate Injection	Etidronate Disodium Injection Concentrate	Exemestane Tablets
Famotidine Injection ***(Received)***	Famotidine Orally Disintegrating Tablets	Felbamate Oral Suspension
Felbamate Tablets	Fentanyl Lozenges	Fentanyl Transdermal System
Ferrous Fumarate and Docusate Sodium Extended- Release Capsules	Flavoxate Hydrochloride	Flavoxate Hydrochloride Tablets
Fluconazole Injection	Flunisolide Nasal Spray	Fluconazole Tablets
Flunisolide Inhalation Aerosol	Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution
Fluticasone Propionate Inhalation Powder	Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***
Fluticasone Propionate Ointment ***(Received)***	Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection
Fosfomycin for Oral Solution	Gabapentin Oral Solution	Gabapentin Tablets
Gadobenate Dimeglumine Injection	Gallium Nitrate Injection	Galantamine Hydrobromide Tablets
Ganirelix Acetate Injection	Ganciclovir Capsules	Gentamicin Sulfate Oral Solution
Gatifloxacin Injection	Gatifloxacin Tablets	Glipizide Extended-Release Tablets
Gentamicin Sulfate Soluble Powder	Glimepiride Tablets	Granisetron Tablets
Granisetron Injection	Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets	Guaifenesin and Salts of Dextromethorphan and Pseudoephedrine Oral Solution

Noncomplex Actives (Drug Products) *(Continued)*

Guanidine Hydrochloride	Guanidine Hydrochloride Tablets	Halobetasol Propionate Ointment
Halobetasol Propionate Cream	Haloperidol Decanoate Injection	Haloperidol Lactate Injection
Haloperidol Lactate Oral Concentrate	Hydrochlorothiazide Oral Solution Concentrate	Hydrocodone Bitartrate and Acetaminophen Oral Solution
Hydralazine Hydrochloride and Hydrochlorothiazide Capsules	Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrochlorothiazide Capsules
Hydrocodone Bitartrate and Guaifenesin Oral Solution	Hydrocodone Bitartrate and Aspirin Tablets	Hydrocortisone Butyrate Lotion
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets	Hydrocortisone Acetate Rectal Foam Aerosol	Hydroquinone Lotion
Hydrocortisone Acetate Dental Paste	Hydroflumethiazide and Reserpine Tablets	Hydromorphone Hydrochloride Oral Solution
Ibuprofen Capsules	Ibandronate Sodium Tablets	Idarubicin Hydrochloride Injection
Imipramine Pamoate Capsules	Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol
Ipratropium Bromide Inhalation Solution	Irinotecan Hydrochloride Injection	Isosulfan Blue Injection
Isradipine Extended-Release Tablets	Itraconazole Injection	Itraconazole Oral Solution
Ketoconazole Cream	Ketoconazole Shampoo	Ketoprofen Capsules
Ketoprofen Extended-Release Capsules	Ketotifen Fumarate	Ketotifen Fumarate Ophthalmic Solution
Ketoprofen Tablets	Lactic Acid Lotion	Lamivudine Tablets
Latanoprost Ophthalmic Solution	Levetriacepam Tablets	Levobetaxolol Ophthalmic Suspension
Levocabastine Ophthalmic Suspension	Leucovorin Calcium for Injection	Levomethadyl Acetate Hydrochloride Oral Concentrate
Levofloxacin Solution	Lidocaine and Prilocaine Cream ***(Received)***	Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder
Liothyronine Injection	Lisinopril and Hydrochlorothiazide Tablets	Lomustine Capsules
Lopinavir Capsules	Lopinavir Solution	Lopinavir and Ritonavir Solution
Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***	Loratadine Orally-Disintegrating Tablets	Losartan Potassium Tablets
Mesalamine Suppositories	Methacholine Chloride for Inhalation Solution	Mesoridazine Besylate Concentrate
Mefloquine Hydrochloride Tablets	Methoxsalen Softgels	Methadone Hydrochloride Oral Concentrate
Melphalan for Injection	Metaraminol Bitartrate Injection	Methyclothiazide and Deserpidine Tablets
Methocarbamol and Aspirin Tablets	Metipranolol Ophthalmic Solution	Metronidazole Cream
Metronidazole Lotion	Metronidazole Extended-Release Tablets	Methylphenidate Hydochloride Chewable Tablets
Metronidazole Capsules	Midazolam Hydrochloride Injection	Metronidazole Hydrochloride for Injection
Miconazole Nitrate Topical Aerosol	Mifepristone Tablets	Miglitol Tablets
Milrinone Injection	Misoprostol Dispersion ***(Received)***	Misoprostol Tablets ***(Received)***
Mivacurium in Dextrose Injection	Mivacurium Injection	Moexipril Hydrochloride and Hydrochlorothiazide Tablets
Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution	Morphine Sulfate for Injection Concentrate
Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate	Morphine Sulfate Tablets
Mycophenolate Mofetil Tablets	Mycophenolate Mofetil Oral Solution	Mycophenolate Mofetil Capsules
Nalbuphine Hydrochloride Injection	Naproxen Extended-Release Tablets	Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution
Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution	Nalmefene Hydrochloride Injection	Nateglinide Tablets
Nedocromil Sodium Inhalation Aerosol	Neomycin Sulfate Oral Powder	Nevirapine Oral Suspension ***(Received)***
Nevirapine Tablets ***(Received)***	Nicardipine Hydrochloride Capsules	Nilutamide Tablets
Nimodipine Capsules	Nisoldipine Extended-Release Tablets	Nitroglycerin Solution In Acrylic Adhesive
Nizatidine Tablets	Ofloxacin Injection	Ofloxacin in Dextrose Injection
Ofloxacin Tablets ***(Received)***	Olopatadine Ophthalmic Solution	Olsalazine Sodium Capsules
Ondansetron Oral Solution	Ondansetron Tablets	Orbifloxacin Tablets
Orlistat Capsule ***(Received)***	Orphenadrine Citrate, Aspirin, and Caffeine Tablets	Orphenadrine Citrate Extended Release Tablets

Noncomplex Actives (Drug Products) *(Continued)*

Oxcarbazepine Suspension	Oxcarbazepine Tablets	Oxiconazole Cream
Pancuronium Bromide Injection ***(Received)***	Pantoprazole Sodium Tablets	Pantoprazole Sodium for Injection
Paroxetine Hydrochloride Extended-Release Tablets	Paroxetine Oral Suspension	Pemirolast Potassium Ophthalmic Solution
Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution	Pentaerythritol Tetranitrate Extended-Release Capsules
Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation	Pentamidine Isethionate for Injection
Pentazocine Hydrochloride and Acetaminophen Tablets	Permethrin Cream ***(Received)***	Phendimetrazine Tartrate Extended-Release Capsules
Phenobarbital Capsules	Phentermine Resin Complex	Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules
Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tablets	Phentermine Resin Complex Capsules	Phosphate Oral Solution
Pilocarpine Hydrochloride Ophthalmic Gel	Pilocarpine Hydrochloride Ophthalmic Ointment	Pilocarpine Hydrochloride Tablets
Piperonyl Butoxide and Pyrethrins Aerosol Foam	Pirbuterol Acetate Inhalation Aerosol	Povacrylate Solution
Poractant Alpha Supension	Porfimer Sodium for Injection	Povacrylate-Iodine Topical Solution
Povidone-Iodine Gauze	Povidone-Iodine Swabsticks	Povidone-Iodine Topical Aerosol Foam
Povidone-Iodine Vaginal Suppositories	Pramipexole Dihydrochloride Tablets	Prazosin Hydrochloride and Polythiazide Capsules
Prednicarbate Cream ***(Received)***	Prednicarbate Ointment ***(Received)***	Prednisolone Sodium Phosphate Oral Solution
Prochlorperazine Maleate Extended-Release Capsules	Progesterone Capsules	Promethazine Hydrochloride and Codeine Phosphate Oral Solution
Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup	Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup	Promethazine and Phenylephrine Hydrochlorides Syrup
Propafenone Hydrochloride Tablets	Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets
Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution	Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets Pyrilamine Maleate Injection
Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution	Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	Quinidine Sulfate Injection
Ramipril Capsules	Ranitidine Capsules	Rauwolfia Serpentina and Endroflumethiazide Tablets
Reserpine and Polythiazide Tablets	Rimantadine Hydrochloride Oral Solution	Risperidone Oral Solution
Risperidone Orally-Disintegrating Tablets	Risperidone Tablets	Rivastigmine Tartrate Capsules
Rivastigmine Tartrate Oral Solution	Rocuronium Bromide Injection	Ropinirole Hydrochloride Tablets
Rose Bengal Ophthalmic Solution	Rosiglitazone Maleate Tablets	Salicylic Acid and Sulfur Cleansing Lotion
Salicylic Acid and Sulfur Lotion	Salicylic Acid and Sulfur Shampoo	Salicylic Acid Cream
Salicylic Acid Ointment	Salmeterol Inhalation Aerosol	Salmeterol Xinafoate Inhalation Powder
Scopolamine Transdermal System	Selegiline Hydrochloride Capsules	Serpacwa Topical Cream
Sertraline Hydrochloride Oral Solution	Sibutramine Hydrochloride Capsules	Sodium Bicarbonate and Sodium Citrate for Oral Solution
Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension	Sodium Chlorophyllin Copper Complex Tablets	Sodium Iodide Injection
Sodium Phenylbutyrate Oral Powder	Sodium Phenylbutyrate Tablets	Sodium Phosphates for Oral Suspension
Sodium Phosphates Tablets	Sodium Salicylate and Sulfur Shampoo	Sterile Talc Aerosol
Streptozocin for Injection	Sucralfate Oral Suspension	Sulconazole Nitrate Cream
Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension	Sulfacytine Tablets
Sulfanilamide Vaginal Cream	Sulfasalazine Oral Suspension	Sumatriptan Tablets

Noncomplex Actives (Drug Products) *(Continued)*

Sulisobenzone Lotion	Sumatriptan Injection	Tacrolimus Capsules
Tacrolimus Ointment	Tacrolimus Injection	Tamsulosin Hydrochloride Capsules
Technetium Tc 99m Teboroxime Injection	Tenofovir Disoproxil Fumarate Tablets	Terbinafine Hydrochloride Cream
Terbinafine Tablets	Terbinafine Topical Solution	Terconazole Vaginal Cream
Terconazole Vaginal Suppositories	Testosterone Transdermal System	Tetracycline Hydrochloride Periodontal Fiber
Theophylline Extended-Release Tablets	Tioconazole Vaginal Ointment	Tiopronin Tablets
Tolnaftate Topical Aerosol Solution	Topiramate Capsules	Topiramate Tablets
Torsemide Injection	Torsemide Tablets	Trandolapril and Verapamil Hydrochloride Extended-Release Tablets
Trandolapril Tablets	Tranexamic Acid Injection	Tranylcypromine Sulfate
Tranylcypromine Sulfate Tablets	Tretinoin Capsules	Tretinoin Microsphere Gel
Triamcinolone Acetonide Metered-Dose Nasal Suspension	Trifluridine Ophthalmic Solution	Trimetrexate for Injection
Trimipramine Maleate Capsules	Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup	Trolamine Salicylate Cream
Trolamine Salicylate Gel	Trolamine Salicylate Topical Emulsion	Trovafloxacin Injection
Trovafloxacin Mesylate for Injection	Undecylenic Acid Topical Foam Aerosol	Unoprostone Isopropyl Ophthalmic Solution
Urea Cream	Valproic Acid Injection ***(Received)***	Vecuronium Bromide for Injection
Venlafaxine Extended-Release Capsules	Venlafaxine Tablets	Verapamil Hydrochloride Capsules
Verapamil Hydrochloride Extended-Release Capsules	Voriconazole Injection	Voriconazole Oral Suspension
Voriconazole Tablets	Yttrium Y-90 Chloride Solution	Yttrium Y-90 Glass Microspheres
Yttrium Y-90 Microspheres Injection	Ziprasidone Hydrochloride Capsules	Zidovudine and Lamivudine Tablets
Zinc Acetate Capsules	Zoledronic Acid for Injection	Zinc Tridosium Pentetate Injection

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	*N*-Acetyl-L-Methionine
Aconitic Acid (Achilleic Acid)	Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal
Aliphatic Polyesters	Aluminum Ammonium Sulfate	Aluminum Hydroxide
Aluminum Lactate	Aluminum Oxide	Aluminum Ammonium Sulfate
Aluminum Potassium Sulfate	Aluminum Silicate	Aluminum Sodium Sulfate
Aluminum Stearate	Allantoin-Sodium Pyrrolidone Carboxylate	Ammonium Bicarbonate
Ammonium Calcium Alginate	Ammonium Phosphate	L-Ascorbyl Stearate
L-Asparagine	Batylalcohol Monostearate	Beeswax, Synthetic
Benzododecinium Bromide	Benzyl Chloride	Benzyl Nicotinate
Brominated Vegetable Oil	Butadiene-Styrene Rubber	Beta Naphthol
Butylene Glycol	Butylphthalyl Butylglycolate	Butylated Hydromethylphenol
Calcium Alginate	Calcium Alginate and Ammonium Alginate	Calcium Acid Pyrophosphate
Calcium Chloride Solution	Calcium Glycerophosphate ***(Received)***	Calcium Bromide
Calcium Phospahte Dibasic, Monohydrate	Calcium Phosphate Monobasic	Calcium Phosphate Dibasic, Anhydrous
Calcium Pyrophosphate	Calcium Sorbate	Calcium Propionate
Calcium Sulfate Dihydrate	Calcium Sulfate, Anhydrous	Calcium Stearoyl Lactylate
Calteridol Calcium	Canola Oil	Caldiamide Sodium
Caprylic/Capric Diglyceril Succinate	Carbon	Capric Acid
Carboxymethylamylopectin Sodium	Carboxymethylcellulose Potassium	Carboxymethyl Starch
Cetostearyl Isononanoate	Cholic Acid	Cinnamaldehyde
Chlorodifluoroethane	Cocamide Diethanolamine	Cocamide Oxide
Coconut Oil Hydrogenated	Cocoyl Caprylocaprate	Coconut Oil
Crystal Gum	Cutina	Copper Sulfate
L-Cysteine Monohydrochloride	Dammar Gum	Cystine

Excipients *(Continued)*		
Decanoic Acid	Decyl Oleate	Dehydroacetic Acid
Desoxycholic Acid	Dextrin Palmitate	Dextrins Modified
Diacetyl Tartaric Acid Esters of Mono- and Diglycerides	Dicetyl Phosphate	Dichlorofluoromethane
Diethylene Glycol Monopalmitostearate	Diethyl Sebacate	Difluoroethane
Diglycol Stearate	Diisopropanolamine ***(Received)***	Diisobutyl Adipate
Diisopropyl Adipate	Diisopropylbenzothiazyl-2-Sulfenamide	Dilauryl Thiodipropionate
Dimethyl Dicarbonate	Dimyristoyl Lecithin	Dimyristoyl Phosphatidylglycerol
Dioctyl Sodium Sulfosuccinate	Dipropylene Glycol	Disodium Edisylate
Disodium Guanylate	Disodium Inosinate	Disodium Monooleamide Sulfasuccinate
Docusate Sodium/Sodium Benzoate	Erythritol ***(Received)***	Erythorbic Acid
Erythrosine	Ethoxylated Mono- and Diglycerides	Ethoxyquin
Ethyl Hexanediol	Ethyl Linoleate	Ethyl Maltol
Ethylene Dichloride	Ethylene Glycol Monopalmitostearate	Ethylurea
Ferric Ammonium Citrate	Ferric Citrate	Ferric Oxide, Brown
Ferric Phosphate	Ferric Pyrophosphate	Ferrous Citrate
Ferrous Glycinate	Ferrous Lactate	Fluorochlorohydrocarbons
Formic Acid	Furcelleran	Gamma-Cyclodextrin
Gentistic Acid	Geraniol	L-Glutamic Acid
Glutamic Acid Hydrochloride	Gluten	Glycerol Ester of Gum Rosin (Ester Gum)
Glyceryl Laurate	Glyceryl Palmitate	Glyceryl Ricinoleate
Glyceryl Tristearate	Glycine Hydrochloride	Glycofurol
Glycol Stearate	Heptafluoropropane	Heptylparaben
Hexadecyl Isostearate	Hexane	Hexanetriol(-1,2,6-)
Hydrocarbon Gel	Hydrogenated Starch Hydrolysate	Hydroxyethylmethylcellulose
Hydroxylated Lecithin	Hydroxypropyl Beta Cyclodextrin	Indigotine
Inositol	Iron Carbonyl	Iron Subcarbonate
Isobutylated-Isoprene Copolymer	Isooctylacrylate	Isopropyl Isostearate
Isopropyl Stearate	Isostearic Acid	Isostearyl Alcohol
Lactobionic Acid	Lactose Ferrin, Bovine	Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol
Lactylic Esters of Fatty Acids	Lanolin Anhydrous	Lanolin Alcohols, Acetylated
Lanolin (Wool Fat), Hydrogenated	Lanolin Hydrous	Lauramine Oxide
Lauric Acid	Lauric Diethanolamide	Lauric Myristic Diethanolamide
Lavender Oil	Lecithin, Hydroxylated	L-Leucine
Linoleic Acid	Macrogol Lauryl Ether	Macrogol Oleate
Macrogol Sorbitan Tristearate	Macrogol Stearyl Ether	Macrogolglycerol Cocoates
Macrogolglycerol Triisostearate	Magnesium Aluminum Silicate Hydrate	Magnesium Aspartate
Magnesium Aspartame Dihydrate	Magnesium Phosphate, Dibasic, Trihydrate	Magnesium Phosphate Tribasic
Magnesium Tartrate	Maltitol ***(Received)***	Maltitol Syrup
Maltol Isobutyrate	Malt Syrup	Manganese Chloride
Manganese Citrate	Manganese Glycerophosphate	Manganese Hypophosphite
D-Mannose	Medical Antifoam Emulsion C	Medronate Disodium
Medronic Acid	Methyl Chloride	Methylchloroisothiazolinone
Methyl Hydroxyethyl Cellulose	Methylisothiazolinone	*N*-Methylpyrrolidone ***(Received)***
Microcrystalline Cellulose, Silicified ***(Received)***	Mineral Spirits	Monoisostearyl Glyceryl Ester
Monopotassium Glutamate Monohydrate	Monosodium Citrate	Mullein Leaf
Myristyl Gamma-Picolinium Chloride	Myristyl Lactate	*N,N*-Bis(2-Hydroxyethyl)Stearamide
Naphtha	Non-Pareil Seeds	Nutmeg Oil
Octanoic Acid	Oleyl Oleate ***(Received)***	Oxystearin
Palm Kernel Oil	Palm Oil	Pentasodium Triphosphate
Pentetate Calcium Trisodium	Pentetate Pentasodium	Phenprobamate

Excipients *(Continued)*

Phenylmercuric Borate	Pine Oil	Polacrilin
Polyacrylate Dispersion 30 Percent ***(Received)***	Polydextrose	Polydextrose Solution
Polyglycerol Esters of Fatty Acids	Polyglycerol Polyricinoleic Acid	Polyoxyethylene Castor Oil (USP has 35)
Polyoxyl Stearate (USP has 40)	Polypropylene Oleate	Polyvinyl Acetate
Polyvinylacetal	Polyvinylacetal Diethylanoacetate	Polyvinylpolypyrrolidone
Polypropylene Stearyl Ether	Polyvinylpyrrolidone Ethylcellulose	Polysorbate 65
Potassium Acid Tartrate	Potassium Alginate ***(Received)***	Potassium Bromate
Potassium Carbonate Solution	Potassium Dichloroisocyanurate	Potassium Gibberellate
Potassium Glycerophospate	Potasssium Iodate	Potassium Nitrite
Potassium Phosphate	Potassium Phosphate Tribasic	Potassium Polymetaphosphate
Potassium Pyrophosphate	Potassium Stearate	Potassium Sulfate
Potassium Sulfite	Potassium Tripolyphosphate	Propylene Glycol Diacetate
Propylene Glycol Mono- and Diesters	Propylene Glycol Monolaurate ***(Received)***	Propyl Propionate
Purified Polyoxyl 35 Castor Oil ***(Received)***	Rapeseed Oil, Hydrogenated	Rapeseed Oil, Superglycerinated
Rice Bran Wax	Rosin	Silicone
Sodium Acid Pyrophosphate	Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic
Sodium Aluminum Phosphate Basic	Sodium Aspartate	Sodium Bisulfate
Sodium Bisulfite	Sodium Carbonate Hydrate	Sodium Carboxymethyl Betaglucan
Sodium Caseinate	Sodium Chlorate	Sodium Citrate, Dibasic
Sodium Citrate, Monobasic	Sodium Cyclamate	Sodium Dehydroacetate
Sodium Diacetate	Sodium Erythorbate	Sodium Ferric Pyrophosphate
Sodium Ferrocyanide	Sodium Hypophosphite	Sodium Laureth Sulfate
Sodium Lauroyl Sarcosinate	Sodium Lauryl Sulfoacetate	Sodium Magnesium Aluminosilicate
Sodium Magnesium Silicate	Sodium Malate	Sodium Metaphosphate, Insoluble
Sodium Metasilicate	Sodium Methylate	Sodium Polyphosphates Glassy
Sodium Potassium Tripolyphosphate	Sodium Pyrophosphate	Sodium Pyrrolidone Carboxylate
Sodium Sesquicarbonate	Sodium Sesquinoleate	Sodium Stearoyl Lactylate
Sodium Thiomalate	Sodium Trimetaphosphate	Sodium Trioleate
Sodium Tripolyphosphate	Soy Polysaccharides	Stannous Chloride
Stannous Tartrate	Starch, Pregelatinized Corn	Starch, Pregelatinized Tapioca
Stearalkonium Chloride	Stearyl Citrate	Stearyl Monoglyceridyl Citrate
Succinylated Monoglycerides	Sucrose Acetate Isobutyrate	Sucrose Fatty Acid Esters
Sucrose Stearate	Sucrose Syrup	Sugar Fruit Fine
Sulfobutyl Ether Beta Cyclodextran	Tallow	Tallow Glycerides
Tallow Oil	Tetrafluoroethane	Thioglycerol
Thyme Oil	Tribehenin	Tricetеareth-4 Phosphate
Trichloroethylene	Trimyristin	Trisidium Citrate
Trolamine Lauryl Sulfate	Vegetable Oil	Wheat Flour
Wheat Gluten	Wheat Germ Oil	Whey

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, other scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2005 and 2006 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

2005–2006 Calendar of Pharmacopeial Education Courses

Date	Name of Course	Location
November 4	Fundamentals of Microbiological Testing	California State University, Fullerton, CA
November 15	Basic Statistics and Their Practical Applications to the *USP–NF*	North Carolina State University, Raleigh, NC
December 7	Effectively Using the *USP–NF:* Session I	Brussels, Belgium
December 8	Effectively Using the *USP–NF:* Session II	Brussels, Belgium
January 18	Effectively Using the *USP–NF:* Sessions I & II	California State University, Fullerton, CA
January 24–25	Fundamentals of Dissolution: Lecture & Lab	North Brunswick, NJ
February 14	Effectively Using the *USP–NF:* Sessions I & II	Basel, Switzerland
February 15	Analytical Method Validation	Basel, Switzerland
February 23	Effectively Using the *USP–NF:* Sessions I & II	North Carolina State University, Raleigh, NC
March 29	Basic Statistics and Their Practical Applications to the *USP–NF*	New Jersey, hosted by NJPQCA
April 19	Effectively Using the *USP–NF:* Session I	USP Headquarters, Rockville, MD
April 20	Effectively Using the *USP–NF:* Session II	USP Headquarters, Rockville, MD

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

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

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

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

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

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

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

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

NEW *PHARMACOPEIAL FORUM* PUBLIC REVIEW AND COMMENT PERIOD DEADLINES. In *Pharmacopeial Forum* 31(5) (page 1308), USP announced that the comment period for *PF* proposals targeted for the *USP–NF* and its *Supplements* has been extended to a period of 90 days from the date of publication, as opposed to the 60-day period previously provided.

The comment deadlines for *PF* 31(6) and beyond were inadvertently omitted from the *Policies and Announcements* section of *PF* 31(6). The full year's listing of comment period deadlines and the targeted official publications appear below. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts*, USP is implementing the 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing. Note that *PF* 31(6) and *PF* 32(1) have a combined comment deadline (April 17, 2006) due to the omission of the comment deadline dates in *PF* 31(6). Individual comment deadlines begin with *PF* 32(2) March–April 2006.

We apologize for any inconvenience this may have caused.

Publication and Comment Schedule

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Publication Date	Official Date
PF 31(6)	April 17, 2006	*USP 30–NF 25*	November 2006	January 2007
PF 32(1)	April 17, 2006			
PF 32(2)	June 15, 2006	*USP 30–NF 25 1st Supplement*	February 2007	April 2007
PF 32(3)	August 15, 2006			
PF 32(4)	October 16, 2006	*USP 30–NF 25 2nd Supplement*	June 2007	August 2007
PF 32(5)	December 15, 2006			
PF 32(6)	February 15, 2007	*USP 31–NF 26*	November 2007	January 2008
PF 33(1)	April 16, 2007			

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, official revisions are published in *PF* in the *Interim Revision Announcement;* these revisions are also incorporated in the upcoming *Supplement.* The official publication in which an *IRA* is incorporated will depend upon publication deadlines. The 5th *IRA* and the 6th *IRA* will not appear until *Supplement 1*. See table below. The electronic version of *USP–NF* is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement.* The new table below outlines the publications and their release and official dates, and the book or supplement which supersedes them.

* ***Section 9.04(b) of the Rules and Procedures of the 2005–2010 Council of Experts***
A period of at least ninety (90) days from the date of publication will be allowed for public review and comment. The time allowed for public comments shall be noted in the publication in the PF. For good cause shown, the Chairperson may alter the time specified.

Publication Schedules

Publication	Release Date	Official Date	Superseded by
USP 29–NF 24	Nov. 1, 2005	Jan. 1, 2006	*1st Supplement*
1st Supplement	Feb. 1, 2006*	Apr. 1, 2006*	*2nd Supplement*
1st *IRA* [*PF* 32(1)]	Jan. 1, 2006*	Feb. 1, 2006*	*2nd Supplement*
2nd *IRA* [*PF* 32(2)]	Mar. 1, 2006*	Apr. 1, 2006*	*2nd Supplement*
3rd *IRA* [*PF* 32(3)]	May 1, 2006*	June 1, 2006*	*USP 30–NF 25*
2nd Supplement	June 1, 2006*	Aug. 1, 2006*	*USP 30–NF 25*
4th *IRA* [*PF* 32(4)]	July 1, 2006*	Aug. 1, 2006*	*USP 30–NF 25*
5th *IRA* [*PF* 32(5)]	Sept. 1, 2006*	Oct. 1, 2006*	*1st Supplement USP 30–NF 25*
6th *IRA* [*PF* 32(6)]	Nov. 1, 2006*	Dec. 1, 2006*	*1st Supplement USP 30–NF 25*
USP 30–NF 25	Nov. 1, 2006*	Jan. 1, 2007*	

*Tentative

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

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

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

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ▪new text▪, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ▪▪, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement*, and ▪2S (*USP29*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 29*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in the next available *Supplement*, and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

FIRST INTERIM REVISION ANNOUNCEMENT to *USP 29* and to *NF 24*

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

John W. Mauger, *Chair*
USP Board of Trustees

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

Eric B. Sheinin, Ph.D., *Chief Science Officer*

Official February 1, 2006 **Released January 1, 2006**

All inquiries and comments regarding *USP 29* text and *NF 24* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were not available when the associated monograph was made official, have since become available. The respective official date of each *USP 29* or *NF 24* standard, test, or assay requiring the use of the following USP Reference Standards is indicated in parentheses after the name of the Reference Standard.

USP Ademetionine Disulfate Tosylate RS (January 1, 2006)
USP Berberine Chloride (May 1, 2006)
USP Bupropion Hydrochloride Related Compound A RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound C RS (January 1, 2006)
USP Bupropion Hydrochloride Related Compound F RS (January 1, 2006)
USP Ciclopirox RS (January 1, 2006)
USP Ciclopirox Related Compound A RS (January 1, 2006)
USP Ciclopirox Related Compound B RS (January 1, 2006)
USP Clopidogrel Bisulfate RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound A RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound B RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound C RS (March 1, 2006)
USP Desoaminylazithromycin RS (January 1, 2006)
USP Eleutheroside B RS (January 1, 2006)
USP Eleutheroside E RS (January 1, 2006)
USP Galactitol RS (January 1, 2006)
USP Hydrastine RS (May 1, 2006)
USP Insulin Lispro RS (March 1, 2006)
USP Maltose Monohydrate RS (January 1, 2006)
USP Mefloquine Hydrochloride RS (May 1, 2006)
USP Mefloquine Related Compound A RS (May 1, 2006)
USP Norphenylephrine Hydrochloride RS (May 1, 2006)
USP Ondansetron RS (May 1, 2006)
USP Polyoxyl 20 Cetostearyl Ether RS (March 1, 2006)
USP Polyoxyl 20 Stearyl Ether RS (March 1, 2006)
USP Prilocaine RS (January 1, 2006)
USP Prilocaine Related Compound A RS (January 1, 2006)
USP Propofol RS (January 1, 2006)
USP Propofol Related Compound A RS (January 1, 2006)
USP Propofol Related Compound B RS (January 1, 2006)
USP Propofol Related Compound C RS (January 1, 2006)
USP Propofol Resolution Mixture C RS (January 1, 2006)
USP Residual Solvents Class 2—Mixture B RS (January 1, 2006)
USP Sodium Benzoate RS (January 1, 2006)
USP Somatropin RS (May 1, 2006)
USP Stavudine RS (January 1, 2006)
USP Stavudine System Suitability Mixture RS (January 1, 2006)
USP Sulfaquinoxaline Related Compound A RS (January 1, 2006)
USP Tiagabine Related Compound A RS (May 1, 2006)
USP Racemic Tiagabine Hydrochloride Mixture RS (May 1, 2006)
USP Tiagabine Hydrochloride RS (May 1, 2006)
USP Tagatose RS (January 1, 2006)

Unavailable First-Time Official USP Reference Standards

The official dates of any *USP 29* or *NF 24* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards. This listing was updated as of November 1, 2005.

USP Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Budesonide RS
USP Cetrimonium Bromide RS
USP Copolymer Polypropylene RS
USP Decoquinate RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS
USP Diethylstilbestrol Diphosphate RS
USP Powdered *Echinacea pallida* Extract RS
USP Escin RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluticasone Propionate RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Fluvastatin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Alpha Lipoic Acid RS
USP Maritime Pine Extract RS
USP Mecamylamine Related Compound A RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Near Infrared Calibrator
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Paricalcitol Solution RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Polyisobutylene RS
USP Polyoxyl 10 Oleyl Ether RS
USP Potassium Perchlorate RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Powdered St John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Sulisobenzone RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Powdered Valerian RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS

MONOGRAPHS (USP)

Lithium Carbonate Extended-Release Tablets

Change to read:

Dissolution ⟨711⟩—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1.*

Medium: dilute hydrochloric acid (7 in 1000); 800 mL.

Apparatus 1: 100 rpm.

Times: 15, 45, 90, and 120 minutes.

Procedure—At each *Time,* withdraw 8.0 mL of the solution under test, and pass through a filter having a 35-µm or finer porosity. Using the filtrate as the *Assay preparation,* suitably diluted with *Medium* if necessary, and using *Medium* to prepare the *Standard preparation,* determine the amount of Li_2CO_3 dissolved by employing a flame photometer, as directed in the *Assay.*

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 2.*

Time (minutes)	Amount dissolved
15	between 2% and 16%
45	between 25% and 45%
90	between 60% and 85%
120	not less than 85%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Apparatus and *Procedure*—Proceed as directed for *Test 1.*

Medium: water; 900 mL.

Times: 1, 3, and 7 hours.

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	not more than 40%
3	between 45% and 75%
7	not less than 70%

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

Medium: water; 250 mL.

Apparatus 3: 6 dips per minute, 20-mesh top screen and 100-mesh bottom screen.

Procedure—Proceed as directed for *Test 1.*

Times and *Tolerances*—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	between 10% and 45%
2	between 25% and 75%
6	not less than 70%

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

Medium, Apparatus, Times, and *Procedure*—Proceed as directed for *Test 1.*

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 2.*

Time (minutes)	Amount dissolved
15	•not more than 15%•1
45	between 20% and 45%
90	•between 50% and 80%•1
120	not less than •70%•1

•TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5.*

Medium: water, 900 mL.

Apparatus 1: 100 rpm.

Times: 30, 90, and 150 minutes.

Procedure—Pass a portion of the solution under test through a 0.8-µm mixed cellulose esters filter discarding the first 10 mL. Using the rest of the filtrate as the *Assay preparation,* suitably diluted with *Medium,* if necessary, and using *Medium* to prepare the *Standard preparation,* determine the amount of Li_2CO_3 dissolved by employing a flame photometer, as directed in the *Assay.*

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 2.*

Time (minutes)	Amount dissolved
30	between 10% and 30%
90	between 55% and 75%
150	not less than 85%

•1

(Official April 1, 2006)

DIETARY SUPPLEMENTS—MONOGRAPHS

Goldenseal

Change to read:

USP Reference standards ⟨11⟩—*USP Berberine Chloride RS. USP Hydrastine* ••1 *RS.*

Change to read:

Thin-layer chromatographic identification test ⟨201⟩—

Test solution—Finely powder the rhizome and the root, transfer 0.5 g of the powder to a suitable glass vial, add 0.5 mL of 10% sodium carbonate, and mix. Add 5 mL of methanol, and heat for 10 minutes in a water bath at 60°. Cool to room temperature, filter, and dry under a stream of nitrogen. Add 0.5 mL of methanol to dissolve the residue.

Standard solution—Dissolve accurately weighed quantities of USP Berberine Chloride RS and USP Hydrastine ••1 RS in methanol to obtain a solution having a concentration of 0.5 mg of each USP Reference Standard per mL.

Application volume: 10 µL to 20 µL, as bands.

Developing solvent system: a mixture of ethyl acetate, butyl alcohol, formic acid, and water (50 : 30 : 10 : 10).

Procedure—Proceed as directed in the chapter, except to air-dry the plates, and examine them under UV light at about 365 nm. The chromatograms show zones having a lemon-yellow fluorescence due to berberine at an R_F value of about 0.53 and a blue-white fluorescence due to hydrastine at an R_F value of about 0.42.

Change to read:

Content of berberine and hydrastine and limit of palmatine—

Mobile phase—Dissolve 9.93 g of monobasic potassium phosphate in 730 mL of distilled water. Add 270 mL of acetonitrile, mix, filter, and degas. Make other adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities of USP Berberine Chloride RS and USP Hydrastine •$_{1}$ RS in a mixture of water and methanol (1 : 1), and dilute quantitatively, and stepwise if necessary, to obtain a solution containing about 0.05 mg of each USP Reference Standard per mL.•$_{1}$

System suitability solution—Prepare a solution of palmatine in a mixture of water and methanol (1 : 1) having a known concentration of about 0.05 mg per mL. Mix equal volumes of this solution and the *Standard solution.*

Test solution—Finely powder a quantity of Goldenseal, and transfer 0.12 g, accurately weighed, to a 50-mL volumetric flask. Add 40 mL of a mixture of 0.1 M monobasic potassium phosphate and acetonitrile (60 : 40). Sonicate for 5 minutes, and shake for 10 minutes on a rotation shaker. Dilute with the mixture of 0.1 M monobasic potassium phosphate and acetonitrile (60 : 40), mix, and filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 4.6- × 150-mm column that contains packing L1. The flow rate is about 1.8 mL per minute. Inject the *Standard solution* into the chromatograph, and record the peak responses as directed for *Procedure:* the capacity factor, k', determined from the hydrastine and berberine peaks is not less than 3.0; the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.5%. Inject the *System suitability solution* into the chromatograph, and record the peak responses as directed for *Procedure:* identify the locus for palmatine, and calculate the resolution, R, with respect to hydrastine and berberine: the resolution, R, between berberine and palmatine is not less than 1.5, and the resolution, R, between hydrastine and palmatine is not less than 1.5.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentages of berberine and hydrastine in the portion of Goldenseal taken by the formula:

$$100(CV/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of berberine or hydrastine in the respective USP Reference Standard in the *Standard solution;* •$_{1}$ V is the final volume, in mL, of the *Test solution;* W is the weight, in mg, of Goldenseal taken; and r_U and r_S are the peak areas for berberine and hydrastine obtained from the *Test solution* and the *Standard solution,* respectively. Using the values obtained from the chromatogram of the *Test solution,* divide the peak area of berberine by the peak area of any peak at the locus for palmatine (if present): the ratio is more than 50 : 1.

Powdered Goldenseal

Change to read:

USP Reference standards ⟨11⟩—*USP Berberine Chloride RS. USP Hydrastine* •$_{1}$ *RS.*

Powdered Goldenseal Extract

Change to read:

USP Reference standards ⟨11⟩—*USP Berberine Chloride RS. USP Hydrastine* •$_{1}$ *RS.*

Interim Revision Announcement

ERRATA

Following is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP 29–NF 24*. If necessary, this list will be updated with every issue of *PF*. This information will also be available as a cumulative table in the next available *Supplement* and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
2144	*Tiamulin Fumarate*	*Limit of residual solvents*	Line 7 under *Procedure:* Change "$1.25(W_S/W_U)(R_U/R_S)$" to: $(W_S/W_U)(R_U/R_S)$
2264	*Sterile Water for Inhalation*	*Ammonia*	Lines 8 and 9: Change "(furnished by using 1.76 mL of 1.0 N ammonium hydroxide)" to: (furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL)
		Oxidizable substances	Lines 3 and 4: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate Lines 5 and 6: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate
2264	*Sterile Water for Injection*	*Ammonia*	Lines 8 and 9: Change "(furnished by using 1.76 mL of 1.0 N ammonium hydroxide)" to: (furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL)
		Oxidizable substances	Lines 3 and 4: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate Lines 5 and 6: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate
2265	*Sterile Water for Irrigation*	*Ammonia*	Lines 8 and 9: Change "(furnished by using 1.76 mL of 1.0 N ammonium hydroxide)" to: (furnished by adding 1 mL of the final solution prepared by diluting 3.0 mL of ammonia TS with *High-Purity Water* to 100 mL; 1.0 mL of this solution is further diluted to 100 mL)
		Oxidizable substances	Lines 3 and 4: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate Lines 5 and 6: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate
2265	*Sterile Purified Water*	*Oxidizable substances*	Lines 3 and 4: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate Lines 5 and 6: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate
2266	*Water for Hemodialysis*	*Oxidizable substances*	Lines 2 and 3: Change "0.1 N potassium permanganate" to: 0.1 M potassium permanganate
3297	*Carbomer Homopolymer*	*Limit of acrylic acid*	Line 1: Change "*0.01 M Phosphate buffer*—Dissolve 1.361 g of monobasic potassium phosphate in 100 mL of water, and mix" to: *0.01 M Phosphate buffer*—Dissolve 1.361 g of monobasic potassium phosphate in 1000 mL of water, and mix
3342	*Glyceryl Monolinoleate*	*Identification A*	Lines 1 and 2 under *Test solution:* Change "a solution in methylene chloride containing about 0.05 µg per mL" to: a solution in methylene chloride containing 0.05 g per mL Lines 1 and 2 under *Spray reagent:* Change "a solution containing 0.02 µg of rhodamine B in 0.2 µL of alcohol" to: a solution containing 0.02 g of rhodamine B in 0.2 L of alcohol

Interim Revision Announcement

IN-PROCESS REVISION

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

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

BRIEFING

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

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

•new text•

if slated for an *Interim Revision Announcement to USP 29–NF 24* (*IRA*);

▲new text▲*USP30*

if slated for *USP 30–NF 25*; and

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, ■2S (*USP 29*) indicates that the proposed revision is slated for the *Second Supplement to USP 29*, and ▲*USP30* and ▲*NF25* indicate that the revisions are proposed for *USP 30* and *NF 25*, respectively.

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

MONOGRAPHS (USP)

BRIEFING

Acetazolamide Oral Solution. Because there are no existing *USP* monographs for several Oral Solutions, new monographs are being proposed. Each monograph is based on its corresponding Oral Suspension, published in *Pharmacopeial Previews,* on pages 915–949 of *PF* 31(3) [May–June 2005]. See also the briefing under *Acetazolamide Oral Suspension.* A vehicle is specified for each Oral Solution. The new monographs are as follows:

Acetazolamide Oral Solution
Bethanechol Chloride Oral Solution
Captopril Oral Solution
Diltiazem Hydrochloride Oral Solution
Dolasetron Mesylate Oral Solution
Labetalol Hydrochloride Oral Solution
Metoprolol Tartrate Oral Solution
Verapamil Hydrochloride Oral Solution

(CRX: C. Okeke) RTS—43131-2

Add the following:

▲Acetazolamide Oral Solution

» Acetazolamide Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of acetazolamide ($C_4H_6N_4O_3S_2$). Prepare Acetazolamide Oral Solution 25 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩.

Acetazolamide powder	2.5 g
Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

See also *Acetazolamide Oral Suspension*): Dissolve Acetazolamide powder in about 20 mL of Cherry Syrup in a mortar, and mix to a uniform paste. Add the Cherry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Cherry Syrup to bring to final volume, and mix.

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

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 3.1 and 3.9.

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Dissolve 4.1 g of anhydrous sodium acetate in 950 mL of water, add 20 mL of methanol and 30 mL of acetonitrile, and mix. Adjust with glacial acetic acid to a pH of 4.0. Filter and degas the solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Transfer about 25 mg of USP Acetazolamide RS, accurately weighed, to a 50-mL volumetric flask, add 5.0 mL of 0.5 N sodium hydroxide, and mix to dissolve. Dilute with water to volume, and mix.

Standard preparation—Transfer 25.0 mL of the *Standard stock preparation* to a 50-mL volumetric flask, and dilute with water to obtain a solution having a known concentration of 250 µg per mL.

Assay preparation—Agitate the container of Oral Solution for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3 minutes, and the relative standard deviation for replicate injections is not more than 1.1%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of acetazolamide ($C_4H_6N_4O_3S_2$) in the volume of Oral Solution taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Acetazolamide RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Acetazolamide Oral Suspension, page 917 of *PF* 31(3) [May–June 2005]. This and the following monographs, which were presented in *Pharmacopeial Previews* in *PF* 31(3) [May–June 2005], are now forwarded to *In-Process Revision* with a few editorial revisions.

Alprazolam Oral Suspension
Azathioprine Oral Suspension
Bethanechol Chloride Oral Suspension
Captopril Oral Suspension
Clonazepam Oral Suspension
Diltiazem Hydrochloride Oral Suspension
Dipyridamole Oral Suspension
Dolasetron Mesylate Oral Suspension
Flucytosine Oral Suspension
Ganciclovir Oral Suspension [A title change is proposed; presented as Ganciclovir Oral Solution in *PF* 31(3)]
Labetalol Hydrochloride Oral Suspension
Metolazone Oral Suspension
Metoprolol Tartrate Oral Suspension
Ondansetron Hydrochloride Oral Suspension
Quinidine Sulfate Oral Suspension
Sumatriptan Succinate Oral Suspension
Verapamil Hydrochloride Oral Suspension

(CRX: C. Okeke) RTS—43131-1

Add the following:

▲Acetazolamide Oral Suspension

» Acetazolamide Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of acetazolamide ($C_4H_6N_4O_3S_2$). Prepare Acetazolamide Oral Suspension 25 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Acetazolamide Oral Solution*):

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Acetazolamide	2.5 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE— ~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets place the Tablets in a mortar and comminute the Tablets to a fine powder, or add Acetazolamide powder. Add about 20 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough liquid Vehicle to bring to final volume, and mix well.

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

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 4.0 and 5.0 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.1 and 3.9 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Dissolve 4.1 g of anhydrous sodium acetate in 950 mL of water, add 20 mL of methanol and 30 mL of acetonitrile, and mix. Adjust with glacial acetic acid to a pH of 4.0. Filter and degas the solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Transfer about 25 mg of USP Acetazolamide RS, accurately weighed, to a 50-mL volumetric flask, add 5.0 mL of 0.5 N sodium hydroxide, and mix to dissolve. Dilute with water to volume, and mix.

Standard preparation—Transfer 25.0 mL of the *Standard stock preparation* to a 50-mL volumetric flask, and dilute with water to obtain a solution having a known concentration of 250 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample solution to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3 minutes, and the relative standard deviation for replicate injections is not more than 1.1%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

measure the responses for the major peaks. Calculate the quantity, in mg, of acetazolamide ($C_4H_6N_4O_3S_2$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Acetazolamide RS in the *Standard preparation;* V is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Albendazole Oral Suspension, *USP 29* page 61. USP acknowledges that Albendazole Oral Suspension is approved in several countries for human use. It is proposed to change the specified labeling requirements so that manufacturers can use the USP Albendazole Oral Suspension monograph for these drug products.

(VET: I. DeVeau) RTS—43400-1

Change to read:

Labeling~~—Label~~

▲For products marketed in the United States, label▲*USP30* it to indicate that it is for veterinary use only.

BRIEFING

Alprazolam Oral Suspension, page 918 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension*.

(CRX: C. Okeke) RTS—43131-3

Add the following:

▲Alprazolam Oral Suspension

» Alprazolam Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$). Prepare Alprazolam Oral Suspension 1 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Alprazolam	100 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, place the Tablets in a suitable mortar, and comminute or triturate to a fine powder, or add Alprazolam powder. Add about 20 mL of the Vehicle, and mix until a uniform paste is formed. Add the Vehicle in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle to bring to final volume, and mix well.

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Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or under refrigeration.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 4.2 and 4.7 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.4 and 4.2 (Cherry Syrup).

Beyond-use date: 45 days after the day on which it was compounded.

Assay—

Buffer solution—Prepare a 0.04 M sodium acetate solution, and adjust with glacial acetic acid to a pH of 2.4.

Mobile phase—Prepare a filtered and degassed solution of *Buffer solution,* methanol, and acetonitrile (47 : 45 : 8). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Alprazolam RS in *Mobile phase,* and quantitatively dilute with *Mobile phase* to obtain a solution having a known concentration of about 20 µg per mL.

Assay preparation—Agitate the container of Alprazolam Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 0.6 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 10 minutes, and the relative standard deviation for replicate injections is not more than 1.4%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of alprazolam ($C_{17}H_{13}ClN_4$) in each mL of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Alprazolam RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Amoxicillin Capsules, *USP 29* page 158. It is proposed to add a *Dissolution Test 2* for a generic product approved by FDA. In the absence of any adverse comments, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of June 1, 2006.

(BPC: M. Marques) RTS— 43726-1; 43727-1

Add the following:

•**Labeling—**When more than one *Dissolution Test* is given, the labeling states the *Dissolution Test* used only if *Test 1* is not used.•3

In-Process Revision

Change to read:

Dissolution ⟨711⟩—

•TEST 1—•[3]

Medium: water; 900 mL.

Apparatus 1: 100 rpm, for Capsules containing 250 mg.

Apparatus 2: 75 rpm, for Capsules containing 500 mg.

Time: 60 minutes.

Procedure—Determine the amount of $C_{16}H_{19}N_3O_5S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 272 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Amoxicillin RS in the same *Medium.*

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 60 minutes.

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: water; 900 mL.

Apparatus 1: 100 rpm.

Time: 90 minutes.

Procedure—Determine the amount of $C_{16}H_{19}N_3O_5S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 272 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Amoxicillin RS in the same *Medium.*

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 90 minutes.•[3]

BRIEFING

Azathioprine Oral Suspension, page 920 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-4

Add the following:

▲Azathioprine Oral Suspension

» Azathioprine Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of azathioprine ($C_9H_7N_7O_2S$). Prepare Azathioprine Oral Suspension 50 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Azathioprine	5 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, comminute them to a fine powder in a suitable mortar, or add Azathioprine powder to the mortar. Add about 10 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle to bring to final volume, and mix well.

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[Caution—Avoid skin contact or inhalation of azathioprine by using protective gloves and a fume hood or surgical mask.]

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 3.9 and 4.7 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.1 and 3.9 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Dissolve 1.1 g of sodium 1-heptanesulfonate in 700 mL of water, add 300 mL of methanol, and mix. Adjust with 1 N hydrochloric acid to a pH of 3.5. Filter, and degas the solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve about 25 mg of USP Azathioprine RS, accurately weighed, in a 50-mL volumetric flask. Add about 15 mL of methanol and 0.5 mL of ammonium hydroxide to the flask, swirl and sonicate for 2 minutes. Dilute with methanol to volume, and mix. Transfer 10 mL of this solution to a 50-mL volumetric flask, dilute with water to volume, and mix.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample solution into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 4 minutes, and the relative standard deviation for replicate injections is not more than 1.3%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of azathioprine ($C_9H_7N_7O_2S$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Azathioprine RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Baclofen Oral Solution, page 921 of *PF* 31(3) [May–June 2005]. This new *USP* monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision.* In the Definition, in the preparation instructions for the Oral Solution, it is proposed to allow the use of only Baclofen powder, rather than the use of either the powder or the Tablet form. Minor editorial changes have also been made.

(CRX: C. Okeke) RTS—43131-5

In-Process Revision

Add the following:

▲Baclofen Oral Solution

» Baclofen Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Baclofen ($C_{10}H_{12}ClNO_2$). Prepare Baclofen Oral Solution 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Baclofen Oral Suspension*):

Baclofen	500 mg
Glycerin	5 mL
Syrup, *NF,* a sufficient quantity to make	100 mL

~~If using Tablets, comminute the Baclofen Tablets to a fine powder in a suitable mortar, or~~ Add Baclofen powder to the mortar. Add about 5 mL of the Glycerin to wet the powder, and triturate the powder to form a fine paste. Add about 5 mL of the Syrup to the paste, triturate well, and transfer the contents, stepwise and quantitatively, to a calibrated bottle. Rinse the mortar with additional portions of the Syrup, and transfer the contents to the container; repeat as necessary with sufficient Syrup to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store in a cold place.

Labeling—Label it to state the beyond-use date.

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

pH ⟨791⟩**:** between 5.0 and 6.0.

Beyond-use date: 35 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a solution of 0.05 M monobasic sodium phosphate and acetonitrile (80 : 20), and adjust with phosphoric acid to a pH of 3.5. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Baclofen RS in water to obtain a concentration of about 1.0 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with water to obtain a solution having a known concentration of 5 µg per mL.

Assay preparation—Shake thoroughly by hand each bottle of Oral Solution. Pipet 0.5 mL of Oral Solution from each bottle into a 500-mL volumetric flask, dilute with water to volume to obtain a concentration of 5 µg per mL, and pass through a 0.22-µm polyvinylidenefluoride (PVDF) filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 5.5 for baclofen; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

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measure the responses for the major peaks. Calculate the quantity, in mg, of baclofen ($C_{10}H_{12}ClNO_2$) in the volume of Oral Solution taken by the formula:

$$1000(C/V)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Baclofen RS in the *Standard preparation;* V is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Baclofen Oral Suspension—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43150-1

Add the following:

▲Baclofen Oral Suspension

» Baclofen Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of baclofen ($C_{10}H_{12}ClNO_2$). Prepare Baclofen Oral Suspension 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Baclofen Oral Solution*). [NOTE—Use Tablets instead of bulk powder.]:

Baclofen	500 mg
Glycerin	5 mL
Syrup, *NF,* a sufficient quantity to make	100 mL

Comminute the Baclofen Tablets to a fine powder in a suitable mortar. Add about 5 mL of the Glycerin to wet the powder, and triturate the powder to form a fine paste. Add about 5 mL of the Syrup to the paste, triturate well, and transfer, stepwise and quantitatively, the contents to a calibrated bottle. Rinse the mortar with additional portions of the Syrup, and transfer the contents to the container; repeat as necessary with sufficient Syrup to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 5.0 and 6.0.

Beyond-use date: 35 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suspension of 0.05 M monobasic sodium phosphate and acetonitrile (80 : 20), and adjust with phosphoric acid to a pH of 3.5. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Baclofen RS in water to obtain a concentration of about 1.0 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with water to obtain a suspension having a known concentration of 5 µg per mL.

Assay preparation—Shake thoroughly by hand each bottle of Oral Suspension. Pipet 0.5 mL of Oral Suspension from each bottle to a 500-mL volumetric flask, dilute with water to volume to obtain a concentration of 5 µg per mL, and pass through a 0.22-µm polyvinylidenefluoride (PVDF) filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 5.5 for baclofen; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of baclofen ($C_{10}H_{12}ClNO_2$) in the volume of Oral Suspension taken by the formula:

$$1000(C/V)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Baclofen RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Benazepril Hydrochloride Tablets, page 606 of *PF* 29(3) [May–June 2003]. It is proposed to revert the composition and volume of the *Medium* in the *Dissolution* test to the original submission to reflect the dissolution conditions approved by FDA for this product.

(BPC: M. Marques) RTS—43361-1

Add the following:

▲Benazepril Hydrochloride Tablets

» Benazepril Hydrochloride Tablets contain ~~an amount of Benazepril Hydrochloride equivalent to~~ not less than 90.0 percent and not more than 110.0 percent of the labeled amount of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—***USP Benazepril Hydrochloride RS. USP Benazepril Related Compound B RS. USP Benazepril Related Compound C RS.*

Identification—

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

Test solution—Finely powder not fewer than 20 Tablets, and transfer an accurately weighed portion of the powder, equivalent to about 50 mg of benazepril hydrochloride, to a 50-mL volumetric flask. Add about 30 mL of methanol,

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and shake by mechanical means for 15 minutes. Dilute with methanol to volume, mix, and centrifuge. Pass an aliquot of the supernatant through a suitable filter, discarding the first 6 mL of the filtrate.

Application volume: 20 µL.

Developing solvent system: a mixture of ethyl acetate, methanol, and ammonium hydroxide (80 : 20 : 15).

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

Dissolution ⟨711⟩—

Medium: ~~water; 500 mL.0.1 N hydrochloric acid; 900 mL.~~ water, 500 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of $C_{24}H_{28}N_2O_5 \cdot HCl$ dissolved by employing the following method.

Tetrabutylammonium bromide solution, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Procedure—Inject ~~about 60 µL~~ about 60 µL, or an amount of a filtered portion of the solution under test, equivalent to about ~~12 µg~~ 1.2 µg of benazepril, into the chromatograph. The amount of benazepril injected should not exceed 1.5 µg. Record the chromatogram, and measure the responses for the major peaks. Determine the quantity, in mg, of $C_{24}H_{28}N_2O_5 \cdot HCl$ dissolved in comparison with a Standard solution having a known concentration of USP Benazepril Hydrochloride RS in the same *Medium* and similarly chromatographed.

Tolerances—Not less than ~~85%~~ 80% *(Q)* of the labeled amount of $C_{24}H_{28}N_2O_5 \cdot HCl$ is dissolved in 30 minutes.

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

PROCEDURE FOR CONTENT UNIFORMITY—

Tetrabutylammonium bromide solution, Mobile phase, System suitability solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test preparation—Transfer 1 Tablet to a ~~100 mL~~ suitable volumetric flask, add ~~about 60-50 mL~~ a volume of *Mobile phase,* equivalent to about 50% of the volume of the flask, sonicate for 5 minutes, and then shake by mechanical means for not less than 10 minutes. Dilute quantitatively, and stepwise if necessary, with ~~sufficient~~ *Mobile phase* to ~~volume,~~ obtain a final concentration of about 0.2 mg per mL, mix, and pass a portion of the solution through a suitable filter, discarding the first 6 mL of the filtrate.

Procedure—Proceed as directed in the *Assay*, except to inject the *Test preparation* instead of the *Assay preparation*. Calculate the quantity, in mg, of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) in the Tablet taken by the formula:

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

$$VDC(r_U/r_S)$$

in which V is the volume, in mL, of the initial flask used to prepare the *Test preparation; D* is the dilution factor in subsequent dilutions of *V,* if necessary, to prepare the *Test preparation; C* is the concentration, in mg per mL, of USP Benazepril Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the benazepril hydrochloride peak responses obtained from the *Test preparation* and the *Standard preparation,* respectively.

Related compounds—

Tetrabutylammonium bromide solution, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Benazepril Related Compound C RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.006 mg per mL.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 80 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses of the peaks for benazepril related compound C. Calculate the percentage of benazepril related compound C in the portion of Tablets taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Benazepril Related Compound C RS in the *Standard solution;* C_T is the concentration, in mg per mL, of benazepril hydrochloride in the *Test solution;* and r_U and r_S are the peak responses for benazepril related compound C obtained from the *Test solution* and the *Standard solution,* respectively: not more than 3.0% of benazepril related compound C is found. Calculate the percentage of each impurity (other than benazepril related compound C) in the portion of Tablets taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the sum of the responses of all the peaks (including benazepril related compound C): not more than 1.0% of any individual impurity is found; and not more than 2.0% of total impurities is found, the results for all impurities (~~including~~ excluding benazepril related compound C) being added.

Assay—

Tetrabutylammonium bromide solution, Mobile phase, System suitability solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Benazepril Hydrochloride.*

Assay preparation—Finely powder not fewer than 20 Tablets, and transfer an accurately weighed portion of the powder, equivalent to about 50 mg of benazepril hydrochloride, to a 250-mL volumetric flask. Add about 150 mL of *Mobile phase,* and shake by mechanical means for 30 minutes. Dilute with *Mobile phase* to volume, mix, and centrifuge. Pass an aliquot of the supernatant through a suitable filter, discarding the first 6 mL of the filtrate.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the quantity, in mg, of benazepril hydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$) in the portion of Tablets taken by the formula:

$$250C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Benazepril Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the benazepril hydrochloride peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

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BRIEFING

Benzonatate Capsules, *USP 29* page 256. It is proposed to add a *Dissolution* test to this monograph.

(BPC: M. Marques) RTS—43360-1

Add the following:

▲**Dissolution** ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of benzonatate dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of 0.04 M monobasic potassium phosphate solution and acetonitrile (3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer 50 mg, accurately weighed, of USP Benzonatate RS to a 100-mL volumetric flask, and add about 50 mL of water. Sonicate for 10 minutes, cool, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, and dilute with water to volume.

Test solution—Pass a portion of the solution under test through a 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 310-nm detector and a 4.0-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of benzonatate dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of USP Benzonatate RS in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of benzonatate is dissolved in 30 minutes.▲*USP30*

BRIEFING

Bethanechol Chloride Oral Solution—See briefing under *Acetazolamide Oral Solution.*

(CRX: C. Okeke) RTS—42993-3

Add the following:

▲Bethanechol Chloride Oral Solution

» Bethanechol Chloride Oral Solution contains not less than 90.0 percent and not more than

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110.0 percent of the labeled amount of bethanechol chloride ($C_7H_{17}ClN_2O_2$). Prepare Bethanechol Chloride Oral Solution 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Bethanechol Chloride Oral Suspension*):

Bethanechol Chloride powder	500 mg
Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

Dissolve Bethanechol Chloride powder in about 20 mL of Cherry Syrup in a mortar, and mix to a uniform paste. Add the Cherry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Cherry Syrup to bring to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Bethanechol Chloride RS.*

pH ⟨791⟩**:** between 2.6 and 3.4.

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

*Mobile phase—*Prepare a filtered and degassed solution of water and acetonitrile (67 : 33). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

*Standard preparation—*Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in *Mobile phase,* and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 500 µg per mL.

*Assay preparation—*Agitate the container of Oral Solution for 30 minutes on a rotating mixer, remove a 10-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 2.0 mL of the sample into a 20-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)*—*The liquid chromatograph is equipped with a 200-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L11. The flow rate is about 0.7 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3 minutes, and the relative standard deviation for replicate injections is not more than 3.1%.

*Procedure—*Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of bethanechol chloride ($C_7H_{17}ClN_2O_2$) in the volume of Oral Solution taken by the formula:

$$10(C/V)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Bethanechol Chloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

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BRIEFING

Bethanechol Chloride Oral Suspension, page 923 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension*.

(CRX: C. Okeke) RTS—43131-6

Add the following:

▲Bethanechol Chloride Oral Suspension

» Bethanechol Chloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of bethanechol chloride ($C_7H_{17}ClN_2O_2$). Prepare Bethanechol Chloride Oral Suspension 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Bethanechol Chloride Oral Solution*):

Bethanechol Chloride	~~500 g~~ 500 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF*, a sufficient quantity	
to make	100 mL

[NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of the bulk powder, the preparation becomes a suspension and should be labeled as such.]

If using Bethanechol Chloride Tablets, add to a suitable mortar and comminute to a fine powder, or add the Bethanechol Chloride powder to the mortar. Add about 20 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in ~~geometric~~ small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Bethanechol Chloride RS.*

pH ⟨791⟩**:** between 4.0 and 4.8 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 2.6 and 3.4 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a filtered and degassed solution of water and acetonitrile (67 : 33). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in *Mobile phase,* and quantitatively dilute with *Mobile phase* to obtain a solution having a known concentration of about 500 µg per mL.

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Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 10-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 5.0 mL of the sample into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 200-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L## (see *Chromatography* ⟨621⟩). The flow rate is about 0.7 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3 minutes, and the relative standard deviation for replicate injections is not more than 3.1%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of bethanechol chloride ($C_7H_{17}ClN_2O_2$) in the volume of Oral Suspension taken by the formula:

$$10(C/V)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Bethanechol Chloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Bromocriptine Mesylate Capsules, *USP 29* page 308. It is proposed to specify that the quantitative procedure used in the *Dissolution* test should be the one described in *Dissolution Test 1* under *Bromocriptine Mesylate Tablets.*

(BPC: M. Marques) RTS—43495-1

Change to read:

Dissolution ⟨711⟩—
Medium: 0.1 N hydrochloric acid; 500 mL.
Apparatus 2: 50 rpm.
Time: 60 minutes.
Procedure—Determine the amount of bromocriptine mesylate ($C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$) dissolved using the *Procedure* for *Dissolution*

▲*Test 1*▲*USP30*
under *Bromocriptine Mesylate Tablets,* making any necessary volumetric adjustments.
Tolerances—Not less than 75% *(Q)* of the labeled amount of bromocriptine mesylate ($C_{32}H_{40}BrN_5O_5 \cdot CH_4SO_3$) is dissolved in 60 minutes.

BRIEFING

Calcitriol, page 1433 of *PF* 29(5) [Sept.–Oct. 2003]. On the basis of comments received, it is proposed to establish limits for individual impurities under the test for *Chromatographic purity.* Because calcitriol in solution exists in equilibrium with pre-calcitriol, and the pharmacological activity of calcitriol is due to both compounds, a clarification is added that the pre-calcitriol peak should be included in the *Assay* calculation. The Definition is revised to specify the calculation on the solvent-free basis. In addition, editorial changes have been made throughout the monograph.

(MD-GRE: E. Gonikberg) RTS—41042-1

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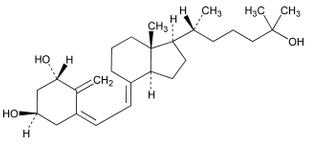
Add the following:

▲Calcitriol



$C_{27}H_{44}O_3$ 416.64

9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1α,3*β*,5*Z*,7*E*)-.

(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3*β*,25-triol [*32222-06-3*].

» Calcitriol contains not less than 97.0 percent and not more than 103.0 percent of $C_{27}H_{44}O_3$, calculated on the ~~anhydrous~~ solvent-free basis.

Caution—Care should be taken to prevent inhaling particles of Calcitriol and exposing the skin to it.

Packaging and storage—Preserve in tight, light-resistant containers, and store under nitrogen in a refrigerator between 2° and 8°.

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

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Chromatographic purity—[NOTE—~~Avoid~~ Carry out the procedure as rapidly as possible, avoiding unnecessary exposure of solutions to light and air.]

Tris buffer solution, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

Standard solution—Transfer 1.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

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

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least two times the retention time of the calcitriol peak, identify the impurities listed in *Table 1,* and measure the peak responses. ~~disregarding any peak having an area less than 0.1 times that of the main peak in the chromatogram of the *Standard solution.*~~ Calculate the percentage of any individual impurity in the portion of Calcitriol taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of any individual peak other than the main calcitriol peak and the pre-calcitriol peak; and r_s is the sum of the responses of all the peaks: ~~not more than~~

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~~0.5% of any individual impurity is found; and~~ in addition to not exceeding the limits in *Table 1,* not more than 1.0% of total impurities is found. Disregard any peak less than 0.1%.

Table 1

Name	Relative Retention Time	Limit (%)
Triazoline adduct of pre-calcitriol	0.43	0.1
trans-Calcitriol[1]	0.96	0.25
1β-Calcitriol[2]	1.15	0.1
Methylene calcitriol[3]	1.5	0.25
Any other individual unidentified impurity	—	0.1

[1] (5*E*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,25-triol
[2] (5*Z*,7*E*)-9,10-secocholesta-5,7,10(19)-triene-1β,3β,25-triol
[3] (5*Z*,7*E*)-1α,3β-dihydroxy-17-((*R*)-7-hydroxy-7-methyloctan-2-yl)-9,10-secoandrosta-5,7,10(19)-triene

Assay—[NOTE—~~Avoid~~ Carry out the procedure as rapidly as possible, avoiding unnecessary exposure of solutions to light and air.]

Tris buffer solution—Dissolve 1.0 g of tris(hydroxymethyl)aminomethane in 900 mL of water, adjust with phosphoric acid to a pH of 7.0 to 7.5, dilute with water to make 1000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Tris buffer solution* (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Prepare a solution of USP Calcitriol RS in *Mobile phase* (without heating) having a known concentration of about 100 µg of calcitriol per mL.

System suitability solution—Heat 2.0 mL of the *Standard preparation* at 80° for 30 minutes.

Assay preparation—~~Transfer about 1.0 mg of Calcitriol, accurately weighed, to a 10 mL volumetric flask, dissolve in and dilute with Mobile phase to volume without heating, and mix.~~ Prepare a solution of Calcitriol in *Mobile phase* (without heating) having a concentration of about 100 µg of calcitriol per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for pre-calcitriol and 1.0 for calcitriol; and the resolution, *R,* between pre-calcitriol and calcitriol is not less than 3.5. ~~and the relative standard deviation for replicate injections, determined from the calcitriol peak, is not more than 1.0%.~~ Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 10,000 theoretical plates; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

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measure the responses for the ~~major~~ calcitriol and pre-calcitriol peaks. Calculate the ~~quantity, in µg,~~ percentage of $C_{27}H_{44}O_3$ in the portion of Calcitriol taken by the formula:

~~$10C(r_U / r_S)$~~

$$100(C_S / C_U)(r_U / r_S)$$

in which ~~*C* is the concentration, in µg per mL, of calcitriol in the *Standard preparation;*~~ C_S and C_U are the concentrations, in µg per mL, of calcitriol in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the sums of calcitriol and pre-calcitriol peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

BRIEFING

Calcitriol Injection, page 1434 of *PF* 29(5) [Sept.–Oct. 2003]. On the basis of comments received, it is proposed to make the following changes:

1. In the Definition, change "terminally sterilized" to "sterile".
2. In the *Packaging and storage* section, delete the specific temperature range.
3. In the *pH* section, widen the range to reflect the characteristics of the FDA-approved products, and modify the instructions.
4. Delete the test for *Aluminum.*
5. In the subsection *Procedure* in the *Assay,* make changes in the formula.

(MD-GRE: E. Gonikberg) RTS—41043-1; 41053-1

Add the following:

▲Calcitriol Injection

» Calcitriol Injection is a ~~terminally sterilized~~ sterile solution of Calcitriol. It contains an amount of Calcitriol equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of calcitriol ($C_{27}H_{44}O_3$). It contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass, protected from light. Store at controlled room temperature. ~~(15° to 30°).~~

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Calcitriol Solution RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩—It contains not more than 100 USP Endotoxin Units per µg of calcitriol.

pH ⟨791⟩**:** between 5.9 and ~~7.0,~~ 8.0, determined on a portion to which, if necessary, 0.30 mL of saturated potassium chloride solution has been added for each 100 mL of Injection.

Particulate matter ⟨788⟩**:** meets the requirements for small-volume injections.

~~**Aluminum** ⟨206⟩**:** not more than 1 µg per mL.~~

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—[NOTE—Avoid unnecessary exposure of solutions to light or air.]

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Mobile phase—Prepare a filtered and degassed mixture of methanol and water (74 : 26). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩) so that the retention time for calcitriol is not less than 20 minutes.

Standard preparation—Transfer 3.0 mL of USP Calcitriol Solution RS, equilibrated to room temperature, to a container; add 3.0 mL of water; and mix.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 3 µg of calcitriol, to a container; add a sufficient amount of water to dilute to a total volume of 3.0 mL; add 3.0 mL of methanol; and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 264-nm detector, a 4.6-mm × 4.5-cm guard column that contains 5-µm packing L1, and a 4.6-mm × 7.5-cm analytical column that contains 3-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of calcitriol ($C_{27}H_{44}O_3$) in each mL of the Injection taken by the formula:

~~$6C(r_U / r_S)$,~~

$$C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of calcitriol ~~in the *Standard preparation,* calculated based on the content of calcitriol~~ in the USP Calcitriol Solution RS; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

BRIEFING

Calcium Pantothenate, *USP 29* page 358. In the preparation of the *Standard solution* in the test for *Ordinary impurities,* it is proposed to substitute USP Beta Alanine RS for 3-aminopropionic acid. Because beta alanine is the common name for 3-aminopropionic acid, this revision does not change the composition of the *Standard solution.*

(DSN: L. Evans) RTS—43719-1

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Beta Alanine RS.* ▲*USP30*
USP Calcium Pantothenate RS.

Change to read:

Ordinary impurities ⟨466⟩—
Test solution: water.
Standard solution: water. Use ~~3-aminopropionic acid,~~ ▲USP Beta Alanine RS, ▲*USP30* in place of USP Calcium Pantothenate RS, as the Standard.
Eluant: a mixture of alcohol and water (65 : 35).
Visualization: 4.
Limit: 1.0%.

In-Process Revision

BRIEFING

Captopril Oral Solution—See briefing under *Acetazolamide Oral Solution.*

(CRX: C. Okeke) RTS—43128-2

Add the following:

▲Captopril Oral Solution

» Captopril Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of captopril ($C_9H_{15}NO_3S$). Prepare Captopril Oral Solution 0.75 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Captopril Oral Suspension*):

Captopril powder	75 mg
Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

Dissolve Captopril powder in about 10 mL of Cherry Syrup in a mortar, and mix to a uniform paste. Add the Cherry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Cherry Syrup to bring to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store in a cold place.

Labeling—Label it to state the beyond-use date.

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

pH ⟨791⟩**:** between 4.0 and 4.2.

Beyond-use date: 7 days after the day on which it was compounded.

Assay—

*Mobile phase—*Prepare a filtered and degassed mixture of methanol and water (11 : 9) containing 0.5 mL of phosphoric acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

*Standard preparation—*Dissolve USP Captopril RS in water to obtain a solution having a known concentration of 7.5 µg per mL.

*Assay preparation—*Agitate the container of Oral Solution for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)*—*The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 5.0 minutes, and the relative standard deviation for replicate injections is not more than 0.9%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of captopril ($C_9H_{15}NO_3S$) in the volume of Oral Solution taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Captopril RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Captopril Oral Suspension, page 924 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-7

In-Process Revision

Add the following:

▲Captopril Oral Suspension

» Captopril Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of captopril ($C_9H_{15}NO_3S$). Prepare Captopril Oral Suspension 0.75 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Captopril Oral Solution*):

Captopril	~~100 mg~~ 75 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	~~134 mL~~ 100 mL

NOTE—If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets place the required number of Captopril Tablets in a suitable mortar and comminute to a fine powder, or add Captopril powder to the mortar. Add about 10 mL of the Vehicle, and mix to a uniform paste. Add the remainder of the Vehicle in small portions, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a graduate. Add sufficient quantity of Vehicle to final volume of 100 mL.

Packaging and storage—Preserve in tight, light-resistant containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 4.0 and 5.0.

Beyond-use date: 7 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (11 : 9) containing 0.5 mL of phosphoric acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Captopril RS in water to obtain a solution having a known concentration of 7.5 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 5.0 minutes, and the relative standard deviation for replicate injections is not more than 0.9%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of captopril ($C_9H_{15}NO_3S$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Captopril RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Carbamazepine, *USP 29* page 369. It is proposed to change the name of the test for *Chromatographic purity* to *Related compounds.* It is also proposed to revise the test for *Related compounds* and the *Assay* to rename 10,11-dihydrocarbamazepine and iminostilbene as carbamazepine related compound A and carbamazepine related compound B, respectively. The *USP Reference standards* section is being revised to add USP Carbamazepine Related Compound A RS and USP Carbamazepine Related Compound B RS.

(MD-PP: R. Ravichandran) RTS—43560-1

Change to read:

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

▲*USP Carbamazepine Related Compound A RS. USP Carbamazepine Related Compound B RS.*▲*USP30*

Change to read:

~~**Chromatographic purity**~~

▲**Related compounds—**▲*USP30*

Mobile phase and *System suitability solution*—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Carbamazepine RS, ~~10,11-dihydrocarbamazepine, and iminostilbene~~

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▲USP Carbamazepine Related Compound A RS, and USP Carbamazepine Related Compound B RS▲*USP30* in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having known concentrations of about 0.02 mg per mL of each component. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with a mixture of methanol and water (50 : 50) to volume, and mix.

Test solution—Transfer about 100 mg of Carbamazepine, accurately weighed, to a 50-mL volumetric flask, and dissolve in and dilute with methanol to volume. Transfer 25.0 mL of this solution to a 50-mL volumetric flask, add about 20 mL of water, and shake. Allow the mixture to cool to room temperature, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ~~the 10,11-dihydrocarbamazepine~~

▲carbamazepine related compound A▲*USP30* and carbamazepine is not less than 1.70; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantities, in mg, of ~~10,11-dihydrocarbamazepine and iminostilbene~~

▲carbamazepine related compound A and carbamazepine related compound B▲*USP30* in the portion of Carbamazepine taken by the formula:

$$100C(r_i / r_{Si})$$

in which C is the concentration, in mg per mL, of ~~10,11-dihydrocarbamazepine or iminostilbene~~

▲carbamazepine related compound A or carbamazepine related compound B▲*USP30* in the *Standard solution;* and r_i and r_{Si} are the peak responses obtained for either ~~10,11-dihydrocarbamazepine or iminostilbene~~

▲carbamazepine related compound A or carbamazepine related compound B▲*USP30* from the *Test solution* and the corresponding peak obtained from the *Standard solution,* respectively. Calculate the quantities, in mg, of all other impurities found in the portion of Carbamazepine taken by the formula:

$$100C(r_i / r_S)$$

in which r_i is the peak response for any other impurity; and r_S is the peak response for carbamazepine obtained from the *Standard solution:* not more than 0.2% of any individual impurity is found; and the total of all impurities ~~(including 10,11-dihydrocarbamazepine and iminostilbene)~~

▲(including carbamazepine related compound A and carbamazepine related compound B)▲*USP30* is not more than 0.5%.

Change to read:

Assay—

Mobile phase—Prepare a 1000-mL mixture of water, methanol, and tetrahydrofuran (85 : 12 : 3), add 0.22 mL of formic acid, mix, then add 0.5 mL of triethylamine, and mix. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Carbamazepine RS and ~~10,11-dihydrocarbamazepine~~

▲USP Carbamazepine Related Compound A RS▲*USP30* in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having known concentrations of about 0.1 and 0.5 mg per mL, respectively. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, and dilute with a mixture of methanol and water (1 : 1) to volume.

Standard preparation—Dissolve an accurately weighed quantity of USP Carbamazepine RS in methanol, and dilute quantitatively with methanol to obtain a solution having a known concentration of about 2 mg per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, and dilute with a mixture of methanol and water (1 : 1) to volume.

Assay preparation—Transfer about 100 mg of Carbamazepine, accurately weighed, to a 50-mL volumetric flask, and dissolve in and dilute with methanol to volume. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, and dissolve in and dilute with a mixture of methanol and water (1 : 1) to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation* and the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ~~10,11-dihydrocarbamazepine~~

▲carbamazepine related compound A▲*USP30* and carbamazepine in the *System suitability solution* is not less than 1.70; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{15}H_{12}N_2O$ in the portion of Carbamazepine taken by the formula:

$$500C(r_U / r_S)$$

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

In-Process Revision

BRIEFING

Cefonicid for Injection, *USP 29* page 417. It is proposed to correct the tailing factor in the *Chromatographic system* and define the terms in the calculation in the *Assay.*

(MD-ANT: B. Gilbert) RTS—43613-1

Change to read:

Assay—

Mobile phase—Prepare a mixture of water, methanol, and 0.2 M monobasic ammonium phosphate (33 : 5 : 3). Pass through a filter having a 0.5-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Cefonicid Sodium RS in *Mobile phase* to obtain a solution having a known concentration of about 200 µg of cefonicid ($C_{18}H_{18}N_6O_8S_3$) per mL.

Assay preparation 1 (where it is represented as being in a single-dose container)—Constitute Cefonicid for Injection in a volume of water, accurately measured, corresponding to the volume of solvent specified in the labeling. Withdraw all of the withdrawable contents, using a suitable hypodermic needle and syringe, and quantitatively dilute with *Mobile phase* to obtain a solution containing about 200 µg of cefonicid per mL.

Assay preparation 2 (where the label states the quantity of cefonicid in a given volume of constituted solution)—Constitute Cefonicid for Injection in a volume of water, accurately measured, corresponding to the volume of solvent specified in the labeling. Quantitatively dilute an accurately measured volume of the constituted solution with *Mobile phase* to obtain a solution containing about 200 µg of cefonicid per mL.

Resolution solution—Dissolve a quantity of USP Cefonicid Sodium RS in *Mobile phase* to obtain a solution containing about 0.2 mg per mL. Heat on a steam bath for 30 minutes, and cool. This *Resolution solution* contains a mixture of cefonicid and desacetyl cefonicid.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm × 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation* and the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the column efficiency determined from the analyte peak is not less than 1500 theoretical plates, the tailing factor for the analyte peak is not more than 1.3,~~

▲▲*USP30*
the resolution, *R,* between the cefonicid peak and the desacetyl cefonicid peak is not less than 1.1; the column efficiency determined from the analyte peak is not less than 1500 theoretical plates; the tailing factor for the analyte peak is not more than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of cefonicid ($C_{18}H_{18}N_6O_8S_3$) withdrawn from the container, or in the portion of constituted solution taken by the formula:

$$(L / D)(C)(r_U / r_S)$$

in which L is the labeled quantity, in mg, of cefonicid in the container, or in the volume of constituted solution taken; D is the concentration, in µg per mL, of cefonicid in *Assay preparation 1* or *Assay preparation 2,* based on the labeled quantity in the container or in the portion of constituted solution taken, respectively, and the extent of dilution;

▲C is the concentration, in µg per mL, of cefonicid in the *Standard preparation;*▲*USP30*
and r_U and r_S are the peak responses obtained from the relevant *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ceftazidime, *USP 29* page 434; **Ceftazidime Injection,** *USP 29* page 435; **Ceftazidime for Injection,** *USP 29* page 435. It is proposed to change the name of USP Delta-3-Ceftazidime Isomer RS to USP Ceftazidime, Delta-3-Isomer RS, in accordance with current USP Reference Standard naming conventions.

(MD-ANT: B. Gilbert) RTS—42483-1

Change to read:

USP Reference standards ⟨11⟩—~~*USP Delta-3-Ceftazidime Isomer RS.*~~

▲*USP Ceftazidime, Delta-3-Isomer RS.*▲*USP30*
USP Ceftazidime Pentahydrate RS. USP Endotoxin RS.

Change to read:

Assay—

pH 7 Buffer—Dissolve 42.59 g of anhydrous dibasic sodium phosphate and 27.22 g of monobasic potassium phosphate in water to make 1000 mL of solution.

Mobile phase—Mix 40 mL of acetonitrile and 200 mL of *pH 7 Buffer*, and dilute with water to obtain 2000 mL of solution. Filter, using a filter having a porosity of 1 µm or finer, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 29 mg of USP Ceftazidime Pentahydrate RS, accurately weighed, to a 25-mL volumetric flask containing 2.5 mL of *pH 7 Buffer,* and shake until dissolved. Dilute with water to volume, and mix. [NOTE—Protect this solution from light.] Immediately prior to chromatography, transfer 5.0 mL of this stock solution to a 50-mL volumetric flask, dilute with water to volume, and mix. This solution contains about 100 µg of ceftazidime ($C_{22}H_{22}N_6O_7S_2$) per mL.

Assay preparation—Transfer about 115 mg of Ceftazidime, accurately weighed, to a 100-mL volumetric flask containing 10.0 mL of *pH 7 Buffer,* and shake until dissolved. Dilute with water to volume, and mix. [NOTE—Protect this solution from light.] Immediately prior to chromatography, transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with water to volume, and mix.

Resolution solution—Prepare a solution of ~~USP Delta-3-Ceftazidime Isomer RS~~

▲USP Ceftazidime, Delta-3-Isomer RS▲*USP30*
in *pH 7 Buffer* containing about 0.1 mg per mL. Immediately prior to chromatography, mix 1 mL of this solution with 8 mL of water and 1 mL of the stock solution used to prepare the *Standard preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between ceftazidime and ~~the delta-3-ceftazidime isomer~~

▲ceftazidime, delta-3-isomer▲*USP30*
is not less than 2.0. Chromatograph the *Standard preparation,* and record the responses as directed for *Procedure:* the tailing factor for the analyte peak is not less than 0.75 and not more than 1.5, and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{22}H_{22}N_6O_7S_2$ in the portion of Ceftazidime taken by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of ceftazidime ($C_{22}H_{22}N_6O_7S_2$) in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ceftazidime Injection, *USP 29* page 435—See briefing under *Ceftazidime*.

(MD-ANT: B. Gilbert) RTS—42483-2

Change to read:

USP Reference standards ⟨11⟩—~~*USP Delta-3-Ceftazidime Isomer RS.*~~

▲*USP Ceftazidime, Delta-3-Isomer RS.*▲*USP30*
USP Ceftazidime Pentahydrate RS.

BRIEFING

Ceftazidime for Injection, *USP 29* page 435—See briefing under *Ceftazidime*.

(MD-ANT: B. Gilbert) RTS—42483-3

Change to read:

USP Reference standards ⟨11⟩—*USP L-Arginine RS.* ~~*USP Delta-3-Ceftazidime Isomer RS.*~~

▲*USP Ceftazidime, Delta-3-Isomer RS.*▲*USP30*
USP Ceftazidime Pentahydrate RS. USP Endotoxin RS.

BRIEFING

Chlorthalidone, *USP 29* page 499. It is proposed to change the name of USP 4′-Chloro-3′-sulfamoyl-2-benzophenone Carboxylic Acid RS to USP Chlorthalidone Related Compound A RS, to be in accordance with the implemented name change for the Reference Standard. The test for *Limit of 4′-chloro-3′-sulfamoyl-2-benzophenone carboxylic acid (CCA)* is renamed to *Limit of chlorthalidone related compound A.* It is also proposed to clarify the calculations for this test. Minor editorial style changes have also been made.

(MD-CV: E. Gonikberg) RTS—43693-1

Change to read:

USP Reference standards ⟨11⟩—*USP Chlorthalidone RS.* ~~*USP 4′-Chloro-3′-sulfamoyl-2-benzophenone Carboxylic Acid RS.*~~

▲*USP Chlorthalidone Related Compound A RS.*▲*USP30*

Change to read:

~~**Limit of 4′-chloro-3′-sulfamoyl-2-benzophenone carboxylic acid (CCA)**~~

▲**Limit of chlorthalidone related compound A**▲*USP30*
—Proceed as directed in the *Assay,* except to calculate ~~the quantity, in mg, of CCA~~

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▲the percentage of chlorthalidone related compound A▲*USP30* in the portion of Chlorthalidone taken by the formula:

~~$(0.5)C(R_U / R_S)$,~~

~~in which *C* is the concentration, in µg per mL, of USP 4′-Chloro-3′-sulfamoyl-2-benzophenone Carboxylic Acid RSin the *Standard preparation*;~~

$$\blacktriangle 0.1(C_R / C_T)(R_U / R_S)$$

in which C_R is the concentration, in µg per mL, of USP Chlorthalidone Related Compound A RS in the *Standard preparation;* C_T is the concentration, in mg per mL, of Chlorthalidone in the *Assay preparation;*▲*USP30* and R_U and R_S are the peak response ratios of ~~CCA~~

▲chlorthalidone related compound A▲*USP30* and the internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively: not more than 1.0% is present.

▲[NOTE—USP Chlorthalidone Related Compound A RS is 4′-chloro-3′-sulfamoyl-2-benzophenone carboxylic acid (CCA).]▲*USP30*

Change to read:

Assay—

Mobile phase—Prepare a suitable degassed mixture of 0.01 M dibasic ammonium phosphate and methanol (3 : 2), adjust dropwise with phosphoric acid to a pH of 5.5 ± 0.1, and filter.

Internal standard solution—Prepare a solution of 2,7-naphthalenediol in methanol having a concentration of about 1.0 mg per mL.

~~*CCA solution*~~

▲*Chlorthalidone related compound A solution*▲*USP30*—Prepare a solution of ~~USP 4′-Chloro-3′-sulfamoyl-2-benzophenone Carboxylic Acid RS~~

▲USP Chlorthalidone Related Compound A RS▲*USP30* in methanol having a known concentration of about 5 µg per mL.

Standard preparation—Prepare a solution of USP Chlorthalidone RS in methanol having a known concentration of about 1 mg per mL. Pipet 5 mL of this solution into a 50-mL volumetric flask containing 5.0 mL of *Internal standard solution* and 10.0 mL of ~~*CCA solution*~~

▲*Chlorthalidone related compound A solution.*▲*USP30* Dilute with water to volume, and mix.

▲This solution contains about 0.1 mg of chlorthalidone and about 1 µg of chlorthalidone related compound A per mL.▲*USP30*

Assay preparation—Transfer about 50 mg of Chlorthalidone, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Pipet 5 mL of this solution into a 50-mL volumetric flask containing 5.0 mL of *Internal standard solution* and 10.0 mL of methanol. Dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. Chromatograph five replicate injections of the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for ~~CCA~~

▲chlorthalidone related compound A,▲*USP30* 0.8 for chlorthalidone, and 1.0 for the internal standard; the resolution, *R,* between chlorthalidone and ~~CCA,~~

▲chlorthalidone related compound A,▲*USP30* and between chlorthalidone and the internal standard is not less than 1.5; the tailing factor for chlorthalidone and ~~CCA~~

▲chlorthalidone related compound A▲*USP30* is not more than 2.0; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{14}H_{11}ClN_2O_4S$ in the portion of Chlorthalidone taken by the formula:

$$500C(R_U / R_S)$$

in which *C* is the concentration, in mg per mL, of USP Chlorthalidone RS in the *Standard preparation;* and R_U and R_S are the peak response ratios of chlorthalidone and the internal standard obtained from the *Assay preparation* and the *Standard preparation*, respectively.

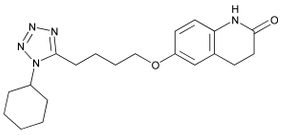
BRIEFING

Cilostazol. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the test for *Related compounds* and in the *Assay* is based on analyses performed with the XTerra RP8 brand of L7 column. The typical retention time for the cilostazol peak is about 7 minutes.

(MD-CV: E. Gonikberg) RTS—42064-1

Add the following:

▲Cilostazol



$C_{20}H_{27}N_5O_2$ 369.46

2(1*H*)-Quinolinone, 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-3,4-dihydro-.

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril [*73963-72-1*].

» Cilostazol contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{27}N_5O_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

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

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Loss on drying ⟨731⟩—Dry it at 110° for 3 hours: it loses not more than 0.25% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Chloride ⟨221⟩**—**

Test solution—Dissolve 0.5 g of Cilostazol in 40 mL of dimethylformamide, add 6 mL of diluted nitric acid and dimethylformamide to make 50 mL.

Control solution—To 25 mL of 0.01 M hydrochloric acid add 6 mL of diluted nitric acid and dimethylformamide to make 50 mL.

Procedure—Add 1 mL of silver nitrate TS to the *Test solution* and to the *Control solution,* mix well, and allow to stand for 5 minutes, protecting from direct sunlight. Compare the opalescence developed in both solutions against a black background by viewing downward or transversely. The opalescence developed in the *Test solution* is not more than that of the *Control solution* (0.018%).

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

Related compounds—

Diluent, Solution A, Solution B, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Cilostazol RS and USP Cilostazol Related Compound C RS in acetonitrile, with sonication if necessary, to obtain a solution having known concentrations of about 0.5 mg per mL of each component. Transfer 4 mL of this solution to a 10-mL volumetric flask, and dilute with water to volume. Further dilute this solution, stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 0.4 µg per mL of each component.

Test solution—Transfer about 20 mg of Cilostazol, accurately weighed, to a 50-mL volumetric flask, dissolve in 20 mL of acetonitrile, with sonication if necessary. Dilute with water to volume, and mix.

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Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of cilostazol related compound C by the formula:

$$0.1(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of cilostazol related compound C in the *Standard solution;* C_T is the concentration, in mg per mL, of cilostazol in the *Test solution;* r_U is the peak response for cilostazol related compound C obtained from the *Test solution;* and r_S is the peak response for cilostazol related compound C obtained from the *Standard solution*. Calculate the percentage of other impurities by the formula:

$$0.1(1/F)(C_S / C_T)(r_U / r_S)$$

in which F is the relative response factor from *Table 1;* C_S is the concentration, in µg per mL, of cilostazol in the *Standard solution;* C_T is the concentration, in mg per mL, of cilostazol in the *Test solution;* r_U is the peak response for any other impurity obtained from the *Test solution;* and r_S is the peak response for cilostazol obtained from the *Standard solution*.

Table 1

Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Cilostazol related compound A[1]	0.2	1.7	0.1
Cilostazol related compound B[2]	0.9	0.58	0.1
Cilostazol	1.0	1.0	—
Cilostazol related compound C[3]	1.9	n/a	0.1
Any other individual impurity	—	1.0	0.1

[1] 6-Hydroxy-3,4-dihydro-1*H*-quinolin-2-one
[2] 6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one
[3] 1,6-Bis-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one

In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.4% of total impurities is found.

Assay—

Diluent—Use a mixture of water and acetonitrile (60 : 40).

Solution A—Use a mixture of water and acetonitrile (70 : 30).

Solution B—Use a mixture of water and acetonitrile (50 : 50).

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

System suitability solution—Prepare a solution in *Diluent* having known concentrations of about 0.05 mg per mL each of USP Cilostazol RS, USP Cilostazol Related Compound A RS, and USP Cilostazol Related Compound B RS.

Standard preparation—Dissolve an accurately weighed quantity of USP Cilostazol RS in acetonitrile, with sonication if necessary, to obtain a solution having a known concentration of about 1.0 mg per mL. Transfer 4 mL of this solution to a 10-mL volumetric flask, and dilute with water

to volume. Further dilute this solution with *Diluent* to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Transfer about 20 mg of Cilostazol, accurately weighed, to a 50-mL volumetric flask, dissolve in 20 mL acetonitrile, sonicate if necessary, dilute with water to volume, and mix. Transfer 1 mL of this solution to a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 10-cm column that contains 3.5-µm packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–6.5	100→50	0→50	linear gradient
6.5–10	50→0	50→100	linear gradient
10–20	0	100	isocratic
20–20.1	0→100	100→0	linear gradient
20.1–28	100	0	re-equilibration

Chromatograph the *System suitability solution,* identify the components using *Table 1,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cilostazol related compound B and cilostazol is not less than 3.0; the tailing factor for the cilostazol peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{20}H_{27}N_5O_2$ in the portion of Cilostazol taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of cilostazol in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

BRIEFING

Cimetidine Tablets, *USP 29* page 512. For the *Dissolution* test, it is proposed to add the option of using a 20-mesh basket for the 800-mg strength of this product because of clogging.

(BPC: M. Marques) RTS—43066-1

Change to read:

Dissolution ⟨711⟩—
Medium: 0.01 N hydrochloric acid; 900 mL.
Apparatus 1: 100 rpm.

▲A 20-mesh basket may be used for 800-mg strength Tablets. ▲*USP30*
Time: 15 minutes.
Procedure—Determine the amount of $C_{10}H_{16}N_6S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 218 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, in comparison with a Standard solution having a known concentration of USP Cimetidine RS in the same *Medium*.
Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{10}H_{16}N_6S$ is dissolved in 15 minutes.

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BRIEFING

Clonazepam Oral Suspension, page 927 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-9

Add the following:

▲Clonazepam Oral Suspension

» Clonazepam Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of clonazepam ($C_{15}H_{10}ClN_3O_3$). Prepare Clonazepam Oral Suspension 0.1 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Clonazepam	10 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE— ~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, comminute the Tablets into a fine powder in a suitable mortar, or add Clonazepam powder to the mortar. Add approximately 10 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Vehicle to bring to final volume, and mix well.

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

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 4.0 and 4.4 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 2.5 and 3.3 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a filtered and degassed solution of water, methanol, and acetonitrile (4 : 3 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Clonazepam RS in acetonitrile to obtain a concentration of about 0.5 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with acetonitrile to obtain a solution having a known concentration of 25 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex

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mixer for 30 seconds. Pipet 2.5 mL of the sample solution into a 10-mL volumetric flask, and dilute with acetonitrile to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 10-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time of clonazepam is about 7 minutes; and the relative standard deviation for replicate injections is not more than 1.8%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of clonazepam ($C_{15}H_{10}ClN_3O_3$) in the volume of Oral Suspension taken by the formula:

$$4(C/V)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Clonazepam RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

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BRIEFING

Clopidogrel Bisulfate, *USP 29* page 562; **Clopidogrel Tablets,** *USP 29* page 562. On the basis of comments received, it is proposed to revise the test for *Related compounds* to modify the preparation of the *Standard solution,* to specify system suitability requirements under the *Chromatographic system,* to clarify the calculation of the content of clopidogrel related compound B in the *Procedure,* and to add a formula for the calculation of the content of unknown impurities.

It is also proposed to revise the *Assay* to modify the composition of the *System suitability solution* and the preparation of the *Standard preparation*. In addition, it is proposed to add a *Note* regarding bisulfate salt equivalents of the USP Clopidogrel Related Compounds RS.

Other editorial revisions have also been made.

(MD-CV: E. Gonikberg) RTS—43631-1

Change to read:

Related compounds—

▲[NOTE—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]▲*USP30*

Phosphate buffer, Mobile phase, ~~*Standard stock solution,* and *Chromatographic system*~~

▲▲*USP30*

and *System suitability solution*—Proceed as directed in the *Assay.*

Standard solution—~~Dissolve accurately weighed quantities of USP Clopidogrel Related Compound A RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS in methanol, and dilute with methanol to obtain a solution having concentrations of about 0.1, 0.4, and 0.3 mg per mL, respectively. Dilute this solution with *Mobile phase,* and mix to obtain a solution having final concentrations of about 10, 40, and 30 µg per mL, respectively.~~

▲Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound A RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS in methanol, and dilute with methanol to obtain a solution having known concentrations of about 20 µg per mL, 40 µg per mL, 120 µg per mL, and 200 µg per mL, respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, and dilute with *Mobile phase* to volume, and mix to obtain a solution having final concentrations of about 0.5 µg per mL, 1 µg per mL, 3 µg per mL, and 5 µg per mL, respectively.▲*USP30*

Test solution—Transfer about 100 mg of Clopidogrel Bisulfate, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

▲*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and 4.6-mm × 15-cm column that contains packing L57. The flow rate is about 1.0 mL per minute.

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for clopidogrel related compound A, 0.8 and 1.2 for the two enantiomers of clopidogrel related compound B, 1.0 for clopidogrel, and 2.0 for clopidogrel related compound C; and the resolution, *R,* between clopidogrel and the first enantiomer of clopidogrel related compound B is greater than 2.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 15% for each peak.▲*USP30*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. ~~Calculate the percentage of related compounds in the portion of Clopidogrel Bisulfate taken by the formula:~~

~~$100(C_S / C_T)(r_U / r_S)$~~

~~in which C_S is the concentration, in mg per mL, of relevant USP Clopidogrel Related Compound RS in the *Standard solution;*~~

▲Calculate the percentage of clopidogrel related compound A and clopidogrel related compound C in the portion of Clopidogrel Bisulfate taken by the formula:

$$100(C_A / C_T)(r_U / r_S)$$

in which C_A is the concentration, in mg per mL, of the relevant clopidogrel related compound in the *Standard solution;*▲*USP30*
C_T is the concentration, in mg per mL, of Clopidogrel Bisulfate in the *Test solution;* r_U is the peak response for the relevant clopidogrel related compound obtained from the *Test solution;* and r_S is the peak response for the relevant clopidogrel related compound obtained from the *Standard solution*.

▲Calculate the percentage of the first enantiomer of clopidogrel related compound B in the portion of Clopidogrel Bisulfate taken by the formula:

$$100 \times 0.5(C_B / C_T)(r_U / r_S)$$

in which C_B is the concentration, in mg per mL, of clopidogrel related compound B in the *Standard solution;* 0.5 is the correction for the content of the first enantiomer in clopidogrel related compound B; r_U and r_S are the peak responses of the first enantiomer of clopidogrel related compound B in the *Test solution* and *Standard solution,* respectively; and the other terms are as defined above.

Calculate the percentage of any impurity other than clopidogrel related compounds A, B, and C in the portion of Clopidogrel Bisulfate taken by the formula:

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

in which C is the concentration of clopidogrel bisulfate, in mg per mL, in the *Standard solution;* r_U is the peak response of any other impurity obtained from the *Test solution;* r_S is the peak response of the clopidogrel peak obtained from the *Standard solution;* and the other terms are as defined above:▲*USP30*
not more than 0.2% of clopidogrel related compound A is found; not more than 0.3% of

▲the first enantiomer of▲*USP30*
clopidogrel related compound B is found; not more than 1.0% of clopidogrel related compound C is found; not more than 0.1% of any other impurity is found; and not more than 1.5% of total impurities is found.

▲Disregard any peak observed in the blank.▲*USP30*

Change to read:

Assay—

▲[NOTE—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]▲*USP30*

Phosphate buffer—Dissolve 1.36 g of monobasic potassium phosphate in about 500 mL of water, and dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (75 : 25). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Standard stock solution*—Transfer about 100 mg of USP Clopidogrel Bisulfate RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with methanol to volume, and mix.~~

~~*Standard preparation*—Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.~~

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▲*Standard preparation*—Dissolve an accurately weighed quantity of USP Clopidogrel Bisulfate RS in methanol to obtain a solution having a known concentration of about 1.0 mg of clopidogrel bisulfate per mL. Dilute a suitable portion of this solution, accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.▲*USP30*

System suitability solution—~~Dissolve an accurately weighed quantity of USP Clopidogrel Related Compound B RS in methanol, and mix with a suitable portion of *Standard stock solution,* to obtain concentrations of about 1.0 and 0.5 mg per mL, respectively. Dilute this solution with *Mobile phase,* and mix to obtain a solution having a final concentration of about 0.05 mg per mL of clopidogrel bisulfate and about 0.1 mg per mL of clopidogrel related compound B.~~

▲Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS and USP Clopidogrel Related Compound B RS in methanol, and quantitatively dilute with methanol to obtain a solution having concentrations of about 100 µg per mL and 200 µg per mL, respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.▲*USP30*

Assay preparation—Transfer about 100 mg of Clopidogrel Bisulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Pipet 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains packing L57. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 and 1.2 for enantiomers of clopidogrel related compound B, respectively, and 1.0 for clopidogrel; and the resolution, *R,* between clopidogrel and the first enantiomer of clopidogrel related compound B is ~~not less~~

▲greater▲*USP30*
than 2.5. Chromatograph the *Standard preparation:* the relative standard deviation for replicate injections determined from clopidogrel bisulfate is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the quantity, in mg, of $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ in the portion of Clopidogrel taken by the formula:

$$1000C(r_U / r_S)$$

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

BRIEFING

Clopidogrel Tablets, *USP 29* page 562. On the basis of comments received, it is proposed to revise the test for *Related compounds* to change the limit of clopidogrel related compound A to 1.2%, the limit of clopidogrel related compound C to 1.5%, and the limit of total impurities to 2.5%. These limits are appropriate for marketed products through their shelf life. In the absence of any significant adverse comments, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of June 1, 2006.

See also the briefing under *Clopidogrel Bisulfate*.

(MD-CV: E. Gonikberg) RTS—43456-1; 43631-2

Change to read:

Related compounds—

▲[NOTE—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]▲*USP30*

Phosphate buffer and *Mobile phase*—Prepare as directed in the *Assay* under *Clopidogrel Bisulfate*.

System suitability solution—~~Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound A RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS in methanol. Dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having concentrations of about 1 µg per mL, 1 µg per mL, 2 µg per mL, and 3 µg per mL, respectively.~~

▲Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS and USP Clopidogrel Related Compound B RS in methanol, and dilute with methanol to obtain a solution having concentrations of about 100 µg per mL and 200 µg per mL, respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.▲*USP30*

Standard solution—~~Dissolve accurately weighed quantities of USP Clopidogrel Related Compound A RS and USP Clopidogrel Related Compound C RS in methanol. Dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 1 µg per mL and 5 µg per mL, respectively.~~

▲Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound A RS, and USP Clopidogrel Related Compound C RS in methanol to obtain a solution having known concentrations of about 40 µg per mL, 250 µg per mL, and 300 µg per mL,

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respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, and dilute with *Mobile phase* to volume. This solution contains about 1 µg of of clopidogrel bisulfate per mL, 6 µg of clopidogrel related compound A per mL, and 7.5 µg of clopidogrel related compound C per mL.▲*USP30*

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg of clopidogrel

▲(free base),▲*USP30*
to a 200-mL volumetric flask, add 5 mL of methanol, dilute with *Mobile phase* to volume, and mix. Allow to stand for 10 minutes, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate after discarding the first 5 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and 4.6-mm × 15-cm column that contains packing L57. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for clopidogrel related compound A, 0.8 and 1.2 for the two enantiomers of clopidogrel related compound B, 1.0 for clopidogrel, and 2.0 for clopidogrel related compound C; and the resolution, *R,* between clopidogrel and ~~each of the two enantiomers~~

▲the first enantiomer▲*USP30*
of clopidogrel related compound B is ~~not less~~

▲greater▲*USP30*
than 2.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 15%

▲for each peak.▲*USP30*

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of clopidogrel related compounds

▲A and C▲*USP30*
in the portion of Tablets taken by the formula:

~~$20(C/W)(r_U/r_S)$~~

~~in which *C* is the concentration, in µg per mL, of the appropriate USP Reference Standard~~

▲$20(321.82/419.90)(C/W)(r_U/r_S)$

in which 321.82 is the molecular weight of clopidogrel; 419.90 is the molecular weight of clopidogrel bisulfate; *C* is the concentration, in µg per mL, of the relevant clopidogrel related compound▲*USP30*
in the *Standard solution; W* is the weight, in mg, of clopidogrel in the portion of Tablets used to prepare the *Test solution* based on the labeled quantity of clopidogrel per Tablet, Tablet weight, and the weight of the portion of Tablets used; and r_U and r_S are the peak responses of the corresponding related compounds obtained from the *Test solution* and the *Standard solution,* respectively.

▲Calculate the percentage of any other impurity (excluding clopidogrel related compound B) in the portion of Tablets taken by the formula:

$$20(321.82/419.90)(C_C/W)(r_U/r_S)$$

in which C_C is the concentration of clopidogrel bisulfate, in µg per mL, in the *Standard solution;* r_U is the peak response of any other impurity obtained from the *Test solution;* r_S is the peak response of clopidogrel peak obtained from the *Standard solution;* and the other terms are as defined above:▲*USP30*
not more than ~~0.2%~~

•1.2%•3
of clopidogrel related compound A is found, not more than ~~1.0%~~

•1.5%•3
of clopidogrel related compound C is found, not more than 0.2% of any other single impurity (excluding clopidogrel related compound B) is found, and not more than ~~1.2%~~

•2.5%•3
of total impurities (excluding clopidogrel related compound B) is found.

Change to read:

Assay—

▲[NOTE—For all clopidogrel related compounds, the concentrations are expressed as bisulfate salts. Use bisulfate salt equivalents stated on USP Reference Standards labels to calculate the concentrations as appropriate.]▲*USP30*

Phosphate buffer, Mobile phase, ~~Standard stock solution, Standard preparation, System suitability solution,~~

▲▲*USP30*
and *Chromatographic system*—Proceed as directed in the *Assay* under *Clopidogrel Bisulfate*.

▲*System suitability preparation*—Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS and USP Clopidogrel Related Compound B RS in methanol, and quantitatively dilute with methanol to obtain a solution having concentrations of about 100 µg per mL and 200 µg per mL, respectively. Transfer 5 mL of this solution to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

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Standard preparation—Dissolve an accurately weighed quantity of USP Clopidogrel Bisulfate RS in methanol to obtain a solution having a known concentration of about 0.1 mg of clopidogrel bisulfate per mL.▲*USP30*

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about ~~100 mg of clopidogrel bisulfate,~~ ▲75 mg of clopidogrel (base),▲*USP30* to a 100-mL volumetric flask, and add 50 mL of methanol. Sonicate for 5 minutes, and stir ~~with a magnetic stirrer~~ ▲▲*USP30* for 30 minutes. Dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to the flask, dilute with methanol to 50.0 mL, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate after discarding the first 5 mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the analyte peaks. Calculate the quantity, in mg, of clopidogrel ($C_{16}H_{16}ClNO_2S$) in the portion of Tablets taken by the formula:

$$1000(321.82/419.90)C(r_U/r_S)$$

in which 321.82 is the molecular weight of clopidogrel; 419.90 is the molecular weight of clopidogrel bisulfate; C is the concentration, in mg per mL, of USP Clopidogrel Bisulfate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Clotrimazole Lozenges, *USP 29* page 569. In the *Dissolution* test, it is proposed to correct the definition of one of the variables in the formula used to calculate the amount of clotrimazole released.

(BPC: M. Marques) RTS—43494-1

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Change to read:

▲**Dissolution** ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 500 mL, deaerated.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amount of $C_{22}H_{17}ClN_2$ dissolved by employing the following method.

25 mM Phosphate buffer—Dissolve 4.4 g of dibasic potassium phosphate in 1000 mL of water.

100 mM Phosphate buffer—Dissolve 17.4 g of dibasic potassium phosphate in 1000 mL of water.

Diluent—Prepare a filtered and degassed mixture of methanol and *100 mM Phosphate buffer* (60 : 40).

Mobile phase—Prepare a filtered and degassed mixture of methanol and *25 mM Phosphate buffer* (4 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Clotrimazole RS, and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a concentration of about 0.02 mg per mL.

Working standard solution—Transfer 5.0 mL of the *Standard solution* to a 25-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Withdraw 25 mL of the solution under test from the vessel. Pass through a 0.45-µm polyvinylidene difluoride filter, discarding the first 10 mL of the filtrate. Transfer 5.0 mL of the filtrate to a 25-mL volumetric flask. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 3.9-mm × 7.5-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in percentage, of $C_{22}H_{17}ClN_2$ released by the formula:

$$\frac{r_U \times C_S \times 500 \times D \times 100}{r_s \times LC}$$

in which r_U and r_S are the peak responses for the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution;* 500 is the volume, in mL, of *Medium; D* is the dilution factor of the ~~*Working standard solution;*~~ ▲*Test solution;*▲*USP30* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{22}H_{17}ClN_2$ is dissolved in 45 minutes.▲*USP29*

BRIEFING

Diltiazem Hydrochloride Oral Solution—See briefing under *Acetazolamide Oral Solution.*

(CRX: C. Okeke) RTS—42993-5

Add the following:

▲Diltiazem Hydrochloride Oral Solution

» Diltiazem Hydrochloride Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$). Prepare Diltiazem Hydrochloride Oral Solution, 12 mg per mL, as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Diltiazem Hydrochloride Oral Suspension*):

Diltiazem Hydrochloride powder . .	1.2 g
Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

Dissolve Diltiazem Hydrochloride powder in about 10 mL of Cherry Syrup in a mortar, and mix to a uniform paste. Add the Cherry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Cherry Syrup to bring to final volume, and mix well.

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

Labeling—Label it to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Diltiazem Hydrochloride RS.*

pH ⟨791⟩**:** between 3.1 and 3.9.

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Buffer solution—Dissolve 1.16 g of *d*-10-camphorsulfonic acid in 1000 mL of 0.1 M sodium acetate, adjust this solution by the addition of 0.1 N sodium hydroxide to a pH of 6.2, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, methanol, and *Buffer solution* (2 : 1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Diltiazem Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of 120 µg per mL.

Assay preparation—Agitate the container of Oral Solution for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At time of analysis remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample solution to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the

peak responses as directed for *Procedure:* the retention time is about 9.6 minutes, and the relative standard deviation for replicate injections is not more than 1.3%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the volume of Oral Solution taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Diltiazem Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Diltiazem Hydrochloride Oral Suspension, page 928 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-10

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Add the following:

▲Diltiazem Hydrochloride Oral Suspension

» Diltiazem Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$). Prepare Diltiazem Hydrochloride Oral Suspension 12 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Diltiazem Hydrochloride Oral Solution*):

Diltiazem Hydrochloride	1.2 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, comminute the Tablets to a fine powder in a suitable mortar, or add Diltiazem Hydrochloride powder to the mortar. Add approximately 10 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle to the mortar in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Vehicle to bring to final volume.

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

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Diltiazem Hydrochloride RS.*

pH ⟨791⟩**:** between 3.8 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.1 and 3.9 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Buffer solution—Dissolve 1.16 g of *d*-10-camphorsulfonic acid in 1000 mL of 0.1 M sodium acetate, adjust this solution by the addition of 0.1 N sodium hydroxide to a pH of 6.2, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, methanol, and *Buffer solution* (2 : 1 : 1). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Diltiazem Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of 120 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample solution into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the 100 µg per mL *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 9.6 minutes, and the relative standard deviation for replicate injections is not more than 1.3%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Diltiazem Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Dipyridamole Oral Suspension, page 930 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-11

Add the following:

▲Dipyridamole Oral Suspension

» Dipyridamole Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dipyridamole ($C_{24}H_{40}N_8O_4$). Prepare Dipyridamole Oral Sus-

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pension 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Dipyridamole	1 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, place the Dipyridamole Tablets in a suitable mortar, and comminute to a fine powder, or add Dipyridamole powder to the mortar. Add about 20 mL of Vehicle, and mix to a uniform paste. Add the Vehicle in small portions, and mix well after each addition. Transfer, stepwise and quantitatively, to a graduated or calibrated bottle. Add the Vehicle in portions to rinse the mortar, add sufficient Vehicle to bring to final volume, and mix well.

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

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 3.9 and 4.7 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.0 and 3.8 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Dissolve 250 mg of dibasic sodium phosphate in 250 mL of water, and adjust with dilute phosphoric acid (1 in 3) to a pH of 4.6. Add 750 mL of methanol, mix, pass through a 0.5-µm membrane filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Dipyridamole RS in *Mobile phase* to obtain a suspension having a known concentration of 100 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 288-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 7.3 minutes, and the relative standard deviation for replicate injections is not more than 2.3%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

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measure the responses for the major peaks. Calculate the quantity, in mg, of dipyridamole ($C_{24}H_{40}N_8O_4$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Dipyridamole RS in the *Standard preparation;* V is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Dolasetron Mesylate Oral Solution—See briefing under *Acetazolamide Oral Solution.*

(CRX: C. Okeke) RTS—42993-7

Add the following:

▲Dolasetron Mesylate Oral Solution

» Dolasetron Mesylate Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dolasetron mesylate ($C_{19}H_{20}N_2O_3 \cdot CH_4O_3S$). Prepare Dolasetron Mesylate Oral Solution 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Dolasetron Mesylate Oral Suspension*):

Dolasetron Mesylate powder	1 g
Strawberry Syrup, *NF,* a sufficient quantity to make	100 mL

Dissolve Dolasetron Mesylate powder in about 15 mL of Strawberry Syrup in a mortar, and mix to a uniform paste. Add the Strawberry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Strawberry Syrup to bring to final volume and mix.

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

Labeling—Label it to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Dolasetron Mesylate RS.*

pH ⟨791⟩**:** between 3.6 and 4.6.

Beyond-use date: 90 days after the day on which it was compounded.

Assay—

Buffer—Prepare a solution of 0.05 M ammonium acetate adjusted with diluted ammonium hydroxide to a pH of 7.5.

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

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Sample diluent—Prepare a solution of water and acetonitrile (76 : 24).

Standard stock preparation—Dissolve USP Dolasetron Mesylate RS in *Sample diluent* to obtain a solution having a known concentration of about 500 µg per mL.

Standard preparation—Transfer 2 mL of *Standard stock preparation* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Transfer 10 mL of this prepared solution to another 100-mL volumetric flask, and dilute with *Mobile phase* to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Transfer 0.1 mL of Oral Solution by micropipet to a 100-mL volumetric flask, and dilute with *Sample diluent* to obtain a 10 µg per mL concentration. Shake each sample thoroughly by hand for about 15 seconds, centrifuge at 1000 rpm for about 2 minutes, and assay the supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm analytical column that contains 3-µm packing L10, and is maintained at a temperature of 30°. The flow rate is about 0.8 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 6.9 minutes, and the relative standard deviation for replicate injections is not more than 1.4%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of dolasetron mesylate ($C_{19}H_{20}N_2O_3 \cdot CH_4O_3S$) in the volume of Oral Solution taken by the formula:

$$1000(C/V)(r_U / r_S)$$

in which C is the concentration, in µg per mL, of USP Dolasetron Mesylate RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Dolasetron Mesylate Oral Suspension, page 931 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-12

Add the following:

▲Dolasetron Mesylate Oral Suspension

» Dolasetron Mesylate Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dolasetron mesylate ($C_{19}H_{20}N_2O_3 \cdot CH_4O_3S$). Prepare Dolasetron Mesylate Oral Suspension 10 mg per mL

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as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Dolasetron Mesylate Oral Solution*):

Dolasetron Mesylate	1 g
Vehicle: a mixture of Vehicle for Oral Suspension, *NF,* and Vehicle for Oral Solution, Sugar-Free, *NF* (1 : 1), or Strawberry Syrup, *NF,* ~~and Vehicle for Oral Suspension,~~ a sufficient quantity to make	100 mL

NOTE— ~~If Strawberry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, comminute into a fine powder in a suitable mortar or add Dolasetron Mesylate powder. Mix separately Vehicle for Oral Suspension and Vehicle for Oral Solution, Sugar-Free, and stir vigorously; or mix with Strawberry Syrup. Add about 15 mL of the mixture to the powder and triturate well to a uniform paste. Transfer mortar contents, stepwise and quantitatively, to a calibrated bottle, and rinse the mortar with about 15 mL of the Vehicle. Repeat the previous step as necessary to bring to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Dolasetron Mesylate RS.*

pH ⟨791⟩**:** between 3.6 and 4.6.

Beyond-use date: 90 days after the day on which it was compounded.

Assay—

Buffer—Prepare a solution of 0.05 M ammonium acetate adjusted with diluted ammonium hydroxide to a pH of 7.5.

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

Sample diluent—Prepare a solution of water and acetonitrile (76 : 24).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Dolasetron Mesylate RS in *Sample diluent* to obtain a solution having a known concentration of about 500 µg per mL.

Standard preparation—Transfer 2 mL of *Standard stock preparation* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Transfer 10 mL of this prepared solution to another 100-mL volumetric flask, and dilute with *Mobile phase* to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Transfer 1.0 mL of Oral Suspension by pipet to a 100-mL volumetric flask, and dilute with *Sample diluent* to obtain a 10 µg per mL concentration. Shake each sample thoroughly by hand for about 15 seconds, centrifuge at 1000 rpm for about 2 minutes, and assay the supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm analytical column that contains 5-µm packing L10, and is maintained at a temperature of 30°. The flow rate is about 0.8 mL per minute. Chromatograph the *Standard preparation,* and record the peak re-

sponses as directed for *Procedure:* the retention time is about 6.9 minutes, and the relative standard deviation for replicate injections is not more than 1.4%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of dolasetron mesylate ($C_{19}H_{20}N_2O_3 \cdot CH_4O_3S$) in the volume of Oral Suspension taken by the formula:

$$1000(C/V)(r_U / r_S)$$

in which C is the concentration, in µg per mL, of USP Dolasetron Mesylate RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Dronabinol, *USP 29* page 769. In the *USP Reference standards* section, it is proposed to delete USP Δ^8-Tetrahydrocannabinol RS and to add USP Exo-tetrahydrocannabinol RS. It is also proposed to develop the necessary USP Reference standards as solutions in methanol, having a concentration of about 1 mg per mL. In addition, it is proposed to make minor revisions in *Identification* tests *A* and *B.* Finally, it is proposed to replace the test for *Limit of* Δ^8*-tetrahydrocannabinol* with a test for *Related compounds,* and to establish limits for individual specified impurities.

A new liquid chromatographic procedure, which provides better separation of impurities, is proposed both for the test for *Related compounds* and for the *Assay.* This procedure is based on analyses performed with the YMC J-Sphere ODS-H80 brand of L1 column. The typical retention time for the Δ^9-tetrahydrocannabinol peak is about 21 minutes.

The procedure was validated with the column temperature maintained at 20°. Manufacturers who can demonstrate equivalency at a higher temperature are encouraged to submit data to the Expert Committee.

(MD-GRE: E. Gonikberg) RTS—41820-1

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Exo-tetrahydrocannabinol RS.*▲*USP30*
USP Δ^9*-Tetrahydrocannabinol RS.* ~~*USP* Δ^8*-Tetrahydrocannabinol RS.*~~

▲▲*USP30*

Change to read:

Identification—

A: The retention time of the major peak ~~(other than that due to the internal standard)~~

▲▲*USP30*
in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation,* as obtained in the *Assay.*

B: ~~[NOTE—Since the visualizing agent used in this test is specific for phenols, solution preparations containing diphenyl phthalate and/or sesame oil may be used without interference.]~~

▲▲*USP30*
Visualizing agent—Transfer about 100 mg of Fast Blue B salt to a suitable flask containing about 100 mL of methanol, stir for about 5 minutes, and allow to settle. Decant the clear liquid into the sprayer reservoir. [NOTE—Prepare fresh daily.]

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

Test solution—Use the *Assay preparation.*

Procedure—Apply separately 10 µL each of the *Identification solution* and the *Test solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel. Allow the spots to dry, and develop the plate in a chromatographic chamber that has been equilibrated (for about 2 minutes) with vapors from a solvent mixture of *n*-hexane and methylene chloride (1 : 1) until the solvent front has moved about 10 cm. Remove the plate from the developing chamber, quickly mark the solvent front, and allow the plate to dry at room temperature for about 5 minutes. Spray the plate with the *Visualizing agent* until it is uniformly damp (not saturated). Heat the plate at about 80° until the spots are developed: the color and R_F value of the spots from the *Test solution* correspond to those obtained from the *Identification solution*.

Delete the following:

~~▲**Limit of** Δ^8**-tetrahydrocannabinol**—~~

~~*Mobile phase, System suitability solution, Standard preparation, and Chromatographic system*—Proceed as directed in the *Assay.*~~

~~Δ^8*-Tetrahydrocannabinol solution*—Dilute an accurately measured volume of USP Δ^8-Tetrahydrocannabinol RS quantitatively, and stepwise if necessary, with dehydrated alcohol to obtain a solution having a known concentration of about 4 µg per mL.~~

~~*Test solution*—Use the *Assay preparation.*~~

~~*Procedure*—Separately inject equal volumes (about 20 µL) of the Δ^8*-Tetrahydrocannabinol solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. Calculate the percentage of Δ^8-tetrahydrocannabinol in the portion of Dronabinol taken by the formula:~~

$$~~10{,}000(C/W)(r_u / r_s),~~$$

~~in which C is the concentration, in mg per mL, of USP Δ^8-Tetrahydrocannabinol RS in the Δ^8*-Tetrahydrocannabinol solution; W* is the weight, in mg, of dronabinol in the portion of Dronabinol

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~~taken to prepare the *Test solution;* and r_U and r_S are the Δ⁹-tetrahydrocannabinol peak responses obtained from the *Test solution* and the Δ⁹-*Tetrahydrocannabinol solution,* respectively: not more than 2.0% is found.~~ ▲*USP30*

Add the following:

▲**Related compounds**—

Mobile phase, System suitability solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dilute an accurately measured volume of the *Standard preparation* quantitatively, and stepwise if necessary, with dehydrated alcohol to obtain a solution having a known concentration of about 0.004 mg per mL.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. Calculate the percentage of each impurity in the portion of Dronabinol taken by the formula:

$$100(1/F)(CV/W)(r_U/r_S)$$

in which F is the relative response factor for each impurity (see *Table 1*); C is the concentration, in mg per mL, of Δ⁹-tetrahydrocannabinol in the *Standard solution; V* is the volume, in mL, of the *Test solution; W* is the weight, in mg, of Dronabinol taken to prepare the *Test solution;* r_U is the peak area response of each impurity in the *Test solution;* and r_S is the peak area response of Δ⁹-tetrahydrocannabinol in the *Standard solution*. In addition to not exceeding the limits in *Table 1,* not more than than 5.0% of total impurities is found.

Table 1

Name	Relative Retention Time	Relative Response Factor	Limit (%)
Cannabinol	0.78	2.7	1.5
Δ⁹-Tetrahydrocannabinol	1.00	1.0	—
Exo-tetrahydrocannabinol[1]	1.07	0.92	0.5
Δ⁸-Tetrahydrocannabinol	1.18	0.90	2.0
Any other individual impurity	—	1.0	1.0

[1] (6a*R*, 10a*R*)-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[c]chromen-1-ol. ▲*USP30*

Change to read:

Assay—

~~*Mobile phase*—Prepare a filtered and degassed mixture of methanol, water, and tetrahydrofuran (71 : 24 : 5), making adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*System suitability solution*—Mix accurately measured volumes of USP Δ⁹-Tetrahydrocannabinol RS and USP Δ⁸-Tetrahydrocannabinol RS in dehydrated alcohol to obtain a solution having a known concentration of about 0.5 mg per mL of each component.~~

~~*Standard preparation*—Dissolve an accurately measured volume of USP Δ⁹-Tetrahydrocannabinol RS in dehydrated alcohol to obtain a solution having a known concentration of about 0.2 mg per mL.~~

~~*Assay preparation*—Transfer about 20 mg of Dronabinol, accurately weighed, to a 100-mL volumetric flask, dissolve in dehydrated alcohol, dilute with dehydrated alcohol to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 228-nm detector, a 4.6- × 30-mm guard column that contains 5-µm packing L1, and a 4.6-mm × 15-cm analytical column that contains 3-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure*: the relative retention times are about 1.0 for Δ⁹-tetrahydrocannabinol and 1.14 for Δ⁸-tetrahydrocannabinol; the resolution, *R,* between dronabinol and Δ⁹-tetrahydrocannabinol is not less than 2.0; and the tailing factor of the Δ⁹-tetrahydrocannabinol peak is not more than 2.0. Chromatograph the *Standard prep-*~~

~~*aration,* and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not greater than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. Calculate the quantity, in mg, of $C_{21}H_{30}O_2$ in the portion of Dronabinol taken by the formula:~~

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

~~in which *C* is the concentration, in mg per mL, of USP Δ⁹-Tetrahydrocannabinol RS in the *Standard preparation;* and r_U and r_S are the dronabinol peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

▲*Mobile phase*—Prepare a filtered and degassed mixture of methanol, water, tetrahydrofuran, and acetonitrile (45 : 25 : 20 : 10), making adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer accurately measured volumes of USP Δ⁹-Tetrahydrocannabinol RS and USP Exo-tetrahydrocannabinol RS to a suitable volumetric flask, and dilute with dehydrated alcohol to prepare a solution that contains about 200 µg of Δ⁹-tetrahydrocannabinol and about 10 µg of exo-tetrahydrocannabinol per mL.

Standard preparation—Quantitatively dilute an accurately measured volume of USP Δ⁹-Tetrahydrocannabinol RS with dehydrated alcohol to obtain a solution having a known concentration of about 0.2 mg per mL.

Sensitivity standard preparation—Quantitatively dilute an accurately measured volume of the *Standard preparation* with dehydrated alcohol to obtain a solution having a concentration of about 0.2 µg per mL.

Assay preparation—Transfer about 20 mg of Dronabinol, accurately weighed, to a 100-mL volumetric flask, dissolve in dehydrated alcohol, dilute with dehydrated alcohol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 228-nm detector and a 4.6-mm × 15-cm analytical column that contains 4-µm packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 20°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between Δ⁹-tetrahydrocannabinol and exo-tetrahydrocannabinol is not less than 1.5; and the tailing factor of Δ⁹-tetrahydrocannabinol is not more than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not greater than 2.0%. Chromatograph the *Sensitivity standard preparation,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all of the peaks. Calculate the quantity, in mg, of $C_{21}H_{30}O_2$ in the portion of Dronabinol taken by the formula:

$$CV(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of Δ⁹-tetrahydrocannabinol in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation;* and r_U and r_S are the Δ⁹-tetrahydrocannabinol peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

In-Process Revision

BRIEFING

Felodipine Extended-Release Tablets, *USP 29* page 885. It is proposed to add *Dissolution Test 2* because FDA recently approved a generic version of this product. The chromatographic procedure in this test was validated using the Hypersil BDS brand of L1 column. In the absence of any adverse comments, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of June 1, 2006.

(BPC: M. Marques) RTS—42719-1

Add the following:

•**Labeling**—When more than one test for *Dissolution* is given, the *Labeling* section states the test for *Dissolution* used only if *Test 1* is not used.•

Change to read:

Dissolution ⟨711⟩—

•TEST 1—•

Medium: pH 6.5 phosphate buffer with 1% sodium lauryl sulfate; 500 mL. (*Medium* is prepared as follows. Transfer 206 mL of 1 M monobasic sodium phosphate monohydrate, 196 mL of 0.5 M dibasic sodium phosphate anhydrous, and 50.0 g of sodium lauryl sulfate to a 5000-mL volumetric flask. Add approximately 4000 mL of water, and mix well. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.5. Dilute with water to volume, and mix well.)

Apparatus 2: 50 rpm.

Times: 2, 6, and 10 hours.

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

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, *Buffer solution,* and methanol (2.5 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Felodipine RS in alcohol to obtain a solution having a known concentration of 0.25 mg per mL.

Standard solution—Dilute an accurately measured volume of the *Standard stock solution* quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of USP Felodipine RS equivalent to the concentration that would result from about 60% dissolution of a single Tablet in 500 mL of *Medium.*

Test solution—Place each Tablet in a specially made quadrangular basket of stainless steel wire gauze, soldered in one of its upper, narrow sides to the end of a steel rod (see *Figure 1*). Place the tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two teflon nuts, 3.2 cm from the center of the vessel, or by any other appropriate means. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade (see *Figure 2*). Orient the large side of the basket tangentially to the flow stream with the Tablet standing on its edge. Pass a 10-mL portion of the solution under test, obtained at each time interval, through a suitable filter.

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved in the *Medium* by the formula:

$$CD(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Felodipine RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the felodipine peak areas obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—The percentages of the labeled amount of $C_{18}H_{19}Cl_2NO_4$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	between 10% and 30%
6	between 42% and 68%
10	not less than 75%

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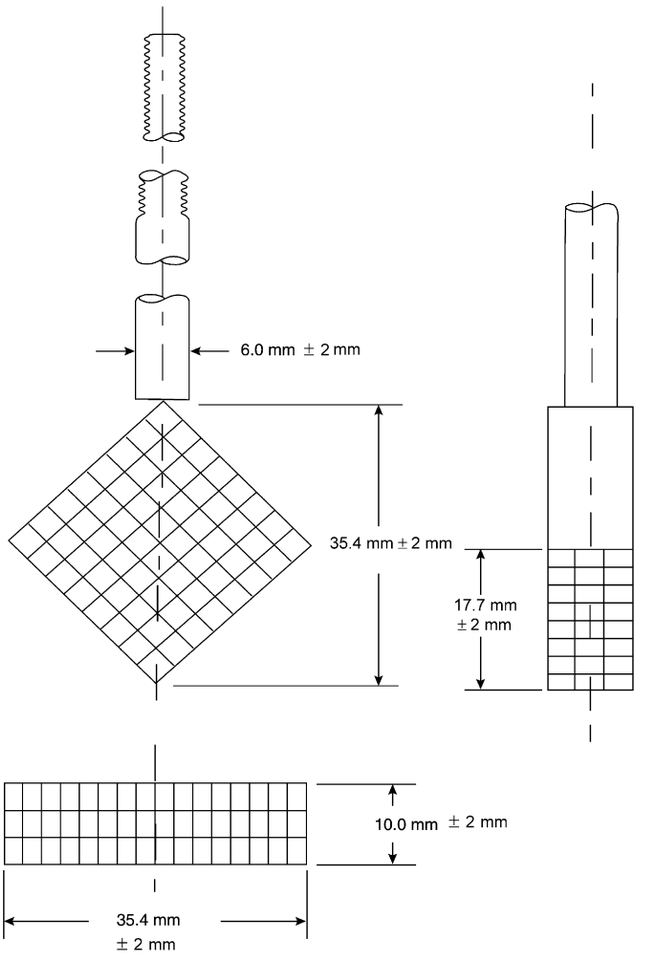

NOTES

1. Rod and Basket with a Tablet cover placed in the horizontal diagonal of the basket.
2. Basket and Tablet cover material; stainless steel.
3. Basket gauze wire size: 8 mesh.

Figure 1. Stationary Tablet Basket

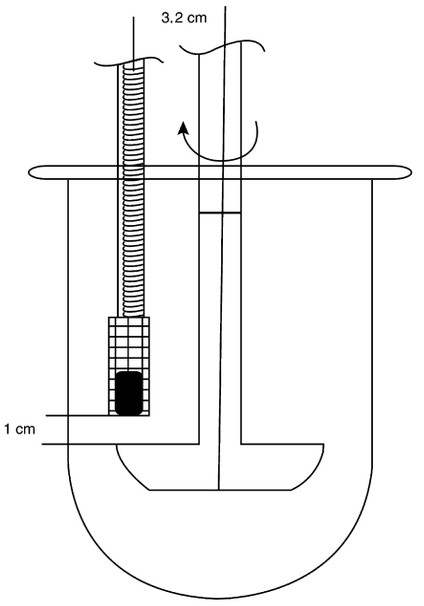

Figure 2. Drug Release Stationary Tablet Basket Configuration Diagram

(Official April 1, 2006)

•TEST 2—

Medium: 1% (w/v) polysorbate 80 in water; 500 mL.

Apparatus 1: 100 rpm.

Times: 1, 4, and 8 hours.

Determine the amount of $C_{18}H_{19}Cl_2NO_4$ dissolved by employing the following method.

Buffer solution—Transfer 6.9 g, accurately weighed, of monobasic sodium phosphate into a 1-L volumetric flask containing about 400 mL of water. Add 8.0 mL of 1 M phosphoric acid, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* acetonitrile, and methanol (2 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer 40 mg, accurately weighed, of USP Felodipine RS into a 200-mL volumetric flask, add about 200 mL of methanol. Sonicate for 2 minutes, cool, dilute with methanol to volume, and mix.

Standard working solutions—Transfer the appropriate volume of *Standard stock solution* into a suitable volumetric flask according to the following table.

Tablet Label Claim (mg)	Volume Transferred (mL)	Volumetric Flask (mL)
10	10	100
5	5	100
2.5	2.5	100

Dilute with *Medium* to volume, and mix.

Test solution—Pass a portion of the solution under test through a suitable 0.45-µm filter. Replace the withdrawn amount with *Medium.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard working solution* and record the peak responses as directed for *Procedure:* the capacity factor (k') is not less than 5, the column efficiency (N) is not less than 1500 theoretical plates, the tailing factor is not more than 1.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard working solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

in which C_U is the concentration, in mg per mL, of felodipine in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard working solution,* respectively; and C_S is the concentration, in mg per mL, of felodipine in the *Standard working solution.*

Calculate the amount, in percentage, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved, with volume correction, by the formula:

$$\left[\frac{r_U \times D_S \times P \times 100}{r_S \times D_U \times 100 \times LC}\right] + \sum_{i=1}^{n-1} \frac{V}{900} \times C_U$$

$$\frac{\left[\left\{C_N \times \left[500 - V_U(n-1)\right]\right\} + \left[\sum_{i=1}^{n-1} C_i \times V_U\right]\right] \times 100}{LC}$$

in which C_N is the concentration, in mg per mL, of felodipine in the *Test solution* at each time point; 500 is the volume, in mL, of *Medium;* V_U is the volume, in mL, of sample withdrawn at each time point; n is the time point (at 4 hours, n + 1), summation of the concentration of the *Test solution* from the first to the $(n-1)^{th}$ time point (only applicable for $n = 2$); 100 is the conversion factor to percentage; and LC is the tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of felodipine dissolved at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	between 5% and 30%
4	between 45% and 70%
8	not less than 80%

●[3]

BRIEFING

Flucytosine Oral Suspension, page 933 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-13

Add the following:

▲Flucytosine Oral Suspension

» Flucytosine Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of flucytosine ($C_4H_4FN_3O$). Prepare Flucytosine Oral Suspension 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Flucytosine	1.0 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE— ~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Capsules are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Flucytosine Capsules, empty the appropriate amount into a suitable mortar, or add Flucytosine powder to the mortar. Add about 10 mL of the Vehicle, and mix to a uniform paste. Add the

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Vehicle in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Vehicle to bring to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store in a cold place.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 4.0 and 4.8 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.2 and 4.0 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Buffer—Dissolve 1g of ammonium acetate and 1 mL of diisopropylamine in 1 L of water, and adjust with glacial acetic acid to a pH of 7.5.

Mobile phase—Prepare a filtered and degassed solution of methanol and *Buffer* (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Flucytosine RS in *Mobile phase,* and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 0.5 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6- × 200-mm analytical column that contains 5-µm packing L3. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 3 minutes, and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of flucytosine ($C_4H_4FN_3O$) in the volume of Oral Suspension taken by the formula:

$$200(C/V)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Flucytosine RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

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BRIEFING

Flumazenil, *USP 29* page 919 and page 1628 of *PF* 31(6) [Nov.–Dec. 2005]. It is proposed to rename *N,N*-dimethylformamide diethyl acetal as USP Flumazenil Related Compound C RS and to revise *Related compounds Test 1* to specify the use of USP Flumazenil Related Compound C RS.

(MD-PP: R. Ravichandran) RTS—43561-1

Change to read:

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

▲*USP Flumazenil Related Compound B RS. USP Flumazenil Related Compound C RS.*▲*USP30*

Change to read:

Related compounds—

TEST 1—

Ninhydrin solution—Dissolve 0.5 g of ninhydrin in 90 mL of alcohol, and add 10 mL of glacial acetic acid.

Diluent—Prepare a mixture of alcohol and chloroform (1 : 1).

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture (see *Chromatography* ⟨621⟩).

Test solution—Transfer about 250 mg of Flumazenil, accurately weighed, to a 5-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Standard solution 1—Prepare a solution of USP Flumazenil RS and ~~*N,N*-dimethylformamide diethyl acetal~~

▲USP Flumazenil Related Compound C RS▲*USP30* in *Diluent* having known concentrations of about 0.5 mg per mL and about 0.6 µL per mL, respectively.

Standard solution 2—Dilute 2.0 mL of *Standard solution 1* with *Diluent* to 10.0 mL.

Application volume: 10 µL.

Developing solvent system: a mixture of chloroform, glacial acetic acid, alcohol, and water (75 : 15 : 7.5 : 2.5).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Dry the plate for 10 minutes in a current of cold air, and view under short-wavelength UV light. Spray the plate with *Ninhydrin solution,* and heat at 105° for 15 minutes. The R_F values of analytes are as follows.

Compound	R_F	Detection
Flumazenil	about 0.8	UV
~~*N,N*-Dimethylformamide diethyl acetal~~	about 0.04	Ninhydrin
▲Flumazenil related compound C▲*USP30*	Any spot at an R_F value corresponding to ~~*N,N*-dimethylformamide diethyl acetal~~	

▲flumazenil related compound C▲*USP30* in the chromatogram obtained from the *Test solution* is not more intense than the corresponding spot in the chromatogram obtained from *Standard solution 2:* not more than 0.2% is found.

TEST 2—

Diluted phosphoric acid, pH 2.0, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution— ~~Dissolve an accurately weighed quantity of USP Flumazenil RS in *Mobile phase,* and dilute quantitatively,~~

▲Dilute the *Standard preparation* quantitatively,▲*USP30* and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1 µg per mL of flumazenil.

Test solution— ~~Transfer about 25.0 mg of Flumazenil, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.~~

▲Use the *Assay preparation.*▲*USP30*

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least three times the retention time of the flumazenil peak, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Flumazenil taken by the formula:

~~$2500(C/W)(1/F)(r_i/r_s)$,~~

▲$100(C_S/C_U)(r_i/r_S)(1/F)$▲*USP30*

~~in which *C* is the concentration, in mg per mL, of USP Flumazenil RS in the *Standard solution; F* is the relative response factor according to the *Table* below; *W* is the weight, in mg, of Flumazenil, on the dried basis, used to prepare the *Test solution; r_i,* is the peak area for any impurity in the *Test solution;* and r_s is the peak area for flumazenil in the *Standard solution:* the impurities meet the requirements given in the *Table* below.~~

▲in which C_S and C_U are the concentrations, in mg per mL, of flumazenil in the *Standard solution* and the *Test solution,* respectively; r_i is the peak area for any impurity in the *Test solution;* r_S is the peak area for flumazenil in the *Standard solution;* and *F* is the relative response factor for each of the known impurities relative to flumazenil. [NOTE—*F* values are given for all the impurities, along with the corresponding limits, in the *Table* below.]▲*USP30*

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Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Flumazenil related compound A	about 0.4	1.1	0.2
7-Fluoro-4-methyl-3,4-dihydro-2,5*H*-1,4-benzodiazepine-2,5-dione	about 0.5	1.5	0.2
Ethyl 5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxylate	about 0.7	1.3	0.2
Flumazenil related compound B	about 0.8	1.1	0.2
Flumazenil	1.0	—	—
Ethyl 8-chloro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepine-3-carboxylate	about 2.2	1.1	0.2
Any individual unknown impurity	—	1.0	0.1
Total	—	—	0.5

Change to read:

Assay—

Diluted phosphoric acid, pH 2.0—Adjust 800 mL of water with phosphoric acid to a pH of 2.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Diluted phosphoric acid, pH 2.0,* methanol, and tetrahydrofuran (80 : 13 : 7). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve appropriate quantities of ~~chlordiazepoxide and~~

▲*USP30*
USP Flumazenil RS

▲and USP Flumazenil Related Compound B RS▲*USP30*
in *Mobile phase,* and dilute, stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 6.4 µg per mL of each compound.

Standard preparation—Dissolve an accurately weighed quantity of USP Flumazenil RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL

▲of flumazenil.▲*USP30*

Assay preparation—Transfer about 25.0 mg of Flumazenil, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph

▲5 µL of▲*USP30*
the *System suitability solution,* and record the peak responses: ~~as directed for *Procedure:*~~

▲▲*USP30*
the relative retention times are about ~~0.82 for chlordiazepoxide~~

▲0.8 for flumazenil related compound B▲*USP30*
and 1.0 for flumazenil; the resolution, *R,* between ~~chlordiazepoxide~~

▲flumazenil related compound B▲*USP30*
and flumazenil is not less than ~~2.0~~

▲4.0;▲*USP30*
the column efficiency is not less than 1500 theoretical plates for the flumazenil peak; and the tailing factor is not more than 1.5 for the flumazenil peak. Chromatograph

▲5 µL of▲*USP30*
the *Standard preparation,* and record the peak responses: ~~as directed for *Procedure:*~~

▲▲*USP30*
the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the flumazenil peaks. ~~Calculate the quantity, in mg, of $C_{15}H_{14}FN_3O_3$ in the portion of Flumazenil taken by the formula:~~

~~$25C(r_U/r_S)$,~~

▲Calculate the percentage of $C_{15}H_{14}FN_3O_3$ in the portion of Flumazenil taken by the formula:

$$100(C_S/C_U)(r_U/r_S)_{▲USP30}$$

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

▲C_S and C_U are the concentrations, in mg per mL, of flumazenil in the *Standard preparation* and the *Assay preparation,* respectively;▲*USP30*
and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Fluticasone Propionate, *USP 29* page 960 and page 1070 of *PF* 31(4) [July–Aug. 2005]. In the test for *Content of acetone,* in the *Procedure,* the proposal to change the acetone peak response limit from 1.0% to 0.5% is canceled, and the official 1.0% limit is re-

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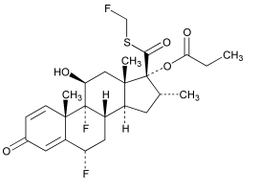
tained. After reviewing the U.S.-marketed products containing this drug substance, the Expert Committee believes that these products will still comply with the limits for Class 3 solvents in guideline Q3C of the International Conference on Harmonization (ICH), because the acetone content will not exceed the patient daily exposure limit of 50 mg per day.

(AER: K. Zaidi) RTS—43627-1

Change to read:



$C_{25}H_{31}F_3O_5S$ 500.57

Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy-, (6α,11β,16α,17α)-*S*-(fluoromethyl) ester.

~~*S*-(Fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate~~

▲*S*-Fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate▲*USP30*
[*80474-14-2*].

Change to read:

» Fluticasone Propionate contains not less than 98.0 percent and not more than 100.5 percent of $C_{25}H_{31}F_3O_5S$, calculated on the anhydrous,

▲solvent-free▲*USP30*
basis.

Change to read:

Content of acetone—

Internal standard solution—Prepare a 0.05% (v/v) solution of tetrahydrofuran in dimethylformamide.

Standard solution—Prepare 0.05% (v/v) of acetone in *Internal standard solution*.

Test solution—Dissolve an accurately weighed quantity of Fluticasone Propionate in *Internal standard solution* to obtain a solution having a concentration of about 50 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 25-m column coated with a 2-µm film of phase G15, and a splitless injector system. The carrier gas is nitrogen or helium, flowing at a rate of about 5.5 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at 60° for 3.5 minutes, then the temperature is increased at the rate of 30° per minute to 180°, and maintained at 180° for 3 minutes. The splitless injector temperature is maintained at 150°, and the detector temperature is maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections

▲of the *Standard solution*▲*USP30*
is not more than 5.0%.

Procedure—Separately inject equal volumes (about 0.1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the peak responses. Calculate the percentage of acetone (w/w) in the portion of Fluticasone Propionate taken by the formula:

$$0.05D/C(R_U/R_S)$$

in which D is the density of acetone at 20°; C is the concentration, in g per mL, of Fluticasone Propionate in the *Test solution;* and R_U and R_S are the ratios of the acetone peak response to the tetrahydrofuran peak response obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.0% (w/w) is found.

Change to read:

Assay—

0.01 M Monobasic ammonium phosphate buffer, pH 3.5—Dissolve ~~11.5 g~~

▲1.15 g▲*USP30*
of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.5 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *0.01 M Monobasic ammonium phosphate buffer, pH 3.5,* and acetonitrile (50 : 35 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve approximately ~~2.0 mg~~

▲2.5 mg▲*USP30*
of USP Fluticasone Propionate Resolution Mixture RS in 50 mL of *Mobile phase.*

Standard preparation—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Fluticasone Propionate in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a concentration of about 0.04 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Resolution solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 1.10 for fluticasone propionate related compound D and 1.0 for fluticasone propionate; and the resolution, *R,* between fluticasone propionate and fluticasone propionate related compound D is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the relative standard deviation for replicate injections

▲of the *Standard preparation*▲*USP30*
is not more than 2%.

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Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{31}F_3O_5S$ in the portion of Fluticasone Propionate taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in mg per mL, in the *Standard preparation;* V is the volume, in mL, of the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

USP Reference standards ⟨11⟩—*USP Fluticasone Propionate RS. USP Fluticasone Propionate Related Compound D RS. USP Fluticasone Propionate Related Compound F RS. USP Phenylethyl Alcohol RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩—

Test specimen—Transfer about 30 g of Nasal Spray equally into two 50-mL centrifuge tubes. Add 10 mL of water to each tube, insert the stopper, and shake the tubes vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake the tubes vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake the tubes vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. To one tube add 10 mL of methanol. Shake to disperse the residue, and transfer to the other tube. Shake this tube for 1 minute. Centrifuge at 3500 rpm for 10 minutes. Decant the supernatant into an agate mortar. Evaporate the methanol either by carefully blowing dry with compressed air or nitrogen, or by allowing the methanol to evaporate naturally. If using an air or nitrogen line, use a suitable in-line filter to avoid contamination. Allow the residue to dry overnight in a desiccator over silica gel.

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

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The total aerobic microbial count does not exceed 100 cfu per g, and the total combined molds and yeasts count does not exceed 50 cfu per g.

BRIEFING

Fluticasone Propionate Nasal Spray, page 1071 of *PF* 31(4) [July–Aug. 2005]. It is proposed to revise the tests for *Delivered dose uniformity* (within container) and *Delivered dose uniformity* (within batch) to delete the unnecessary container weight measurements specified for the *Test solution.* The typical retention time for fluticasone propionate in the *Assay* is about 7 minutes.

(AER: K. Zaidi) RTS— 43696-1

Add the following:

▲Fluticasone Propionate Nasal Spray

» Fluticasone Propionate Nasal Spray is a white opaque suspension of fluticasone propionate in water. It is supplied in a form suitable for nasal administration. It contains not less than 95.0 percent and not more than 115.0 percent of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$).

Packaging and storage—Preserve in tight, light-resistant containers, and store between 4° and 30°.

pH ⟨791⟩**:** between 5.0 and 7.0.

Particle size—Remove the pump system after shaking the test bottle to ensure product uniformity. Transfer 1 drop of the Nasal Spray onto a clean microscope slide. Examine 10 random fields of view on the slide using 400 × magnification. Record the number of individual particles that are less than 5 µm in diameter: not less than 98% by number. Record the number of the individual particles that are greater than 5 µm in diameter but less than 15 µm in diameter: not more than 1.8% by number. Record the number of the individual particles that are greater than 15 µm in diameter: not more than 0.2% by number.

Foreign particulates—Shake the required number of bottles to ensure uniformity. Remove the pump system carefully to minimize contamination of the sample. Collect about 100 g of Nasal Spray, and pass it through a wetted 250-µm screen. Rinse each bottle with a portion of water equal to twice the volume of each bottle. Pass the rinse through the 250-µm screen. Visually observe the screen and filtrate for any foreign particulates. Also examine the screen under a microscope using transmitted light: free from any visible foreign particulates greater than 250 µm.

Delivered dose uniformity (within container)—

Diluent, 0.01 M Monobasic ammonium phosphate buffer, pH 3.5, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Resolution solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS and USP Fluticasone Propionate Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 4 µg per mL of each.

Standard solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in *Diluent* to obtain a solution having a known concentration of about 4 µg per mL.

Test solution—Wipe clean the pump. ~~and record the weight of the bottle prior to actuation.~~ Shake the bottle for 30 seconds, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations (1 dose) into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after the collection of two actuations. ~~Weigh the bottle after sample collection.~~ Discharge actuations 3 to 48 (50-spray pack) or 3 to 118 (120-spray pack) to waste. Wipe clean the bottle, and ~~record the weight of the bottle. Collect~~ collect the last two actuations (49 and 50 or 119 and 120) into a second 25-mL volumetric flask. Turn the flask to the upright position immediately after each actuation, ~~Insert the stopper into the flask,~~ and insert the stopper into the flask. ~~and record the weight of the bottle.~~ Add 20 mL of the *Diluent* to each flask, and shake well for 10 minutes to disperse the suspension. Dilute with *Diluent* to volume, and mix thoroughly. Allow the flask to stand until the excipients have settled. Transfer a portion of the clear supernatant to an HPLC vial and inject. Repeat this procedure with 4 additional bottles.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of $C_{25}H_{31}F_3O_5S$ per dose taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in µg per mL, in the *Standard solution; V* is the total volume of *Test solution,* in mL; and r_U and r_S are the

peak responses obtained from the *Test solution* and the *Standard solution,* respectively. The mean dose delivered from 10 doses is within 85% to 115% of label claim. Not more than 1 dose is outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim. Test an additional 10 bottles if 2 or 3 doses are outside ±20% of label claim. The mean dose delivered from ~~30~~ 20 doses should be within 85% to 115% of the label claim. Not more than 3 doses are outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim.

Delivered dose uniformity (within batch)—

Diluent, 0.01 M Monobasic ammonium phosphate buffer, pH 3.5, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Resolution solution—Prepare as directed in the test for *Delivered dose uniformity* (within container).

Standard solution—Prepare as directed in the test for *Delivered dose uniformity* (within container).

Test solution—Wipe clean the pump. ~~and record the weight of the bottle prior to actuation.~~ Shake the bottle for 30 seconds, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after the collection of two actuations (1 dose). Repeat this procedure with 9 additional bottles.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of $C_{25}H_{31}F_3O_5S$ per dose taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in µg per mL, in the *Standard solution; V* is the total volume of *Test solution,* in mL; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. The mean dose delivered from 10 doses is within 85% to 115% of label claim. Not more than 1 dose is outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim. Test an additional 20 bottles if 2 or 3 doses are outside ±20% of label claim. The mean dose delivered from the two actuations at the beginning of the 30 bottles (30 doses) is within 85% to 115% of the label claim. Not more than 3 doses are outside 80% to 120% of label claim. No doses are outside 75% to 125% of label claim.

Related compounds—

Solution A—Prepare a mixture of methanol and acetonitrile (77 : 23).

0.01 M Monobasic ammonium phosphate buffer—Dissolve 1.15 g of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.4 ± 0.1, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and *0.01 M Monobasic ammonium phosphate buffer* (60 : 40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of acetonitrile and 0.001 M hydrochloric acid (60 : 40).

Control solution—Prepare a solution in a mixture of *Diluent* and water (4 : 1) containing about 0.5 mg per mL of USP Phenylethyl Alcohol RS and 0.08 mg per mL of benzalkonium chloride.

System suitability solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS, USP Fluticasone Related Compound D RS, USP Fluticasone Propionate Related Compound F RS, and USP Phenylethyl Alcohol RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a

known concentration of about 100 µg per mL, 1.0 µg per mL, 1.0 µg per mL, and 500 µg per mL of each Reference Standard, respectively.

Test solution—Transfer accurately about 1.0 g of the Nasal Spray to a 5-mL volumetric flask, dissolve in and dilute with *Diluent* to volume. Shake the flask vigorously to dissolve. Pass through a 0.5-µm porosity filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The column is maintained at a temperature of 40°. Chromatograph the *System suitability solution,* and measure the peak responses as directed for *Procedure:* the resolution, *R,* between fluticasone propionate related compound F and phenylethyl alcohol is not less than 1.5; the resolution, *R,* between fluticasone propionate related compound D and fluticasone propionate is not less than 2; and the relative retention times and limits are as provided in *Table 1.*

Procedure—Separately inject a volume (about 50 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Nasal Spray taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks, excluding the peaks obtained from the *Control solution.*

Table 1

Compound	Approximate Relative Retention Time	Limit (%)
S-Fluoromethyl 17α-acetyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioate/ *S*-Fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-3,6-dioxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate	0.7	0.3
Fluticasone propionate related compound D	1.1	0.3
6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio) carbonyl-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-dien-17α-yl ester	2.1	0.3
Unknown impurities	—	0.2
Total	—	1.5

Content of phenylethyl alcohol—

Diluent, Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Phenylethyl Alcohol RS in *Diluent* to obtain a solution having a known concentration of about 50 µg per mL.

Test solution—Use the *Assay preparation.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg per g, of phenylethyl alcohol in the portion of Nasal Spray taken by the formula:

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

in which C is the concentration, in mg per mL, of the USP Phenylethyl Alcohol RS in the *Standard solution;* W_U is the weight, in g, of the Nasal Spray taken to prepare the *Test solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. For 50 sprays: not less than 1.75 mg per g and not more than 2.63 mg per g. For 120 sprays: not less than 1.88 mg per g and not more than 2.63 mg per g.

Content of benzalkonium chloride—

Citric acid buffer solution—Dissolve 50 g of citric acid in 200 mL of water. Adjust the solution with 2 N sodium hydroxide to a pH of 3.5 ± 0.05.

Docusate sodium titrant—Dissolve 0.22 g of docusate sodium in 100 mL of warm water, and dilute with water to make 1000 mL.

Eosin Y indicator—Dissolve about 25 mg of eosin Y in 50 mL of acetone. Add 450 mL of chloroform and 5.0 ± 0.5 g of citric acid. Shake thoroughly until no discoloration occurs. Filter the mixture to remove any undissolved citric acid. Store in an amber bottle.

Benzalkonium chloride standard stock solution—Use 50% (w/v) solution of benzalkonium chloride.*

Benzalkonium chloride standard solution—Transfer accurately about 0.4 g of *Benzalkonium chloride standard stock solution* to a 1000-mL volumetric flask. Dilute with water to volume, and mix. Sonicate for 5 minutes to dissolve.

Procedure—Pipet 10 mL of *Benzalkonium chloride standard solution* into a 250-mL glass-stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator,* and 2 mL of *Citric acid buffer solution.* Insert the stopper into the flask, and shake the mixture, releasing any build-up of pressure. Titrate with *Docusate sodium titrant* with vigorous shaking to a point when pink coloration is discharged from the chloroform layer. Perform a blank determination, substituting 10 mL of water for the *Benzalkonium chloride standard solution,* and make any necessary correction (see *Titrimetry* ⟨541⟩). Calculate the titer value of the *Docusate sodium titrant,* in µg of benzalkonium chloride per mL of *Docusate sodium titrant,* by the formula:

$$W_B/V_D$$

in which W_B is the weight, in µg, of benzalkonium chloride titrated; and V_D is the volume, in mL, of *Ducosate sodium titrant.* Transfer accurately about 10 g of Nasal Spray into a 250-mL glass-stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator,* and 2 mL of *Citric acid buffer solution.* Repeat the procedure as given above for *Benzalkonium chloride standard solution.* To clarify the endpoint, place the flask in an ultrasonic bath for 1 to 2 minutes to separate the chloroform layer from the aqueous phase. Per-

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* A suitable grade is available from Merck, Germany (www.merck.com).

form a blank determination. Calculate the concentration of benzalkonium chloride, in µg per g, in the portion of Nasal Spray taken by the formula:

$$TV/W$$

in which T is the titer value of *Ducosate sodium titrant; V* is the volume, in mL, of the *Docusate sodium titrant* used in the titration of the Nasal Spray; and W is the weight, in g, of the portion of Nasal Spray taken: not less than 160 µg per g and not more than 210 µg per g.

Assay—

Diluent—Prepare a mixture of acetonitrile and 0.001 M hydrochloric acid (60 : 40).

0.01 M Monobasic ammonium phosphate buffer, pH 3.5—Dissolve 1.15 g of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.5 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *0.01 M Monobasic ammonium phosphate buffer, pH 3.5,* and acetonitrile (50 : 35 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve accurately weighed quantities of USP Phenylethyl Alcohol RS, USP Fluticasone Propionate RS, and USP Fluticasone Propionate Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 50 µg per mL, 10 µg per mL, and 1 µg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of the USP Fluticasone Propionate RS in *Diluent* to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Transfer accurately about 1.0 g of the Nasal Spray to a 50-mL volumetric flask, add about 40 mL of *Diluent,* and sonicate the flask for 10 minutes. Dilute with *Diluent* to volume, and shake. Allow to stand for about 10 minutes until the supernatant is a clear solution. Inject the clear supernatant into the chromatograph.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 4.6-mm × 25-cm column that contains 5-µm packing L1, and a programmable variable wavelength detector capable of monitoring at 210 nm and 239 nm. The flow rate is about 1.5 mL per minute. The column is maintained at a temperature of 40°. Chromatograph the *Resolution solution* and the *Standard preparation,* record the peak areas at 210 nm for 5 minutes, and then change the wavelength to 239 nm and record the peak areas: the relative retention times are about 0.42 for phenylethyl alcohol, 1.0 for fluticasone propionate, and 1.10 for fluticasone propionate related compound D; the resolution, R, between fluticasone propionate and fluticasone propionate related compound D is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in the portion of Nasal Spray taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in mg per mL, in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

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BRIEFING

Fluvastatin Sodium, *USP 29* page 961; **Fluvastatin Capsules,** *USP 29* page 962. Previously proposed changes (see pages 43 and 47 of *PF* 31(1) [Jan.–Feb. 2005]) in the composition of the USP Fluvastatin for System Suitability RS, as well as the resulting changes in the *System suitability solution* in the test for *Chromatographic purity,* are now being canceled. The following changes are proposed:

1. Because the USP was unable to establish a USP Fluvastatin Related Compound A RS, it is proposed to revise the monographs to exclude the use of this Reference Standard. This revision necessitates changes in the *System suitability solution* in the test for *Chromatographic purity.*
2. Delete *Identification* test *B* (UV absorption). Two remaining *Identification* tests, employing *Infrared Absorption* ⟨197K⟩ and *Sodium* ⟨191⟩, are sufficient for identifying the material.
3. The *Relative Response Factors* under *Chromatographic purity* are revised to implement a uniform and consistent approach as proposed in the *Stimuli* article, *The Use of Relative Response Factors to Determine Impurities,* published on page 960 of *PF* 31(3) [May–June 2005]. The new *F* values are recalculated from the unrounded values provided by the monograph sponsor.
4. Chemical names for related impurities are added to *Table 1* in the *Chromatographic purity* test.
5. Revise the *Packaging and storage* statement to indicate storage at a temperature not exceeding 40°.
6. Replace the test for *Water* with the test for *Loss on drying*.

(MD-GRE: E. Gonikberg) RTS—43735-1

Change to read:

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

▲Store at a temperature not exceeding 40°.▲*USP30*

Change to read:

USP Reference standards ⟨11⟩—*USP Fluvastatin Sodium RS.* ~~*USP Fluvastatin Related Compound A RS.*~~

▲▲*USP30*
USP Fluvastatin Related Compound B RS. USP Fluvastatin for System Suitability RS.

▲[NOTE—*USP Fluvastatin for System Suitability RS* contains 1% to 2% of the fluvastatin sodium anti-isomer.]▲*USP30*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.
~~**B:** *Ultraviolet Absorption* ⟨197U⟩.~~
▲
▲*USP30*
~~**C:**~~

▲**B:**▲*USP30*
A solution (0.2 in 1) meets the requirements of the flame test for *Sodium* ⟨191⟩.

Add the following:

▲**Loss on drying** ⟨731⟩—Dry it at 105° for 6 hours: it loses not more than 4.0% of its weight.▲*USP30*

Delete the following:

▲~~**Water,** *Method I* ⟨921⟩: not more than 4.0%.~~▲*USP30*

Change to read:

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

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

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

▲
▲*USP30*
System suitability solution—~~Transfer about 50 mg of USP Fluvastatin for System Suitability RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in 35 mL of *Solution B.* Add 5.0 mL of *System suitability stock solution* into the flask, dilute with *Solution A* to volume, and mix.~~

▲Prepare a solution in a mixture of methanol and acetonitrile (3 : 2) containing about 0.1 mg of USP Fluvastatin Related Compound B RS per mL. Transfer about 0.5 mL of this solution to a 10-mL volumetric flask, and dilute to volume with the *System suitability preparation,* prepared as directed in the *Assay.*▲*USP30*
[NOTE—The ~~*System suitability stock solution* and the~~

▲
▲*USP30*
System suitability solution is stable for up to 6 months if stored in a refrigerator.]

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

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

Chromatographic system—Proceed as directed in the *Assay,* except use the liquid chromatograph equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 305 nm and at 365 nm. Chromatograph the *System suitability solution,* and record the peak responses at 305 nm as directed for *Procedure.* Identify the peaks corresponding to fluvastatin, fluvastatin anti-isomer, ~~fluvastatin hydroxydiene,~~

▲
▲*USP30*
and fluvastatin *t*-butyl ester. The resolution, *R,* between fluvastatin anti-isomer and fluvastatin is not less than 1.6; the column efficiency is not less than 700 theoretical plates for the fluvastatin peak; and the tailing factor is not more than 3.0. Chromatograph the *Standard solution,* and record the peak responses at 305 nm as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms at 305 nm and 365 nm, identify the impurities listed in *Table 1,* and measure the peak responses. [NOTE—3-Hydroxy-5-keto fluvastatin is monitored using a wavelength of

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

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

$$\blacktriangle 100(1/F)(C_S/C_T)(r_{i\,(305)}/r_{S\,(305)}) \blacktriangle_{USP30}$$

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

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

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

$$\blacktriangle 100(1/F)(C_S/C_T)(r_{i\,(365)}/r_{S\,(365)}) \blacktriangle_{USP30}$$

in which F, C_S, and C_T are as defined above; $r_{i\,(365)}$ is the peak response at 365 nm for 3-hydroxy-5-keto fluvastatin obtained from the *Test solution;* and $r_{S\,(365)}$ is the peak response at 365 nm for the fluvastatin peak obtained from the *Standard solution.* In addition to not exceeding the limits for each impurity in *Table 1,* not more than 0.1% of any other individual impurity is found; and not more than 1.0% of total impurities is found.

Table 1

Name	Relative Retention Time	Relative Response Factor (F)	Limit (%)
Fluvastatin *N*-ethyl analog ▲2▲*USP30*	0.7	~~0.9~~ ▲1.2▲*USP30*	0.1
Fluvastatin anti-isomer ▲3▲*USP30*	1.2	1.0	0.8
3-Hydroxy-5-keto fluvastatin ▲4▲*USP30*	1.5	~~0.037~~[1] ▲27.0[1]▲*USP30*	0.1
3-Keto-5-hydroxy fluvastatin ▲5▲*USP30*	1.6	~~1.6~~ ▲0.63▲*USP30*	0.1
Fluvastatin hydroxy-diene[2] ▲6▲*USP30*	2.0	~~1.1~~ ▲0.92▲*USP30*	0.1
Fluvastatin short chain aldehyde ▲7▲*USP30*	3.0	~~0.7~~ ▲1.4▲*USP30*	0.1
Fluvastatin *t*-butyl ester ▲(fluvastatin related compound B)▲*USP30* [3] ▲8▲*USP30*	3.4	~~1.1~~ ▲0.94▲*USP30*	0.2

[1] At 365 nm

[2] ~~Fluvastatin related compound A~~

▲[*R**,*S**-*E*]-(±)-7-[3-(4-Fluorophenyl)-1-ethyl-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt▲*USP30*

[3] ~~Fluvastatin related compound B~~

▲[*R**,*R**-*E*]-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt▲*USP30*

▲4 *E*-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3-hydroxy-5-oxo-6-heptenoic acid monosodium salt▲*USP30*

▲5 *E*-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3-oxo-5-hydroxy-6-heptenoic acid monosodium salt▲*USP30*

▲6 [*E,E*]-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3-hydroxy-4,6-heptadienoic acid monosodium salt▲*USP30*

▲7 3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indole]-2-carboxaldehyde▲*USP30*

▲8 [*R**,*S**-*E*]-(±)-7-[3-(4-Fluorophenyl)-1-methylethyl-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1,dimethylethyl ester▲*USP30*

In-Process Revision

BRIEFING

Fluvastatin Capsules, *USP 29* page 962—See briefing under *Fluvastatin Sodium*. It is also proposed to delete *Identification* test *B* employing *Sodium* ⟨191⟩ from this dosage form monograph.

(MD-GRE: E. Gonikberg) RTS—43735-2

Change to read:

USP Reference standards ⟨11⟩—*USP Fluvastatin Sodium RS.* ~~*USP Fluvastatin Related Compound A RS.*~~

▲▲*USP30*
USP Fluvastatin for System Suitability RS.

▲[NOTE—*USP Fluvastatin for System Suitability RS* contains 1% to 2% of the fluvastatin sodium anti-isomer.]▲*USP30*

Change to read:

Identification—

~~**A:**~~

▲▲*USP30*
The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

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

▲▲*USP30*

Change to read:

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

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

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

▲▲*USP30*
System suitability solution—~~Transfer about 50 mg of USP Fluvastatin for System Suitability RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in 35 mL of methanol. Add 5.0 mL of *System suitability stock solution* into the flask, dilute with *Diluent* to volume, and mix. [NOTE—The *System suitability stock solution* and the *System suitability solution* are stable for up to 6 months if stored in a refrigerator.]~~

▲Use the *System suitability preparation,* prepared as directed in the *Assay.*▲*USP30*

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

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

Chromatographic system—Proceed as directed in the *Assay,* except use the liquid chromatograph equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 305 nm and at 365 nm. Chromatograph the *System suitability solution,* and record the peak responses at 305 nm as directed for *Procedure.* Identify the peaks corresponding to fluvastatin

▲and▲*USP30*
fluvastatin anti-isomer. ~~, and fluvastatin hydroxydiene~~

▲▲*USP30*
Chromatograph the *System suitability solution,* and record the peak responses at 305 nm as directed for *Procedure:* the resolution, *R,* between fluvastatin anti-isomer and fluvastatin is not less than 1.4; and the relative standard deviation for replicate injections is not more than 1.5%.

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

~~$100F(411.48/433.45)(C_S/C_T)(r_{i(305)}/r_{S(305)})$~~

▲$100(1/F)(411.48/433.45)(C_S/C_T)(r_{i(305)}/r_{S(305)})$▲*USP30*

in which F is the relative response factor as listed in *Table 1* [NOTE—Use F equal to 1.0 for unknown impurities]; 411.48 and 433.45 are the molecular weights of fluvastatin and fluvastatin sodium, respectively; C_S is the concentration, in mg per mL, of USP Fluvastatin Sodium RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fluvastatin in the *Test solution,* based on the label claim; $r_{i\,(305)}$ is the peak response at 305 nm for each impurity obtained from the *Test solution;* and $r_{S\,(305)}$ is the peak response at 305 nm for the fluvastatin peak, obtained from the *Standard solution*.

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

~~$100F(411.48/433.45)(C_S/C_T)(r_{i(365)}/r_{S(365)})$~~

▲$100(1/F)(411.48/433.45)(C_S/C_T)(r_{i(365)}/r_{S(365)})$▲*USP30*

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

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Table 1

Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Fluvastatin anti-isomer	1.2	1.0	1.5
3-Hydroxy-5-keto fluvastatin	1.6	~~0.037~~[1] ▲27.0[1] ▲*USP30*	1.0
Fluvastatin hydroxy-diene[2] ▲ ▲*USP30*	2.2	~~1.1~~ ▲0.92 ▲*USP30*	1.0
Fluvastatin short chain aldehyde	3.2	~~0.7~~ ▲1.4 ▲*USP30*	0.5

[1] At 365 nm
[2] ~~Fluvastatin related compound A~~
▲ ▲*USP30*

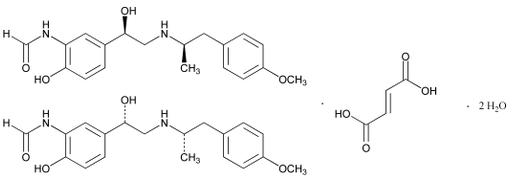
BRIEFING

Formoterol Fumarate. Because there is no existing *USP* monograph for this drug substance, the following new monograph is being proposed. The liquid chromatographic procedure in the test for *Related compounds* is based on analyses performed with the Zorbax SB brand of L7. The typical retention time for formoterol fumarate is about 12 minutes. The gas chromatographic procedure in the test for *Content of related compound I (diastereoisomer)* is based on the analyses performed with apHera brand of L1 column.

(AER: K. Zaidi) RTS—40261-1; 43069-1; 43069-2

Add the following:

▲Formoterol Fumarate



$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$ 804.88

(±)-2′-Hydroxy-5′-[*(R*)*-1-hydroxy-2-[[*(R*)-p*-methoxy-α-methylphenethyl]amino]ethyl]formanilide fumarate (2 : 1) (salt) [*43229-80-7*].

» Formoterol Fumarate contains not less than 98.0 percent and not more than 102.0 percent of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Formoterol Fumarate RS. USP Formoterol Fumarate System Suitability Mixture RS. USP Formoterol Related Compound I RS.*

Identification, *Infrared Absorption* ⟨197K⟩**.**

pH ⟨791⟩**:** between 5.5 and 6.5, in a solution in water containing 1 mg per mL.

Water, *Method I* ⟨921⟩**:** not more than 5.0%.

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Specific rotation ⟨781S⟩**:** between –0.10° and +0.10°.

Test solution: 10 mg per mL, in methanol.

Residue on ignition ⟨281⟩**:** not more than 0.1%, determined on 1 g.

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

Residual solvents ⟨467⟩**:** meets the requirements.

Related compounds—

Solution A—Dissolve 3.73 g of sodium dihydrogen phosphate monohydrate and 0.35 g of phosphoric acid in water, dilute with water to 1000 mL, and mix. The pH of this solution is 3.1 ± 0.1.

Solution B—Use acetonitrile.

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

Solution C—Transfer 6.10 g of sodium dihydrogen phosphate monohydrate and 1.03 g of disodium hydrogen phosphate dihydrate to a 1000-mL volumetric flask, add 500 mL of water, and dissolve. Dilute with water to volume, and mix. The pH is 6.0 ± 0.1.

Diluent—Prepare a filtered and degassed mixture of *Solution C* and acetonitrile (84 : 16, v/v).

System suitability solution—Transfer about 5 mg of USP Formoterol Fumarate System Suitability Mixture RS (containing formoterol related compounds A, B, C, D, E, F, G, and H), accurately weighed, to a 25-mL volumetric flask, add 10 mL of *Diluent,* and sonicate to dissolve. Dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 20.0 mg of Formoterol Fumarate, accurately weighed, to a 100-mL volumetric flask, add 50 mL of *Diluent,* and sonicate to dissolve. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	84	16	equilibration
0–10	84	16	isocratic
10–37	84→30	16→70	linear gradient
37–40	30→84	70→16	linear gradient
40–55	84	16	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between formoterol related compound G and formoterol related compound A is not less than 1.5; the peak-to-valley ratio (H_P / H_V) of formoterol related compound C and formoterol fumarate is not less than 2.5, where H_P is the height above the baseline of the peak due to formoterol related compound C and H_V is the height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol fumarate; and the relative retention times and limits are as provided in *Table 1* below.

Table 1

Related Compound	Related Compound Chemical Name	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
G	(2*RS*)-1-(4-methoxyphenyl)propan-2-amine	0.4	1.00	0.1
A	1-(3-amino-4-hydroxyphenyl)-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethanol	0.5	1.75	0.3
B	*N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]formamide	0.7	1.00	0.2
C	*N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-acetamide	1.2	1.00	0.2
D	*N*-[2-hydroxy-5-[1-hydroxy-2-[methyl[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-formamide	1.3	1.00	0.2
E	*N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-3-methylphenyl)-1-methylethyl]amino]ethyl]-phenyl]formamide	1.8	1.00	0.1
F	*N*-[2-hydroxy-5-[1-[[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-phenyl]formamide	2.0	1.00	0.2
H	*N*-[5-[(1*RS*)-2-[benzyl[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]formamide (monobenzyl-analogue)	2.2	1.00	0.1
	Any other individual impurity			0.1
	Total impurities			0.5

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Procedure—Separately inject equal volumes (about 20 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Disregard any peak representing less than 0.05%. Calculate the percentage of each formoterol related compound in the portion of Formoterol Fumarate taken by the formula:

$$100F(r_i / r_s)$$

in which F is the relative response factor for each formoterol related compound according to *Table 1;* r_i is the peak response for each formoterol related compound; and r_s is the sum of the responses for all the peaks.

Content of related compound I *(diastereoisomer)*—

Standard solution—Dissolve 10 mg of USP Formoterol Related Compound I RS in 1 mL of dimethylformamide. Add 100 µL of *N*-(trimethylsilyl)imidazole, and mix.

Test solution—Dissolve 10 mg of Formoterol Fumarate in 1 mL of dimethylformamide. Add 100 µL of *N*-(trimethylsilyl)imidazole, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica capillary column coated with a 0.25-µm film of stationary phase G27, and a split injection system. The carrier gas is helium, flowing at a rate of about 2 mL per minute and a split ratio of about 75 : 1. The injection port and the detector temperatures are maintained at about 280° and 300°, respectively. The column temperature is programmed as follows. Initially the column temperature is equilibrated at 220° for 5 minutes, then the temperature is increased at a rate of 1° per minute to 250°, and maintained at 250° for 20 minutes. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between formoterol related compound I and formoterol fumarate is not less than 2.0.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for formoterol related compound I and formoterol fumarate. Disregard all other peaks. Calculate the percentage of formoterol related compound I in the portion of Formoterol Fumarate taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for formoterol related compound I, and r_s is the sum of the responses of both formoterol fumarate and formoterol related compound I peaks: not more than 0.3% of formoterol related compound I is found.

Assay—Transfer about 350 mg of Formoterol Fumarate, accurately weighed, to a titration vessel, dissolve in 50 mL of anhydrous acetic acid, and titrate with 0.1 M perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 M perchloric acid is equivalent to 40.24 mg of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$. ▲*USP30*

In-Process Revision

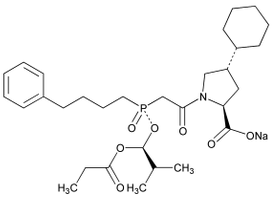
BRIEFING

Fosinopril Sodium, page 2001 of *PF* 30(6) [Nov.–Dec. 2004]. On the basis of comments received, this new monograph is being revised. The method for determination in the test for *Water* is being corrected as well as the chemical name of fosinopril related compound E in the table under *Related compounds.* The compositions of the *Resolution solutions* used in the test for *Related compounds* and in the *Assay* are also being corrected.

(MD-CV: A. Wilk) RTS—42492-1

Add the following:

▲Fosinopril Sodium



$C_{30}H_{45}NNaO_7P$ 585.64

L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)-propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, [1[*S*(R*)*],2α,4β]-.

(4*S*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt [*88889-14-9*].

» Fosinopril Sodium contains not less than 97.5 percent and not more than 102.0 percent of $C_{30}H_{45}NNaO_7P$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Fosinopril Sodium RS. USP Fosinopril Related Compound A RS. USP Fosinopril Related Compound B RS. USP Fosinopril Related Compound C RS. USP Fosinopril Related Compound D RS. USP Fosinopril Related Compound E RS. USP Fosinopril Related Compound F RS.*

Identification, *Infrared Absorption* ⟨197M⟩.

Water, ~~*Method II*~~ *Method I* ⟨921⟩**:** not more than 0.2%.

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

Related compounds—

TEST 1—

Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure—Proceed as directed in the *Assay,* and measure the areas for each component in the chromatogram obtained, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentage of each individual related compound by the formula:

$$100(r_i / r_s)$$

in which r_i is the response of any individual peak, other than the fosinopril sodium peak, and r_s is the sum of the responses of all the peaks. [NOTE—If present, two more diastereomers may not be resolved from fosinopril related compound

In-Process Revision

B by this method. These peaks, appearing at a relative retention time of 0.7, should be integrated together to determine conformance with the limit in *Table 1.*]

Table 1

Relative Retention Time	Fosinopril Related Compound	Test	Limit (%)
2.0	A[1]	1	0.3
0.7	B[2]	1	1.0
1.2	C[3]	2	0.3
1.3	D[4]	2	0.3
0.8	E[5]	3	0.3
0.9	F[6]	3	0.3

[1] (4*S*)-4-Cyclohexyl-1-[(4-phenylbutyl)phosphinyl]acetyl-L-proline
[2] (4*R*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-D-proline propionate (ester)
[3] Mixture of (4*S*)-4-Cyclohexyl-1-[*(S)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt and (4*S*)-4-Cyclohexyl-1-[[*(R)*-[*(R)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
[4] (4*R*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
[5] (4*S*)-4-~~Cyclohexyl~~ Phenyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
[6] (4*S*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-ethoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester)

TEST 2—

Mobile phase—Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (4000 : 15 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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

Test solution—Use the *Assay preparation.*

Resolution solution—Transfer about 1 mg each of USP Fosinopril Sodium RS, USP Fosinopril Related Compound C RS, and USP Fosinopril Related Compound D RS to a 100-mL volumetric flask. Dissolve in and dilute with the *Standard solution* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains packing L12. The column temperature is maintained at 45°. The flow rate is about 0.9 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the fosinopril sodium and the fosinopril related compound C peaks is not less than 1.5.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to two times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compounds C and D only by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak of fosinopril related compound C or D, and r_s is the sum of the responses of all the peaks.

TEST 3—

0.2% Phosphoric acid solution—Prepare a 1 in 500 solution of phosphoric acid.

Mobile phase—Prepare a degassed mixture of acetonitrile and *0.2% Phosphoric acid solution* (560 : 440). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Transfer about 1 mg each of USP Fosinopril Sodium RS, USP Fosinopril Related Compound E RS, and USP Fosinopril Related Compound F RS to a 100-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer about 10 mg of Fosinopril Sodium, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 25-cm column that contains packing L11. The column temperature is maintained at 45°. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the fosinopril related compound F and the fosinopril sodium peaks is not less than 1.5.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compounds E and F only by the formula:

$$100(r_i / r_s)$$

in which r_i is the response of the peak of fosinopril related compound E or F, and r_s is the sum of the responses of all the peaks. In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.1% of any other individual impurity is found, and not more than 1.5% of total impurities is found.

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

Assay—

Mobile phase—Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (2000 : 10 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Transfer about 10 mg of USP Fosinopril Sodium RS, and about 1 mg each of USP Fosinopril Related Compound A RS and USP Fosinopril Related Compound B RS to a 100-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Fosinopril Sodium RS in *Mobile phase* to obtain a solution having a known concentration of about 0.10 mg per mL.

Assay preparation—Transfer about 25 mg of Fosinopril Sodium, accurately weighed, to a 250-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 3.9-mm × 15-cm column that contains packing L3. The column temperature is maintained at 33°. The flow rate is about 1.2 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the fosinopril related compound B and the fosinopril sodium peaks is not less than 2.0; and the relative standard deviation of the fosinopril sodium peak response for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the major peaks. Calculate the amount, in mg, of $C_{30}H_{45}NNaO_7P$ in the portion of Fosinopril Sodium taken by the formula:

$$250C_S(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Fosinopril Sodium RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard prepapration,* respectively.▲*USP30*

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BRIEFING

Ganciclovir Oral Solution, page 934 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.* Also, the title of the monograph is being changed to Ganciclovir Oral Suspension.

(CRX: C. Okeke) RTS—43131-14

Add the following:

▲Ganciclovir Oral ~~Solution~~ Suspension

» Ganciclovir Oral ~~Solution~~ Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ganciclovir ($C_9H_{13}N_5O_4$). Prepare Ganciclovir Oral ~~Solution,~~ Suspension 100 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Ganciclovir	10 g
~~Vehicle for Oral Solution, *NF* (regular or sugar-free)~~ Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (3 : 1), a sufficient quantity to make . . .	100 mL

If using Capsules, empty the contents of the Capsules into a suitable mortar, or add Ganciclovir powder to the mortar. Add sufficient Vehicle to wet the powder, and work to a smooth paste. Add additional Vehicle to about half the final volume, and transfer the contents of the mortar to a calibrated bottle. Using additional Vehicle, rinse out the mortar, and transfer the contents, stepwise and quantitatively, to bring to final volume, and mix well.

Caution—Avoid skin contact or inhalation of ganciclovir by using protective gloves and a fume hood or surgical mask.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 4.0 and 5.0.

Beyond-use date: 90 days after the day on which it was compounded.

Assay—

25 mM Monobasic sodium phosphate buffer—Prepare a 25 mM monobasic sodium phosphate solution, and adjust with phosphoric acid to a pH of 2.5.

Mobile phase—Prepare a solution of *25 mM Monobasic sodium phosphate buffer* and acetonitrile (97.5 : 2.5). Filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Sample diluent—Prepare a solution of water, acetonitrile, and methanol (80 : 15 : 5).

Internal standard solution—Prepare a 4 mg per mL aqueous solution of hypoxanthine.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Ganciclovir RS in water to obtain a concentration of about 1.0 mg per mL.

Standard preparation—Transfer an appropriate volume of *Standard stock preparation* to a suitable container, and add an appropriate volume of *Internal standard solution* to obtain a solution having known concentrations of 6 µg per mL and 4 µg per mL, respectively.

Assay preparation—Transfer about 1 mL of Oral ~~Solution~~ Suspension from each bottle to a plastic weighing cup, and weigh to determine density. [NOTE—The exact volume of Oral ~~Solution~~ Suspension taken from each bottle is calculated by the suspension density.] Transfer the suspension to a 100-mL volumetric flask, and add about 50 mL of water. Place the volumetric flask on a mechanical shaker for 30 minutes, and then dilute with water to volume. Transfer 0.6 mL from this solution and 1 mL of the *Internal standard solution* to a 100-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 10-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are 1.0 for ganciclovir and 0.75 for hypoxanthine; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ganciclovir ($C_9H_{13}N_5O_4$) in the volume of Oral ~~Solution~~ Suspension taken by the formula:

$$100(C/V)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Ganciclovir RS in the *Standard preparation; V* is the volume, in mL, of ~~solution~~ Oral Suspension taken; and R_U and R_S are the peak response ratios of the analyte peak to the internal standard peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Gemcitabine Hydrochloride, *USP 29* page 990. Because USP Cytosine RS is used in the test for *Chromatographic purity,* it is proposed to add it to the *USP Reference standards* section.

(MD-OOD: F. Mao) RTS—43706-1

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Cytosine RS.*▲*USP30*
USP Endotoxin RS. USP Gemcitabine Hydrochloride RS.

BRIEFING

Hydroxyzine Hydrochloride, *USP 29* page 1089. USP *p*-Chlorobenzhydrylpiperazine RS has been renamed in the USP Reference Standard Catalog as USP Hydroxyzine Related Compound A RS. It is proposed to revise the monograph to reflect this name change.

(MD-PP: R. Ravichandran) RTS—43699-1

Change to read:

USP Reference standards ⟨11⟩~~— *USP p-Chlorobenzhydrylpiperazine RS.*~~

▲▲*USP30*
USP Hydroxyzine Hydrochloride RS.

▲*USP Hydroxyzine Related Compound A RS.*▲*USP30*

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Change to read:

Chromatographic purity—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and 0.12 N sulfuric acid (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Quantitatively dissolve an accurately weighed quantity of USP Hydroxyzine Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 1.8 µg per mL.

Resolution solution—Dissolve suitable quantities of USP Hydroxyzine Hydrochloride RS and ~~USP *p*-Chlorobenzhydrylpiperazine RS~~

▲USP Hydroxyzine Related Compound A RS▲*USP30*
in *Mobile phase* to obtain a solution containing 3.6 µg of each per mL.

Test solution—Transfer an accurately weighed quantity of Hydroxyzine Hydrochloride to a suitable volumetric flask, dissolve in and dilute with *Mobile phase* to volume to obtain a solution containing a concentration of about 0.6 mg of specimen per mL, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector, and two series-coupled 3-mm × 10-cm columns that contain packing L3. The flow rate is about 0.4 mL per minute. Chromatograph the *Resolution solution* and the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the ~~*p*-chlorobenzhydrylpiperazine~~

▲hydroxyzine related compound A▲*USP30*
and hydroxyzine peaks is not less than 1.2, and the relative standard deviation for replicate injections of the *Standard solution* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for a total time of not less than 1.8 times the retention time of the hydroxyzine peak, and measure the response for each peak, except for the main hydroxyzine peak in the chromatogram obtained from the *Test solution*. Calculate the apparent percentage of each impurity in the specimen taken by the formula:

$$0.1(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of USP Hydroxyzine Hydrochloride RS in the *Standard solution;* C_U is the concentration, in mg per mL, of specimen in the *Test solution;* r_U is the peak response of a given impurity in the chromatogram obtained from the *Test solution;* and r_S is the peak response of hydroxyzine in the chromatogram obtained from the *Standard solution:* not more than 0.3% of any impurity is found, and the sum of all impurities found is not greater than 1.5%.

BRIEFING

Iodoform, *USP 29* page 1156. It is proposed to revise the molecular weight of iodoform. The revised value is consistent with that in the *2005 USP Dictionary* and other sources.

(MD-AA: B. Davani) RTS—43193-1

Change to read:

Triiodomethane
CHI_3 ~~393.85~~

▲393.73▲*USP30*
[*75-47-8*].

BRIEFING

Irbesartan, *USP 29* page 1177. It is proposed to correct the column designation used in the test for *Limit of azide.* The test was validated with the IonPac AS10 brand of L31 column.

(BPC: M. Marques) RTS—43230-1

Change to read:

Limit of azide—

Mobile phase—Prepare a filtered and degassed 0.1 N sodium hydroxide solution (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 25 mg of sodium azide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 250 µL of this solution into a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 0.312 µg of sodium azide per mL.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductimetric detector and a 4.0-mm × 25-cm column that contains packing ~~L46~~

▲L31.▲*USP30*
The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the azide peak is not less than 10.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas for azide. Calculate the amount of azide, in ppm, in the portion of Irbesartan taken by the formula:

$$1000(C_S / C_T)(42.02/65.01)(r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of sodium azide in the *Standard solution;* C_T is the concentration, in mg per mL, of Irbesartan in the *Test solution;* r_U is the peak area for azide obtained from the *Test solution;* and r_S is the peak area for azide obtained from the *Standard solution:* not more than 10 ppm of azide is found.

BRIEFING

Labetalol Hydrochloride Oral Solution—See briefing under *Acetazolamide Oral Solution.*

(CRX: C. Okeke) RTS—42993-9

Add the following:

▲Labetalol Hydrochloride Oral Solution

» Labetalol Hydrochloride Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of labetalol hydrochloride ($C_{19}H_{24}N_2O_3 \cdot HCl$). Prepare Labetalol Hydrochloride Oral Solution 40 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Labetalol Hydrochloride Oral Suspension*):

Labetalol Hydrochloride powder . . .	4 g
Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

Dissolve Labetalol Hydrochloride powder in about 20 mL of Cherry Syrup in a mortar, and mix to a uniform paste. Add the Cherry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Cherry Syrup to bring to final volume, and mix well.

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

Labeling—Label it to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Labetalol Hydrochloride RS.*

pH ⟨791⟩**:** between 3.0 and 4.0.

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of 0.1 M monobasic sodium phosphate and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Labetalol Hydrochloride RS in water to obtain a solution having a known concentration of 400 µg per mL.

Assay preparation—Agitate the container of Oral Solution for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

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Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 7.5 minutes, and the relative standard deviation for replicate injections is not more than 1.6%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of labetalol hydrochloride ($C_{19}H_{24}N_2O_3 \cdot HCl$) in the volume of Oral Solution taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Labetalol Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Labetalol Hydrochloride Oral Suspension, page 937 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-16

Add the following:

▲Labetalol Hydrochloride Oral Suspension

» Labetalol Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of labetalol hydrochloride ($C_{19}H_{24}N_2O_3 \cdot HCl$). Prepare Labetalol Hydrochloride Oral Suspension 40 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Labetalol Hydrochloride Oral Solution*):

Labetalol Hydrochloride	4 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, place the Labetalol Hydrochloride Tablets in a suitable mortar. Comminute the Tablets to a fine powder or add Labetalol Hydrochloride powder. Add about 20 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in small portions almost to volume. Transfer the contents of the mortar, stepwise and quantitatively, to

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a calibrated bottle. Add the Vehicle in portions to rinse the mortar, combine with the final preparation to final volume, and mix well.

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

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Labetalol Hydrochloride RS.*

pH ⟨791⟩**:** between 4.0 and 5.0 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.0 and 4.0 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of 0.1 M monobasic sodium phosphate and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Labetolol Hydrochloride RS in water to obtain a solution having a known concentration of 400 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 7.5 minutes, and the relative standard deviation for replicate injections is not more than 1.6%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of labetalol hydrochloride ($C_{19}H_{24}N_2O_3 \cdot HCl$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Labetalol RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Lovastatin, *USP 29* page 1281. In the *Assay,* it is proposed to clarify the preparation of the *Mobile phase.*

(MD-GRE: E. Gonikberg) RTS—43273-1

Change to read:

Assay—

▲*Dilute phosphoric acid*—Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with water to volume.▲*USP30*

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and ~~0.1% phosphoric acid solution (65 : 35).~~

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▲*Dilute phosphoric acid* (65 : 35).▲*USP30*
Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Lovastatin RS in acetonitrile to obtain a solution having a known concentration of about 0.3 mg per mL.

Assay preparation—Transfer about 30 mg of Lovastatin, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 238-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3000 theoretical plates, the tailing factor is not more than 1.4, and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{24}H_{36}O_5$ in the portion of Lovastatin taken by the formula:

$$100C(r_U / r_S)$$

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

BRIEFING

Mebendazole Oral Suspension, *USP 29* page 1316. USP acknowledges that Mebendazole Oral Suspension is approved in several countries for human use. It is proposed to change the specified labeling requirements so that manufacturers can use the USP Mebendazole Oral Suspension monograph for these drug products.

(VET: I. DeVeau) RTS—43400-2

Change to read:

Labeling—~~Label~~

▲For products marketed in the United States, label▲*USP30* it to indicate that it is for veterinary use only.

BRIEFING

Metolazone Oral Suspension, page 940 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-17

Add the following:

▲Metolazone Oral Suspension

» Metolazone Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metolazone ($C_{16}H_{16}ClN_3O_3S$). Prepare Metolazone Oral Suspension 1 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Metolazone	100 mg
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, place the Metolazone Tablets in a suitable mortar, and comminute to a fine powder, or add Metolazone powder to the mortar. Add

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about 20 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in small portions, and transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle in portions to rinse the mortar, add sufficient Vehicle to final volume, and mix well.

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

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

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

pH ⟨791⟩**:** between 3.6 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 2.5 and 3.3 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of 700 mL of methanol, 300 mL of 1.5 g ammonium acetate, and 1 mL of diisopropylamine. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Metolazone RS in water to obtain a solution having a known concentration of 1.0 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 1000-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 20-cm analytical column that contains 5-µm packing L3. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for metolazone is about 6.0 minutes, and the relative standard deviation for replicate injections is not more than 2.2%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of metolazone ($C_{16}H_{16}ClN_3O_3S$) in the volume of Oral Suspension taken by the formula:

$$1000(C/V)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Metolazone RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

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BRIEFING

Metoprolol Tartrate Oral Solution—See briefing under *Acetazolamide Oral Solution.*

(CRX: C. Okeke) RTS—42993-10

Add the following:

▲Metoprolol Tartrate Oral Solution

» Metoprolol Tartrate Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metoprolol tartrate [$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$]. Prepare Metoprolol Tartrate Oral Solution 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Metoprolol Tartrate Oral Suspension*):

Metoprolol Tartrate powder	1 g
Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

Dissolve Metoprolol Tartrate powder in Cherry Syrup in a mortar, and mix to a uniform paste. Add the Cherry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Cherry Syrup to bring to final volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or under refrigeration.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Metoprolol Tartrate RS.*

pH ⟨791⟩**:** between 3.0 and 3.8.

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed solution by dissolving 961 mg of 1-pentanesulfonic acid sodium salt, monohydrate, and 82 mg of anhydrous sodium acetate in a mixture of 550 mL of methanol, 470 mL of water, and 0.57 mL of glacial acetic acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Metoprolol Tartrate RS in water to obtain a solution having a known concentration of 100 µg per mL.

Assay preparation—Agitate the container of Oral Solution for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time

for metoprolol tartrate is about 7.3 minutes; and the relative standard deviation for replicate injections is not more than 1.3%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ in the volume of Oral Solution taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Metoprolol Tartrate RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Metoprolol Tartrate Oral Suspension, page 941 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-18

Add the following:

▲Metoprolol Tartrate Oral Suspension

» Metoprolol Tartrate Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Metoprolol Tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6)]$. Prepare Metoprolol Tartrate Oral Suspension 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Metoprolol Tartrate Oral Solution*):

Metoprolol Tartrate	1 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE— ~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, place the Metoprolol Tartrate Tablets in a suitable mortar, and comminute the Tablets, or add Metoprolol Tartrate powder. Add the Vehicle in small portions, and mix well. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add the Vehicle in portions to rinse the mortar. Add to the preparation to final volume, and mix well.

In-Process Revision

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature, or under refrigeration.

Labeling—Label it to state that it is to be well shaken, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Metoprolol Tartrate RS.*

pH ⟨791⟩**:** between 3.6 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension) and between 3.0 and 3.8 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed solution by dissolving 961 mg of 1-pentanesulfonic acid sodium salt, monohydrate, and 82 mg of anhydrous sodium acetate in a mixture of 550 mL of methanol, 470 mL of water, and 0.57 mL of glacial acetic acid. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Metoprolol Tartrate RS in water to obtain a solution having a known concentration of 100 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix with a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample solution into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for metoprolol tartrate is about 7.3 minutes; and the relative standard deviation for replicate injections is not more than 1.3%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of metoprolol tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$ in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Metoprolol Tartrate RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Miconazole Nitrate Cream, *USP 29* page 1435. It is proposed to replace the present *Identification* test with one that contains HPLC retention time agreement between the major peak in the *Assay preparation* and in the *Standard preparation*. The stock solution used in the current *Identification* test is based on the previous GC assay for this monograph published in *USP 27*. This proposed revision eliminates the need for extensive sample preparation, including the use of chloroform. The proposed revision is also consistent with current pharmaceutical industry practice.

(MD-AA: B. Davani) RTS—43705-1

In-Process Revision

Change to read:

Identification~~— Place about 25 mL of the stock solution, prepared as directed in the *Assay*, in a 50-mL beaker, and evaporate on a steam bath with the aid of a current of filtered air to dryness. Dry the residue at 105° for 10 minutes: the IR absorption spectrum of a potassium bromide dispersion of it so obtained exhibits maxima only at the same wavelengths as that of a similar preparation of USP Miconazole Nitrate RS~~

▲The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*▲*USP30*

BRIEFING

Morphine Sulfate Extended-Release Capsules, *USP 29* page 1459 and page 1822 of *PF* 28(6) [Nov.–Dec. 2002]. On the basis of comments received, additional information has been included in the proposed *Packaging and storage* section of the monograph.

(MD-CCA: C. Anthony; D. Hunt) RTS—43626-1

Add the following:

▲**Packaging and storage**—Preserve in tight, ~~containers~~ light-resistant containers, and store at controlled room temperature.▲*USP30*

BRIEFING

Naproxen Delayed-Release Tablets, *USP 29* page 1484 and page 1264 of *PF* 30(4) [July–Aug. 2004]. On the basis of comments received, it is proposed to add a *Packaging and storage* statement.

(MD-CCA: C. Anthony; P&S: D. Hunt) RTS—43632-1

Add the following:

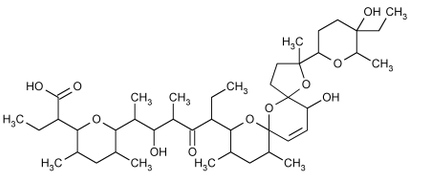
▲**Packaging and storage**—Preserve in well-closed containers, and store at controlled room temperature.▲*USP30*

BRIEFING

Narasin Granular, *USP 29* page 1486; **Narasin Premix,** *USP 29* page 1487. On the basis of comments received regarding the potency of the candidate narasin reference standard, it is proposed to change the values of the specified biopotency conversion factors in the *Assay.* Additional changes are being made for clarification.

(VET: I. DeVeau) RTS—42220-1

Change to read:



$C_{43}H_{72}O_{11}$ (narasin A) 765.03
$C_{43}H_{71}O_{11}$ (narasin B) ~~764.02~~

▲764.03▲*USP30*
$C_{44}H_{74}O_{11}$ (narasin D) ~~779.05~~

▲779.07▲*USP30*
$C_{44}H_{74}O_{11}$ (narasin I) ~~779.05~~

▲779.07▲*USP30*
Narasin.
2*H*-Pyran-2-acetic acid, α-ethyl-6-[5-[2-(5-ethyltetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl)-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl]tetrahydro-3,5-dimethyl-.
α-Ethyl-6-[5-[2-(5-ethyltetrahydro-5-hydroxy-6-methyl-2*H*-pyran-2-yl)-15-hydroxy-2,10,12-trimethyl-1,6,8-trioxadispiro[4.1.5.3]pentadec-13-en-9-yl]-2-hydroxy-1,3-dimethyl-4-oxoheptyl]tetrahydro-3,5-dimethyl-2*H*-pyran-2-acetic acid [*55134-13-9*].

In-Process Revision

Change to read:

Assay—

Diluent—Prepare a mixture of methanol and water (9 : 1).

Mobile phase—Prepare a degassed mixture of methanol, water, and glacial acetic acid (94 : 6 : 0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Neutralized methanol—Add 1 g of sodium bicarbonate to 4 L of methanol, mix, and filter.

Derivatizing reagent—Dissolve 30 g of vanillin in a mixture of methanol and sulfuric acid (950 : 20) in a container protected from light. *[Caution—To avoid splattering, add the sulfuric acid carefully and slowly with a pipet; do not pour. Allow the mixture of methanol and sulfuric acid to cool before adding the vanillin.]* Do not filter.

Resolution solution—Prepare a solution in *Neutralized methanol* containing about 3 mg of USP Narasin RS and 1 mg of USP Monensin Sodium RS per mL. Transfer 2 mL of this solution to a 200-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard preparations—Dissolve an accurately weighed quantity of USP Narasin RS in *Neutralized methanol* to obtain a solution having a known concentration of about 1 mg per mL. Transfer 1.0 mL of this stock solution to a 200-mL volumetric flask, and transfer 2.0 mL and 4.0 mL of the stock solution to two separate 100-mL volumetric flasks, dilute each with *Diluent* to volume, and mix. These solutions contain about 5, 20, and 40 µg of USP Narasin RS per mL. Using the designated percentage of narasin A in the USP Narasin RS, calculate the exact narasin A concentration, in µg per mL, in each of the *Standard preparations.*

Assay preparation—Transfer about 5 g of Narasin Granular, accurately weighed, to a suitable container, add 200.0 mL of *Diluent,* and shake by mechanical means for 1 hour. Allow the solids to settle, and quantitatively dilute an accurately measured volume of the supernatant with *Diluent* to obtain a solution containing about 20 µg of narasin per mL. Pass a portion of this solution through a filter having a 0.5-µm or finer porosity, and use the filtrate as the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 4.6-mm × 25-cm column that contains packing L1. The column outlet is attached to a tee, the opposing arm is attached to a tube from which is pumped the *Derivatizing reagent,* and the outlet is connected to a 2-mL postcolumn reaction coil maintained at 98°. The outlet of the reaction coil is connected to a detector set at 520 nm. The *Mobile phase* and the *Derivatizing reagent* flow at the rate of about 0.7 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for monensin B, 0.75 for monensin A, 1.0 for narasin A, and 1.1 for narasin D + I; and the resolution, *R,* between the monensin B peak and the monensin A peak is not less than 1.25, and between the monensin A peak and the narasin A peak not less than 3.5. Chromatograph the *Standard preparations,* and record the peak responses as directed for *Procedure:* the tailing factor for the narasin A peak is not more than 1.4 when calculated by the formula:

$$W_{0.1} / 2f$$

in which $W_{0.1}$ is the width of the peak at 10% of peak height; and f is the distance from the peak maximum to the leading edge of the peak, the distance being measured at a point on the baseline at which 10% peak height is reached. The relative standard deviation for replicate injections is not more than 10%. [NOTE—After use, flush the system with methanol.]

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard preparations* and the *Assay preparation* into the chromatograph, and measure the areas of the peak responses for the narasin A and narasin D + I peaks ▲[NOTE—Narasin D and narasin I will co-elute under this chromatographic system.]▲*USP30*

Plot the three narasin peak responses in the chromatograms obtained from the *Standard preparations* versus the concentration, in µg per mL, of narasin A, and draw the straight line best fitting the three plotted points. From the graph so obtained, and the narasin A peak response in the chromatogram obtained from the *Assay preparation,* determine the concentration, C_A, in µg per mL, of narasin A in the *Assay preparation.* From the same graph and the narasin D + I peak response in the chromatogram obtained from the *Assay preparation,* determine the concentration, C_{D+I}, in µg per mL, of narasin D + I in the *Assay preparation.* Calculate the biopotency, in mg per g, in the portion of Narasin Granular taken by the formula:

~~$(C_A + C_{D+I}F)(VE/M)$~~

▲$(0.001)(C_AF_A + C_{D+I}F_{D+I})(VE/M)$▲*USP30*

in which ~~*F* is the biopotency conversion factor for narasin D + I~~ ▲F_A is 1.077 representing the biopotency conversion factor for narasin A; F_{D+I} is the biopotency conversion factor for narasin D + I;▲*USP30*

V is the extraction volume, in mL; E is the dilution factor used in diluting the extract to the final estimated concentration of 20 µg per mL; and M is the weight, in g, of Narasin Granular taken to prepare the *Assay preparation.* Calculate the bioconversion factor, ~~*F*~~ ▲F_{D+I},▲*USP30* for narasin D + I by the formula:

~~$(1.402D + 0.0111I)/(D + I)$~~

▲$(1.510D + 0.012I)/(D + I)$▲*USP30*

in which D and I are the specified percentages of narasin D and narasin I, respectively, in USP Narasin RS; ~~1.402~~ ▲1.510▲*USP30* is the factor for converting narasin D to narasin D biopotency; and ~~0.0111~~ ▲0.012▲*USP30* is the factor for converting narasin I to narasin I biopotency.

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BRIEFING

Narasin Premix, *USP 29* page 1487—See briefing under *Narasin Granular.*

(VET: I. DeVeau) RTS—43506-1

Change to read:

Assay—

Diluent, Mobile phase, Neutralized methanol, Derivatizing reagent, Resolution solution, Standard preparations, and *Chromatographic system*—Proceed as directed in the *Assay* under *Narasin Granular.*

Assay preparation—Transfer about 5 g of Narasin Premix, accurately weighed, to a suitable container, add 200.0 mL of *Diluent,* and shake by mechanical means for 1 hour. Allow the solids to settle, and quantitatively dilute an accurately measured volume of the supernatant with *Diluent* to obtain a solution containing about 20 µg of narasin per mL. Pass a portion of this solution through a filter having a 0.5-µm or finer porosity, and use the filtrate as the *Assay preparation*.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Narasin Granular*. Calculate the biopotency, in mg per g, in the portion of Narasin Premix taken by the formula:

~~$(C_A F_A + C_{D+I} F)(VE/M)$~~

$$\blacktriangle(0.001)(C_A F_A + C_{D+I} F_{D+I})(VE/M)_{\blacktriangle USP30}$$

in which *M* is the weight, in g, of Narasin Premix taken to prepare the *Assay preparation;* and the other terms are as defined therein.

BRIEFING

Ondansetron Hydrochloride, *USP 29* page 1582. The test for *Limit of ondansetron related compound D* and the *Assay* use a 20-cm long L10 column, as well as the test for *Chromatographic purity, Method II* by cross reference. Because the 20-cm column is not commercially available, it is proposed to change the column length to 25 cm.

(MD-PP: R. Ravichandran) RTS—43547-1

Change to read:

Limit of ondansetron related compound D—

Mobile phase—Prepare a filtered and degassed mixture of 0.02 M monobasic potassium phosphate (previously adjusted with 1 M sodium hydroxide to a pH of 5.4) and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Ondansetron Related Compound D RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.4 µg per mL.

System suitability solution—Dissolve suitable quantities of USP Ondansetron Related Compound D RS and USP Ondansetron Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.6 µg per mL and 1 µg per mL, respectively.

Test solution—Transfer about 50 mg of Ondansetron Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 328-nm detector and a 4.6-mm × ~~20-cm~~ ▲25-cm▲*USP30* column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for ondansetron related compound C and 1.0 for ondansetron related compound D; and the resolution, *R,* between ondansetron related compound C and ondansetron related compound D is not less than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency determined from the analyte peak is not less than 400 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of ondansetron related compound D in the portion of Ondansetron Hydrochloride taken by the formula:

$$10{,}000(C/W)(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Ondansetron Related Compound D RS in the *Standard solution; W* is the weight, in mg, of Ondansetron Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak areas obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.10% is found.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of 0.02 M monobasic sodium phosphate (previously adjusted with 1 M sodium hydroxide to a pH of 5.4) and acetonitrile (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Ondansetron Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 90 µg per mL.

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System suitability solution—Dissolve suitable quantities of USP Ondansetron Hydrochloride RS and USP Ondansetron Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 90 µg per mL and 20 µg per mL, respectively.

Assay preparation—Transfer about 45 mg of Ondansetron Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 216-nm detector and a 4.6-mm × ~~20-cm~~ ▲25-cm▲*USP30* column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for ondansetron and 1.1 for ondansetron related compound A; and the resolution, *R,* between ondansetron related compound A and ondansetron is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{18}H_{19}N_3O \cdot HCl$ in the portion of Ondansetron Hydrochloride taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Ondansetron Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ondansetron Hydrochloride Oral Suspension, page 944 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-20

Add the following:

▲Ondansetron Hydrochloride Oral Suspension

» Ondansetron Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ondansetron hydrochloride ($C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$). Prepare Ondansetron Hydrochloride Oral Suspension 0.8 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Ondansetron Hydrochloride	80 mg
Vehicle: a mixture of Vehicle for Oral Suspension, *NF,* Vehicle for Oral Solution, *NF* (regular or sugar-free) (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE— ~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Tablets, place the Tablets in a suitable glass mortar, and comminute well, or add Ondansetron Hydrochloride powder. Add the mixed Vehicle ~~for Oral Suspension~~ in 5-mL portions, and mix well. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add the mixed Vehicle ~~for Oral Suspension~~ in small portions to rinse the mortar, add to the preparation

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to final volume, and mix well. If using Cherry Syrup, repeat as above, replacing the mixed Vehicle ~~for Oral Suspension~~ with Cherry Syrup.

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

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Ondansetron Hydrochloride RS.*

pH ⟨791⟩**:** between 3.6 and 4.6 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.0 and 4.0 (Cherry Syrup).

Beyond-use date: 42 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a filtered and degassed solution of 43 mM monobasic potassium phosphate buffer adjusted with a mixture of 1 N sodium hydroxide and acetonitrile (85 : 15) to a pH of 5.4. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Ondansetron Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 4 µg per mL.

Assay preparation—After each amber plastic vial containing Oral Suspension that is stored at 4° is brought to room temperature, pipet 500 µL of Oral Suspension from each bottle into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass through a 0.45-µm filter, and keep frozen at –70° until assayed.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 216-nm detector, a 3.9-mm × 20-mm guard column that contains 4-µm packing L10, and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L10. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 30 minutes for ondansetron hydrochloride; and the relative standard deviation for replicate injections is not more than 1.6%.

Procedure—Separately inject equal volumes (about 80 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ondansetron hydrochloride ($C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$) in the volume of Oral Suspension taken by the formula:

$$200(C/V)(r_U / r_S)$$

in which C is the concentration, in µg per mL, of USP Ondansetron Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Ondansetron Oral Solution, *USP 29* page 1585 and page 905 of *PF* 30(3) [May–June 2004]. It is proposed to revise the column length in the test for *Limit of related compound D* from 30 cm to 25 cm because the 30-cm column is no longer available. The analysis can be performed with the L10 type Spherisorb brand CN column. It is also proposed to correct the calculation of impurities using relative response factors (RRF) in the test for *Related compounds* and to add a table with information regarding impurities.

(MD-PP: R. Ravichandran) RTS—43208-1

In-Process Revision

Add the following:

■**Packaging and storage**—Preserve in well-closed, light-resistant containers.■2S *(USP29)*

Change to read:

Limit of ondansetron related compound D—

Mobile phase—Proceed as directed in the test for *Limit of ondansetron related compound D* under *Ondansetron Hydrochloride*.

System suitability solution—Dissolve suitable quantities of USP Ondansetron Related Compound D RS and USP Ondansetron Related Compound C RS in *Mobile phase;* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 0.5 µg per mL and 2 µg per mL, respectively.

Standard solution—Dissolve an accurately weighed quantity of USP Ondansetron Related Compound D RS in *Mobile phase;* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.5 µg per mL.

Test solution—Quantitatively dilute, if necessary, an accurately measured volume of Oral Solution with *Mobile phase* to obtain a solution containing about 0.8 mg of ondansetron per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 328-nm detector and a 4.6-mm × ~~30-cm~~

▲25-cm▲*USP30*
column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ondansetron related compound D and ondansetron related compound C is not less than 2.0; the tailing factor for ondansetron related compound D is not more than 2.0; and the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of ondansetron related compound D in the volume of Oral Solution taken by the formula:

$$100D(C_S/C_A)(r_U/r_S)$$

in which D is the dilution factor for the Oral Solution in the *Test solution;* C_S is the concentration, in µg per mL, of USP Ondansetron Related Compound D RS in the *Standard solution;* C_A is the concentration, in µg per mL, of ondansetron in the Oral Solution, as determined in the *Assay;* and r_U and r_S are the peak responses of ondansetron related compound D obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% is found.

Change to read:

Related compounds—

Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Ondansetron Hydrochloride.*

Standard solution—Prepare as directed for the *Standard preparation,* in the *Assay* under *Ondansetron Hydrochloride*.

Test solution—Use the *Assay preparation.*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound in the volume of Oral Solution taken by the formula:

~~$(293.36/329.82)1000(F/V)(C_s/C_u)(r_i/r_s)$,~~

▲$(293.36/329.82)10{,}000(1/F)(1/V)(C_S/C_A)(r_i/r_S)$▲*USP30*

in which 293.36 and 329.82 are the molecular weights of ondansetron and anhydrous ondansetron hydrochloride, respectively; F is the relative response factor ~~and is equal to 0.5 for ondansetron related compounds at relative retention times of about 0.45,and 0.58, 0.75for ondansetron related compounds at relative retention times of about 0.63, 0.84 and 1.1, and 1 for all other impurities;~~

▲for each known and unknown impurity (the values of relative response factors [RRF] and the limits can be obtained from *Table 1*);▲*USP30*
V is the volume, in mL, of Oral Solution taken; C_S is the concentration, in mg per mL, on the anhydrous basis, of USP Ondansetron Hydrochloride RS in the *Standard solution;* C_A is the concentration, in mg per mL, of ondansetron in the Oral Solution; r_i is the peak response for any related compound obtained from the *Test solution;* and r_S is the peak response for ondansetron obtained from the *Standard solution.* ~~: not more than 0.2% of any related compound is found, and the sum of all impurities is not more than 0.5%.~~

▲**Table 1**

Related Compound	Approx. RRT	RRF	Limit (%)
Imidazole	0.40	0.46	0.2
2-Methyl imidazole	0.53	0.54	0.2
Des-*C*-methyl ondansetron hydrochloride	0.62	0.76	0.2
N-Desmethyl ondansetron maleate	0.83	0.73	0.2
Ondansetron related compound A	1.2	0.81	0.2
Unknown		1.0	0.1
Total (including ondansetron related compound D)		—	0.5

▲*USP30*

BRIEFING

Oxaprozin, *USP 29* page 1593 and page 1059 of *PF* 29(4) [July–Aug. 2003]; **Oxaprozin Tablets,** *USP 29* page 1594 and page 1061 of *PF* 29(4) [July–Aug. 2003]. On the basis of comments received, a storage statement has been added to the proposed *Packaging and storage* section of the monograph.

(MD-CCA: C. Anthony; D. Hunt) RTS—43624-1

Add the following:

▲**Packaging and storage—**Preserve in tight, light-resistant containers, and store at controlled room temperature.▲*USP30*

BRIEFING

Oxaprozin Tablets, *USP 29* page 1594 and page 1061 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Oxaprozin.*

(MD-CCA: C. Anthony; D. Hunt) RTS—43625-1

Add the following:

▲**Packaging and storage**—Preserve in tight, light-resistant containers, and store at controlled room temperature.▲*USP30*

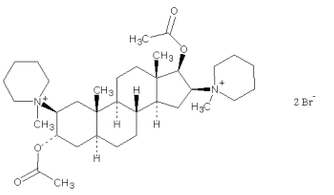
BRIEFING

Pancuronium Bromide. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed.

(MD-PS: D. Bempong) RTS—41982-1

Add the following:

▲Pancuronium Bromide



$C_{35}H_{60}Br_2N_2O_4$ 732.67

Piperidinium, 1,1′-[(2*β*,3α,5α,16*β*,17*β*)-3,17-bis(acetyloxy)androstane-2,16-diyl]bis[1-methyl]-, dibromide.

1,1′-(3α,17*β*-Dihydroxy-5α-androstan-2*β*,16*β*-ylene)bis[1-methylpiperidinium] dibromide diacetate.

2*β*,16*β*-Dipiperidino-5α-androstane-3α,17*β*-diol diacetate dimethobromide [*15500-66-0*].

» Pancuronium Bromide contains not less than 98.0 percent and not more than 102.0 percent of $C_{35}H_{60}Br_2N_2O_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, protected from light and moisture. Store between 15° and 25°.

USP Reference standards ⟨11⟩—*USP Pancuronium Bromide RS. USP Vecuronium Bromide RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The R_F value of the principal spot in the chromatogram of the *Test solution* corresponds to that of the chromatogram of *Standard solution 2,* as obtained in the test for *Related compounds.*

C: A solution (1 in 10) meets the requirements of the tests for *Bromide* ⟨191⟩.

In-Process Revision

Clarity of solution—

Hydrazine sulfate solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours before use.

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—[NOTE—This suspension is stable for two months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of *Hydrazine sulfate solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension A*. Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension B*.

Test solution—Dissolve 50 mg of Pancuronium Bromide in about 20 mL of water, dilute with water to 25 mL, and mix.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A, Reference suspension B,* and water to separate matching test tubes. Compare the *Test solution, Reference suspension A, Reference suspension B,* and water in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The diffusion of light must be such that *Reference suspension A* can readily be distinguished from water, and *Reference suspension B* can readily be distinguished from *Reference suspension A*.] The *Test solution* shows the same or more clarity than *Reference suspension A*.

Color of solution—

Standard stock solution—Prepare a solution of ferric chloride CS, cobaltous chloride CS, cupric sulfate CS, and a 10 g per L hydrochloric acid solution (3 : 3 : 2.4 : 1.6).

Standard solution—[NOTE—Prepare this solution just before use.] Transfer 1 mL of *Standard stock solution* to a 100-mL volumetric flask, dilute with hydrochloric acid (10 g per L) solution to volume, and mix.

Test solution—Use the *Test solution* prepared as directed in the test for *Clarity of solution*.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an external diameter of 15 to 25 mm to obtain a depth of 40 mm. Similarly transfer a portion of the *Standard solution* and water to separate matching test tubes. Compare the *Test solution,* (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩): the *Test solution* is not more intensely colored than the *Standard solution* or water.

Specific rotation ⟨781S⟩**:** between +39° and +43°.

Test solution: 30 mg per mL, in water.

Water, *Method I* ⟨921⟩**:** not more than 8.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Related compounds—

Adsorbent: 0.2-mm layer of chromatographic silica gel mixture.

In-Process Revision

Test solution—Prepare a solution of Pancuronium Bromide in methylene chloride containing 10 mg per mL.

Diluted test solution—Dilute 1.0 mL of the *Test solution* with methylene chloride to 50 mL, and mix. Dilute 1.0 mL of the resulting solution with methylene chloride to 20 mL, and mix.

Standard solution 1—Prepare a solution in methylene chloride containing 0.1 mg of USP Vecuronium Bromide RS and 10 mg of USP Pancuronium Bromide RS per mL.

Standard solution 2—Prepare a solution of USP Pancuronium Bromide RS in methylene chloride containing 10 mg per mL.

Developing solvent system: a mixture of isopropyl alcohol, acetonitrile, and a 400 g per L solution of sodium iodide (85 : 10 : 5).

Procedure—Apply separate 5-µL portions of the *Test solution, Diluted test solution, Standard solution 1,* and *Standard solution 2* to a suitable thin-layer chromatographic plate (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩). Spray the plate with a 20 g per L solution of sodium nitrate, and allow to dry for 5 minutes. Spray the plate with Dragendorff's TS, and cover the plate with a transparent glass cover. Any spot in the chromatogram obtained from the *Test solution* due to vecuronium bromide is not more intense than the corresponding spot in the chromatogram obtained from *Standard solution 1:* equivalent to not more than 1.0% of vecuronium bromide. Any other spot in the chromatogram obtained from the *Test solution,* except for the principal spot and any spot due to vecuronium bromide, is not more intense than the spot in the chromatogram obtained from the *Diluted test solution:* equivalent to not more than 0.1% of any individual impurity. In a valid test, the chromatogram obtained from *Standard solution 1* shows two clearly separated spots. The R_F values for pancuronium bromide and vancuronium bromide are about 0.5 and 0.64, respectively.

Assay—Transfer about 200 mg of Pancuronium Bromide, accurately weighed, to a 100-mL beaker, and dissolve by stirring in 50 mL of acetic anhydride. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid is equivalent to 36.63 mg of $C_{35}H_{60}Br_2N_2O_4$. ▲*USP30*

BRIEFING

Paricalcitol, *USP 29* page 1640. On the basis of comments received, it is proposed to revise *Identification* test *B* by replacing the test for *Ultraviolet Absorption* ⟨197U⟩ with HPLC retention time agreement of the major peak in the *Assay preparation* and the *Standard preparation.* The proposed revision is consistent with current pharmaceutical industry practice. In the test for *Chromatographic purity* and in the *Assay,* it is proposed to specify the final concentrations of the solutions, and to change the format of the formulas, as recommended in the *Stimuli* article, "Common Pharmacopeial Calculations in USP Monographs," published on page 626 of *PF* 31(2) [Mar.–Apr. 2005]. Finally, in the test for *Chromatographic purity* and the *Assay,* it is proposed to add a *Note* to use low-actinic glassware.

(MD-GRE: E. Gonikberg) RTS—43700-1

In-Process Revision

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: ~~—*Ultraviolet Absorption* ⟨197U⟩~~

~~*Solution:* 5 µg per mL.~~

~~*Medium:* dehydrated alcohol.~~

~~*Ratios:* A_{242}/A_{264}, between 0.80 and 0.86; and A_{264}/A_{244}, between 0.63 and 0.69.~~

▲The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.* ▲*USP30*

Change to read:

Chromatographic purity—

▲[NOTE—Use low-actinic glassware to prepare solutions of Paricalcitol.]▲*USP30*

Diluent—Prepare a mixture of water and dehydrated alcohol (1 : 1).

Butylparaben solution—Transfer about 25 mg of butylparaben to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Solution A—Use filtered and degassed water.

Solution B—Use filtered and degassed acetonitrile.

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

Standard solution—Dilute USP Paricalcitol Solution RS in *Diluent* to a known concentration of about 0.1 µg of paricalcitol per mL.

Control standard solution—Transfer 3.0 mL of the *Standard solution* to a 10.0-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test stock solution—~~Transfer about 10 mg of Paricalcitol, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with dehydrated alcohol to volume, and mix.~~

▲Prepare a solution of Paricalcitol in dehydrated alcohol, having a known concentration of about 200 µg per mL.▲*USP30*

Resolution solution—Transfer 1 mL of the *Butylparaben solution* and 1 mL of the *Test stock solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Transfer 1 mL of this solution to a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Prepare a mixture of the *Test stock solution* and water (1 : 1).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 252-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	95	5	isocratic
10–30	95→45	5→55	linear gradient
30–40	45	55	isocratic
40–45	45→0	55→100	linear gradient
45–50	0	100	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between paricalcitol and butylparaben is not less than 12.0. Chromatograph the *Standard solution* and the *Control standard solution,* and record the peak responses as directed for *Procedure:* the area ratio for the paricalcitol peak from the *Standard solution* to that from the *Control standard solution* is between 1.8 and 4.0; and the relative standard deviation for replicate injections of the *Standard solution* is not more than 10.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Diluent,* the *Standard solution,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses, disregarding any peaks corresponding to those obtained from the *Diluent.* Calculate the percentage of each impurity in the portion of Paricalcitol taken by the formula:

~~$10(C/W)(r_i/r_s)$~~

~~in which C is the concentration, in µg per mL, of USP Paricalcitol RS in the *Standard solution; W* is the weight, in mg, of Paricalcitol taken to prepare the *Test stock solution;*~~

▲$100(C_S / C_U)(r_i / r_S)$

in which C_S and C_U are the concentrations, in µg per mL, of paricalcitol in the *Standard solution* and the *Test solution,* respectively;▲*USP30*
r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the paricalcitol peak response obtained from the *Standard solution:* not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found.

Change to read:

Assay—

▲[NOTE—Use low-actinic glassware to prepare solutions of paricalcitol.]▲*USP30*

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (4 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of methanol and water (1 : 1).

Standard preparation—~~Prepare a solution of USP Paricalcitol RS in dehydrated alcohol having a known concentration of about 0.5 mg per mL.~~

▲Transfer an accurately weighed amount of USP Paricalcitol RS to a suitable volumetric flask, dissolve in a minimum amount of dehydrated alcohol, and dilute with *Diluent* to volume. Further▲*USP30*
dilute this solution quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 5.0 µg per mL.

Assay preparation—~~Transfer about 25 mg of Paricalcitol, accurately weighed, to a 50-mL low actinic volumetric flask, dissolve in and dilute with dehydrated alcohol to volume, and mix. Transfer 2.0 mL of this solution to a 200-mL volumetric flask, dilute with *Diluent* to volume, and mix.~~

▲Transfer an accurately weighed amount of Paricalcitol to a suitable volumetric flask, dissolve in a minimum amount of dehydrated alcohol, and dilute with *Diluent* to volume. Further dilute this solution quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 5.0 µg per mL.▲*USP30*

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 252-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the ~~quantity, in µg,~~

▲percentage$_{\blacktriangle USP30}$ of $C_{27}H_{44}O_3$ in the portion of Paricalcitol taken by the formula:

~~$5C(r_U / r_S)$,~~

$$\blacktriangle 100(C_S / C_U)(r_U / r_S)_{\blacktriangle USP30}$$

in which ~~C is the concentration, in µg per mL, of USP Paricalcitol RS in the *Standard preparation;*~~

▲C_U and C_S are the concentrations, in µg per mL, of paricalcitol in the *Assay preparation* and the *Standard preparation,* respectively;$_{\blacktriangle USP30}$ and r_U and r_S are the paricalcitol peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Piroxicam Cream. Because there is no existing *USP* monograph for this dosage form, a new monograph is being proposed.

(CRX: C. Okeke) RTS—43150-2

In-Process Revision

Add the following:

▲Piroxicam Cream

» Piroxicam Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of piroxicam ($C_{15}H_{13}N_3O_4S$). Prepare Piroxicam Cream as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

White Petrolatum	25 g
Stearyl Alcohol	15 g
Propylparaben	0.06 g
Methylparaben	0.15 g
Propylene Glycol	12.0 g
Sodium Lauryl Sulfate	1 g
Sodium Hydroxide 1 M	2.5 mL
Piroxicam	3 g
Purified Water, a sufficient quantity to make	100 g

In an appropriate container (final weight tared), mix the White Petrolatum and Stearyl Alcohol together, and heat to 80 ± 5° to form a clear oil phase. In a separate container, mix the Propylparaben, Methylparaben, Propylene Glycol, Sodium Lauryl Sulfate, and about 30 mL of Purified Water together, and heat to 80 ± 5° to form a clear aqueous phase. Add the aqueous phase to the oil phase with continuous stirring, and allow it to cool to 50° to form an emulsion. In a mortar, triturate the Piroxicam with the Sodium Hydroxide to form a suspension. Using additional water to rinse out the mortar, add the Piroxicam suspension to the previously prepared emulsion, transferring the suspension stepwise and quantitatively to the emulsion. Add sufficient Purified Water with stirring to bring to final weight. Package and label.

Packaging and storage—Preserve in a tight, light-resistant plastic resealable container, and store at controlled room temperature.

Labeling—Label it to state the beyond-use date.

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

Beyond-use date: 90 days at room temperature after the day on which it was compounded.

Assay—

Buffer solution—Dissolve 5.4 g of citric acid and 10.8 g of dibasic sodium phosphate in 2 L of Purified Water, and pass through a 0.45-µm filter.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: 0.01 N methanolic hydrochloric acid, made by diluting 0.9 mL of hydrochloric acid with methanol to a volume of 1 L.

Standard preparation—Dissolve an accurately weighed quantity of USP Piroxicam RS in 2 mL of chloroform, and dilute with *Diluent* to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Add about 340 mg of Piroxicam Cream to 4 mL of chloroform and 150 mL of *Diluent.* Shake the mixture on a wrist action shaker for 15 minutes, and dilute with *Diluent* to 200 mL. Pass the solution through a 0.45-µm filter, and discard the first 5 mL of the filtrate.

Blank—Prepare as directed for the *Assay preparation,* without adding Piroxicam. Use Purified Water to offset the difference in weight between the *Blank* and the *Assay preparation.* Pass the solution through a 0.45-µm filter, and discard the first 5 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector, a 4.6-mm × 30-cm analytical column that contains 10-µm packing L1, and a 4.6-mm × 2-cm guard column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time is about 7 minutes, and the relative standard deviation for replicate injections is not more than 2.8%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation,* the *Assay preparation,* and the *Blank* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of piroxicam ($C_{15}H_{13}N_3O_4S$) in each mL of Piroxicam Cream taken by the formula:

$$200(C/V)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of USP Piroxicam RS in the *Standard preparation; V* is the volume, in mL, of liquid taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Pseudoephedrine Sulfate, *USP 29* page 1861. It is proposed to use iodine vapors instead of iodine spray as a visualizing agent in the test for *Ordinary impurities.*

(MD-CCA: C. Anthony) RTS—43723-1

In-Process Revision

Change to read:

Ordinary impurities ⟨466⟩—
Test solution: alcohol.
Standard solution: alcohol.
Eluant: a mixture of alcohol, glacial acetic acid, and water (10 : 3 : 1).
Visualization: ~~16~~

▲Expose the plate for 24 hours to iodine vapors in a pre-equilibrated closed chamber, on the bottom of which there are iodine crystals.▲*USP30*

BRIEFING

Quinidine Sulfate Oral Suspension, page 946 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-21

Add the following:

▲Quinidine Sulfate Oral Suspension

» Quinidine Sulfate Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of quinidine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$. Prepare Quinidine Sulfate Oral Suspension 10 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Quinidine Sulfate	1 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE— ~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.

If using Quinidine Sulfate Tablets, place in a suitable mortar, and comminute into a fine powder, or add Quinidine Sulfate powder to the mortar. Add about 15 mL of the Vehicle, and mix to a uniform paste. Add the Vehicle in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to the calibrated bottle. Add sufficient Vehicle to volume, and mix well.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature, or in a cold place.

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Quinindine Sulfate RS.*

In-Process Revision

pH ⟨791⟩**:** between 3.4 and 4.4 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.2 and 4.0 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Methanesulfonic acid solution—Add 35.0 mL of methanesulfonic acid to 20.0 mL of glacial acetic acid, dilute with water to 500 mL, and mix.

Diethylamine solution—Dissolve 10.0 mL of diethylamine in water to obtain 100 mL of solution.

Mobile phase—Prepare a suitable filtered and degassed solution of water, acetonitrile, *Methanesulfonic acid solution,* and *Diethylamine solution* (80 : 20 : 2 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Quinidine Sulfate RS in *Mobile phase* to obtain a solution having a known concentration of about 100 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample solution into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the 100 µg per mL *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for quinidine sulfate is about 8.5 minutes, and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of quinidine sulfate $[(C_{20}H_{24}N_2O_2)_2 \cdot H_2SO_4 \cdot 2H_2O]$ in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Quinidine Sulfate RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Senna, *USP 29* page 1959. A new monograph, *Senna Pods,* is proposed elsewhere in this issue of *PF*. Accordingly, changes in the Title and Definition of this monograph are proposed to indicate that the plant part contained in this article is the leaflet. A limit for the minimum content of sennosides is proposed. Also, the following proposals are presented: under *Packaging and storage,* storage conditions are defined; a *Labeling* section is added; a USP Reference Standard is added because of the addition of the *Assay;* limits for *Loss on drying, Total ash,* and *Microbial enumeration* are added; and an *Assay,* which is harmonized with other Pharmacopeias, is proposed.

(DSB: M. Sharaf) RTS—43697-1

Change to read:

Senna

▲Leaf▲*USP30*

Change to read:

» Senna

▲Leaf▲*USP30*
consists of the dried leaflet of *Senna alexandrina* Mill also known as *Cassia acutifolia* Delile (Alexandrian senna) or *C. angustifolia* Vahl (Tinnevelly senna) (Fam. Fabaceae). Senna Leaf contains not less than 2.5 percent of anthraquinone glucosides, calculated as sennosides, on the dried basis.

Change to read:

Packaging and storage—Preserve against attack by insects and rodents (see *Vegetable and Animal Drugs—Preservation* in the *General Notices*).

▲Store protected from light and moisture, at room temperature.▲*USP30*

Add the following:

▲**Labeling**—The label states the Latin binomial and, following the official name, the part of the plant contained in the article.▲*USP30*

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Sennosides RS.*▲*USP30*

Change to read:

Botanic characteristics—

Unground Alexandrian ~~Senna~~

▲*senna leaf*▲*USP30*
—Inequilaterally lanceolate or lance-ovate leaflets, frequently broken; from 1.5 cm to 3.5 cm in length and from 5 mm to 10 mm in width, unequal at the base, with very short, stout petiolules. The leaflets are acutely cuspidate, entire, brittle, and subcoriaceous, with short and somewhat appressed hairs, few on the upper surface, more numerous on the lower surface, where they occur spreading on the midrib, especially on its lower part. The color is weak yellow to light grayish-green to pale olive. The odor is characteristic.

Unground Tinnevelly ~~Senna~~

▲*senna leaf*▲*USP30*
—Usually unbroken leaflets, from 2 cm to 5 cm in length and from 6 mm to 15 mm in width; acute at the apex; and slightly hairy. The color of the leaves is weak yellow to pale olive.

Histology—Senna

▲leaf▲*USP30*
shows polygonal epidermal cells with straight walls and frequently containing mucilage; numerous, broadly elliptical stomata mostly from 20 to 35 µm in length, usually bordered by two neighbor-cells with their long axes parallel to that of the stoma, and rarely, though more frequently in ~~Alexandria Senna,~~

▲Alexandrian senna leaf,▲*USP30*
a third epidermal cell at the end of the stoma. The hairs are nonglandular, one-celled, conical, often curved, with thick papillose walls, from 100 to 350 µm in length. Palisade cells in a single layer underlie both surfaces except in the midrib region where they occur only beneath the upper epidermis. A meristele occurs in the midrib composed of several radially arranged fibrovascular bundles, the latter separated by narrow vascular rays and supported above and below by arcs of lignified pericyclic fibers. Calcium oxalate occurs in rosette aggregates in the spongy parenchyma and in six- to eight-sided prisms in the crystal fibers, which lie on the outer surface of each group of pericyclic fibers.

~~Powdered Senna~~

▲*Powdered senna leaf*▲*USP30*
—Dusky greenish-yellow to light olive-brown, displaying fragments of veins bearing lignified vessels, tracheids, and crystal fibers, isolated hairs, masses of palisade and spongy parenchyma, fragments of epidermis with stomata, free calcium oxalate rosette aggregates, and prisms from 10 to 20 µm in length. In powdered ~~Alexandrian senna,~~

▲Alexandrian senna leaf,▲*USP30*
the hairs are more numerous than in powdered ~~Tinnevelly senna~~

▲Tinnevelly senna leaf.▲*USP30*

Change to read:

Identification—Mix 500 mg

▲of finely powdered Senna Leaf▲*USP30*
with 10 mL of a 1 in 10 solution of potassium hydroxide in alcohol, boil for about 2 minutes, dilute with 10 mL of water, and filter. Acidify the filtrate with hydrochloric acid, shake it with ether, remove the ether layer, and shake it with 5 mL of 6 N ammonium hydroxide: the latter is colored orange or bluish-red.

Add the following:

▲**Microbial enumeration** ⟨2021⟩—The total bacterial count does not exceed 10^5 cfu per g, the total combined molds and yeasts count does not exceed 10^3 cfu per g, the bile-tolerant Gram-negative bacteria does not exceed 10^3 cfu per g, and it meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.▲*USP30*

In-Process Revision

Add the following:

▲**Loss on drying** ⟨731⟩—Dry 1.0 g of finely powdered Senna Leaf at 105° for 2 hours: it loses not more than 12.0% of its weight.▲*USP30*

Add the following:

▲**Total ash** ⟨561⟩: not more than 12.0%.▲*USP30*

Add the following:

▲**Assay—**[NOTE—Conduct all sample preparations with minimal exposure to subdued light, and use low-actinic glassware to protect solutions from light.]

Ferric chloride solution—Dissolve 10.5 g of ferric chloride in 100 mL of water.

Methanolic magnesium acetate solution—Dissolve 5.0 g of magnesium acetate in 1 L of methanol.

Sodium bicarbonate solution—Dissolve 5.0 g of sodium bicarbonate in 1 L of water.

Standard preparation—Dissolve accurately weighed quantities of USP Sennosides RS in *Sodium bicarbonate solution* to obtain a solution having a known concentration of about 0.13 mg per mL.

Assay preparation—Weigh and pulverize about 10 g of Senna Leaf. Transfer about 0.15 g, accurately weighed, to a 100-mL round-bottom flask, add 30 mL of water, mix, weigh, attach a condenser, and reflux in a water bath for 15 minutes. Cool to room temperature, weigh, and adjust to the original weight with water. Centrifuge, and transfer 20.0 mL of the supernatant to a 150-mL separatory funnel. Add 0.1 mL of diluted hydrochloric acid, and shake with three quantities, each of 15 mL, of chloroform. Allow to separate, and discard the chloroform layer after each addition. Add about 0.1 g of sodium bicarbonate, shake for 3 minutes, and centrifuge. Use the supernatant as the *Assay preparation.*

Procedure—Transfer 10.0 mL each of the *Standard preparation* and the *Assay preparation* to separate 100-mL round-bottom flasks equipped with condensers, add 20 mL of *Ferric chloride solution,* and mix. Reflux in a water bath for 20 minutes. Add 1 mL of hydrochloric acid, and reflux for an additional 20 minutes, with frequent shaking, to dissolve the precipitates. Cool to room temperature, transfer the mixtures to separate 100-mL separatory funnels, and shake with three quantities, each of 25 mL, of ether previously used to rinse the flasks. Combine the ether extracts, mix, and wash with two quantities, each of 15 mL, of water. Tranfer the ether layers to separate 100-mL volumetric flasks, dilute with ether to volume, and mix. Evaporate 10.0 mL of the ether extracts to dryness, and dissolve the residue in 10.0 mL of *Methanolic magnesium acetate solution*. Determine the absorbance of the resulting solution from the *Standard preparation* and the *Assay preparation* at 515 nm, with a suitable spectrophotometer fitted with matched quartz cells, using methanol as the blank. Calculate the percentage of sennosides in the Senna Leaf by the formula:

$$3000(A_U / A_S)(C_S / W)$$

in which A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively; C_S is the concentration, in mg per mL, of sennosides in the *Standard preparation;* and W is the weight, in mg, of powdered Senna Leaf used.▲*USP30*

BRIEFING

Senna Pods. A new monograph for Senna pods is proposed. The pericarp of the pods is used as the source of sennosides. This new monograph is based on the *Senna* (leaflets) monograph in *USP 29* page 1959 and is harmonized with other Pharmacopeias. Proposed revisions to the *Senna (leaf)* monograph are also appearing in this number of *PF*.

(DSB: M. Sharaf) RTS—43728-1

Add the following:

▲Senna Pods

» Senna Pods are the dried ripe fruits of *Senna alexandrina* Mill also known as *Cassia acutifolia* Delile (Alexandrian senna) or *C. angustifolia* Vahl (Tinnevelly senna) (Fam. Fabaceae). Senna Pods contain not less than 3.4 percent (Alexandrian senna) and not less than 2.2 percent (Tinnevelly senna), of anthraquinone glucosides, calculated as sennosides, on the dried basis.

Packaging and storage—Preserve against attack by insects and rodents (see *Vegetable and Animal Drugs—Preservation* in the *General Notices*). Store protected from light and moisture, at room temperature.

Labeling—The label states the Latin binomial and, following the official name, the part of the plant contained in the article.

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

Botanic characteristics—

Unground Alexandrian senna pods—Occur as flattened, reniform, membranous, leathery pods; green to greenish-brown with brown patches at the positions corresponding to the seeds; from 40 to 50 mm in length and at least 20 mm wide; at one end is a stylar point and at the other a short stalk. The pods contain six or seven flattened and obovate seeds, green to pale brown, with a continuous network of prominent ridges on the testa.

Unground Tinnevelly senna pods—Occur as flattened, slightly reniform, membranous, leathery pods; brown to yellowish-brown with brown patches at the positions corresponding to the seeds; slightly longer but narrower than Alexandrian senna pods, from 35 to 60 mm in length and 14 to 18 mm wide; at one end is a stylar point and at the other a short stalk. The pods contain five to eight flattened and obovate seeds, green to pale brown, with incomplete, wavy, transverse ridges on the testa.

Histology—Senna pods show epicarp with very thick cuticulized polygonal cells, occasional anomocytic or paracytic stomata, and very few nonglandular, one-celled, conical, often curved hairs, with thick papillose walls, from 100 to 350 µm in length; mesocarp consists of parenchymatous tissue containing a layer of calcium oxalate prisms and vascular bundles partially enclosed by fibers; endocarp with two crossed layers of fibers; seeds with a subepidermal layer of palisade cells with thick outer walls and endosperm of polyhedral cells with mucilaginous walls.

Powdered senna pods—Brown powder displaying polygonal cells with occasional small numbers of nonglandular hairs and anomocytic or paracytic stomata, fibers in two crossed layers accompanied by a crystal sheath of calcium oxalate prisms, isolated hairs, masses of palisade cells of the seeds, clusters, and prisms of calcium oxalate.

Identification—Proceed as directed in the *Identification* test under *Senna Leaf,* except to use 500 mg of finely powdered Senna Pods.

In-Process Revision

Microbial enumeration ⟨2021⟩—The total bacterial count does not exceed 10^5 cfu per g, the total combined molds and yeasts count does not exceed 10^3 cfu per g, the bile-tolerant Gram-negative bacteria does not exceed 10^3 cfu per g, and it meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.*

Loss on drying ⟨731⟩—Dry 1.0 g of finely powdered Senna Pods at 105° for 2 hours: it loses not more than 12.0% of its weight.

Foreign organic matter ⟨561⟩: not more than 1.0%.

Total ash ⟨561⟩: not more than 9.0%.

Acid-insoluble ash ⟨561⟩: not more than 2.0%.

Assay—Proceed as directed in the *Assay* under *Senna Leaf,* using 0.15 g of finely powdered Senna Pods to prepare the *Assay preparation.*▲*USP30*

BRIEFING

Sennosides, *USP 29* page 1959. On the basis of comments received, the following revisions are proposed: changes in the Definition; senna pods as a source of sennosides are included; under *Packaging and storage,* storage conditions are defined; and in the section *Residue on ignition,* it is proposed to change the temperature back to the original conditions specified in *USP 26* of 800° because USP received reports of out-of-specification results for USP-grade sennosides using the 600° temperature indicated in the harmonized general chapter, *Residue on Ignition* ⟨281⟩. See also the proposed title change for *Senna* and the new proposed monograph *Senna Pods,* published elsewhere in this number of *PF.*

(DSB: M. Sharaf) RTS—43502-1

Change to read:

~~» Sennosides is a partially purified natural complex of anthraquinone glucosides found in senna, isolated from *Cassia angustifolia* or *C. acutifolia* as calcium salts. It contains not less than 90.0 percent and not more than 110.0 percent of sennosides, calculated on the dried basis, or, if the sennosides is in higher concentration, not less than 90.0 percent and not more than 110.0 percent of the concentration indicated on the label.~~

▲» Sennosides is a partially purified natural complex of anthraquinone glucosides, isolated from senna leaflets and/or senna pods, *Senna alexandrina* Mill (*Cassia acutifolia* or *C. angustifolia*), as calcium salts. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of sennosides. The labeled amount is not less than 60.0 percent (w/w), calculated on the dried basis.▲*USP30*

Change to read:

Packaging and storage—Preserve in well-closed containers.

▲Store protected from light and moisture, at controlled room temperature.▲*USP30*

Change to read:

Residue on ignition ⟨281⟩: between 5.0% and 8.0%,

▲ignited at 800 ± 25°,▲*USP30*
the use of sulfuric acid being omitted.

BRIEFING

Simvastatin, *USP 29* page 1964 and page 792 of *PF* 31(3) [May–June 2005]. It is proposed to clarify the preparation of *Solution A* and *Solution B* used in the test for *Chromatographic purity* and in the *Assay.* It is also proposed to add a *Note* regarding the stability of the Simvastatin solutions. In addition, minor editorial style changes have been made.

(MD-GRE: E. Gonikberg) RTS—43269-1

In-Process Revision

Change to read:

Identification—

A: *Infrared Absorption* ⟨197M⟩.
B: ~~*Ultraviolet Absorption* ⟨197U⟩~~
~~*Solution:* 10 µg per mL.~~
~~*Medium:* acetonitrile.~~

▲The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*▲*USP30*

Change to read:

Chromatographic purity—

▲[NOTE—The Simvastatin solutions are stable for up to 3 days when stored at 4°. Without refrigeration, they should be injected immediately after preparation.]▲*USP30*

~~*Diluting solution*—Prepare a solution of butylated hydroxytoluene in acetonitrile containing 0.5 mg per mL.~~

~~*Standard solutions*—Dissolve an accurately weighed quantity of USP Simvastatin RS in *Diluting solution* to obtain *Standard solution A* having a known concentration of about 0.2 mg per mL. Transfer 4.0, 2.0, and 1.0 mL of *Standard solution A* to separate 10-mL volumetric flasks, and dilute with *Diluting solution* to volume to obtain *Standard solutions B*, *C*, and *D*, respectively.~~

~~*Test solution*—Dissolve an accurately weighed quantity of simvastatin in *Diluting solution* to obtain a solution having a concentration of about 20 mg per mL.~~

~~*Procedure*—Separately apply 4 µL portions of each of the *Standard solutions* and the *Test solution* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of silica gel mixture, previously washed with methanol and air-dried. Dry the spots with the aid of a stream of nitrogen. Position the plate in a chromatographic chamber previously equilibrated with a solvent system consisting of a mixture of cyclohexane, chloroform, and isopropyl alcohol (5 : 2 : 1) containing 0.5 mg of butylated hydroxytoluene per mL, and develop the chromatogram until the solvent front has moved about three-quarters of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate under a stream of nitrogen. Spray the plate with a mixture of methanol and sulfuric acid (8 : 2), heat at 110° for 30 minutes, and immediately examine the plate: no secondary spot in the chromatogram of the *Test solution* is greater in size or intensity than the principal spot from *Standard solution B* (0.4%), and the sum of all such secondary spots obtained from the *Test solution* is not greater than 1.0%.~~

▲*Mobile phase, Diluent,* and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure—Inject about 5 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for all the peaks. Calculate the percentage of each impurity in the portion of Simvastatin taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak area for each impurity; and r_s is the sum of the areas of all the peaks. Not more than 1.0% of the sum of lovastatin and epilovastatin is found. [NOTE—If present, lovastatin and epilovastatin may not be completely resolved by the method. These peaks, appearing at a relative retention time of 0.6, are integrated together to determine conformance.] Not more than 0.4% of any individual impurity other than lovastatin and epilovastatin is found; and not more than 1.0% of total impurities other than lovastatin and epilovastatin is found.▲*USP30*

Delete the following:

▲~~**Limit of lovastatin**—From the chromatograms of the *Assay preparation* and the *Standard preparation*, obtained as directed in the *Assay*, calculate the percentage of lovastatin in the portion of Simvastatin taken by the formula:~~

~~$$10{,}000(C/W)(r_u/r_s),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Lovastatin RS in the *Standard preparation*; *W* is the weight, in mg, of Simvastatin taken for the *Assay preparation*; and r_u and r_s are the lovastatin peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively: not more than 1% is found.~~▲*USP30*

Change to read:

Assay—

▲[NOTE—The Simvastatin solutions are stable for up to 3 days when stored at 4°. Without refrigeration, they should be injected immediately after preparation.]▲*USP30*

~~*Mobile phase*—Prepare a filtered and degassed mixture of acetonitrile and dilute phosphoric acid (1 in 1000) (50 : 50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Diluting solution*—Prepare a mixture of acetonitrile and 0.01 M monobasic potassium phosphate (60 : 40), filter, and adjust with phosphoric acid to a pH of 4.0.~~

~~*Standard preparation*—Dissolve accurately weighed quantities of USP Simvastatin RS and USP Lovastatin RS in *Diluting solution*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 0.3 mg per mL of USP Simvastatin RS and 0.003 mg per mL of USP Lovastatin RS.~~

In-Process Revision

~~*Assay preparation*—Transfer about 30 mg of Simvastatin, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Diluting solution* to volume.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 238-nm detector and a 4.6- × 33-mm column that contains packing L1. The flow rate is about 3.0 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.65 for lovastatin and 1.0 for simvastatin, the resolution, *R*, between simvastatin and lovastatin is not less than 3.0, the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 1.0%.~~

~~*Procedure*—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas of the responses for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{38}O_5$ in the portion of Simvastatin taken by the formula:~~

~~$$100C(r_u/r_s)$$~~

~~in which *C* is the concentration, in mg per mL, of USP Simvastatin RS in the *Standard preparation*, and r_u and r_s are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

▲*Dilute phosphoric acid*—Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with water to volume.

Solution A—Prepare a mixture of acetonitrile and ~~0.1% phosphoric acid in water (1 : 1).~~ *Dilute phosphoric acid* (50 : 50).

Solution B—~~Prepare a 0.1% solution of phosphoric acid in acetonitrile.~~ Transfer 1 mL of phosphoric acid to a 1-L volumetric flask, and dilute with acetonitrile to volume.

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

Buffer solution—Prepare a solution containing 1.4 g of monobasic potassium phosphate per L, and adjust with phosphoric acid to a pH of 4.0.

Diluent—Prepare a mixture of acetonitrile and *Buffer solution* (3 : 2).

System suitability preparation—Dissolve accurately weighed quantities of USP Simvastatin RS and USP Lovastatin RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 1.5 mg per mL of USP Simvastatin RS and 0.015 mg per mL of USP Lovastatin RS.

Standard preparation—Dissolve an accurately weighed quantity of USP Simvastatin RS in *Diluent* to obtain a solution having a known concentration of about 1.5 mg per mL.

Assay preparation—Transfer about 75 mg of Simvastatin, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩—The liquid chromatograph is equipped with a 238-nm detector and a 4.6- × 33-mm column that contains packing L1. The flow rate is about 3.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–4.5	100	0	isocratic
4.5–4.6	100→95	0→5	linear gradient
4.6–8.0	95→25	5→75	linear gradient
8.0–11.5	25	75	isocratic
11.5–11.6	25→100	75→0	linear gradient
11.6–13	100	0	re-equilibration

Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.60 for lovastatin and 1.0 for simvastatin; and the resolution, *R,* between simvastatin and lovastatin is greater than 3. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure

the areas for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{38}O_5$ in the portion of Simvastatin taken by the formula:

$$VC(r_U / r_S)$$

in which V is the volume, in mL, of the *Assay preparation;* C is the concentration, in mg per mL, of USP Simvastatin RS in the *Standard preparation;* and r_U and r_S are the responses of the simvastatin peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Sumatriptan Succinate Oral Suspension, page 947 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension*.

(CRX: C. Okeke) RTS—43131-22

Add the following:

▲Sumatriptan Succinate Oral Suspension

» Sumatriptan Succinate Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of sumatriptan succinate ($C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$). Prepare Sumatriptan Succinate Oral Suspension 5 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Sumatriptan Succinate	500 mg
Vehicle: a mixture of Vehicle for Oral Suspension, *NF,* and Vehicle for Oral Solution (regular or sugar-free), *NF* (1 : 1), a sufficient quantity to make . . .	~~25 mL~~ 100 mL

If using Tablets, comminute into a fine powder using a suitable mortar, or add Sumatriptan Succinate powder to the mortar. Add about 25 mL of ~~the~~ Vehicle ~~for Oral Suspension~~ in ~~5 mL~~ portions, mixing thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add sufficient Vehicle ~~for Oral Solution~~ to bring to final volume, and mix well.

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

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Sumatriptan Succinate RS.*

pH ⟨791⟩**:** between 3.6 and 4.6.

Beyond-use date: 14 days after the day on which it was compounded.

In-Process Revision

Assay—

Mobile phase—Prepare a solution of 0.01 M dibutylamine in 0.025 M aqueous monobasic sodium phosphate dihydrate and acetonitrile (75 : 25). Adjust *Mobile phase* with 1 N sodium hydroxide to a pH of 8.0, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Dissolve an accurately weighed quantity of *N*-hydroxymethylsumatriptan succinate in *Mobile phase* to obtain a known concentration of about 3.0 mg per mL.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Sumatriptan Succinate RS in *Mobile phase* to obtain a known concentration of about 4.0 mg per mL.

Standard preparation—Dilute the *Standard stock preparation* with *Mobile phase* to obtain a solution having a known concentration of about 120 µg per mL. Each solution contains 30 µg per mL of *Internal standard solution.*

Assay preparation—Transfer about 1 mL of Oral Suspension from each bottle to a suitable container, and dilute with 0.1 M hydrochloric acid to obtain a concentration of about 0.15 mg per mL. Pass the solution through a 0.22-µm syringe filter into a 0.3-mL polypropylene sample vial for assay.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 282-nm detector and a 4.6-mm × 10-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention times for sumatriptan and *N*-hydroxymethylsumatriptan are 11 and 14 minutes, respectively; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of sumatriptan succinate ($C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Sumatriptan Succinate RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

BRIEFING

Temazepam, *USP 29* page 2077. It is proposed to simplify *Identification* test *A* because drying of the test article is no longer required. This is in accordance with General Chapter *Spectrophotometric Identification Tests* ⟨197⟩. It is also proposed to delete the redundant *Identification* test *B* pertaining to UV identification. *Identification* test *C* is to be renamed *Identification* test *B*.

(MD-PP: R. Ravichandran) RTS—43549-1

Change to read:

Identification—

~~**A:** The IR absorption spectrum of a potassium bromide dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Temazepam RS.~~

In-Process Revision

~~**B:** The UV absorption spectrum of a 1 in 80,000 solution in methanol exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Temazepam RS, concomitantly measured.~~

▲**A:** *Infrared Absorption* ⟨197K⟩.▲*USP30*
~~**C:**~~

▲**B:**▲*USP30*
The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

BRIEFING

Thalidomide, *USP 29* page 2106. On the basis of comments received, it is proposed to revise the *Microbial limits* section to specify the required tests and specifications. Minor changes in the test for *Chromatographic purity* are also proposed.

(MD-OOD: F. Mao) RTS—43543-1

Change to read:

Microbial limits ⟨61⟩**:** ~~meets the requirements.~~

▲The total aerobic microbial count using the *Plate Method* is not more than 1000 cfu per g, and the total combined molds and yeasts count is not more than 100 cfu per g. It meets the requirements of the tests for absence of *Escherichia coli.*▲*USP30*

Change to read:

Chromatographic purity—

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (95 : 5 : 0.1).

Solution B—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (85 : 15 : 0.1).

Diluent—Prepare a mixture of water, acetonitrile, and phosphoric acid (50 : 50 : 0.1).

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

Phthalic acid stock solution—Transfer about 100 mg of phthalic acid to a 100-mL volumetric flask, dissolve in a mixture of acetonitrile and water (80 : 5), and dilute with acetonitrile to volume. Mix, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.1 mg per mL.

Standard stock solution—Dissolve, with the aid of sonication, an accurately weighed quantity of USP Thalidomide RS in acetonitrile to obtain a solution having a known concentration of about 1 mg per mL.

Standard solution—Pipet 2.0 mL of the *Standard stock solution* and 2.0 mL of the *Phthalic acid stock solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, add 10.0 mL of phosphoric acid solution (1 in 100), dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.0002 mg of phthalic acid per mL.

Test solution—Transfer about 100 mg of Thalidomide, accurately weighed, to a 50-mL volumetric flask, and dissolve, with the aid of sonication, in 40 mL of a mixture of water, acetonitrile, and phosphoric acid (50 : 50 : 0.1). Dilute with *Diluent* to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, add 10.0 mL of phosphoric acid solution (1 in 100), dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 3.9-mm × 15-cm column that contains 4-µm packing L1. The flow rate is about 2 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–15	100→50	0→50	linear gradient
15–20	50→100	50→0	linear gradient
20–30	100	0	isocratic

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.35 for phthalic acid and about 1.0 for thalidomide; the tailing factor for the phthalic acid and thalidomide peaks is not more than 2.0; and the relative standard deviation determined from the phthalic acid peak for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the percentage of each impurity in ~~the portion of~~

▲▲*USP30*
Thalidomide ~~taken~~

▲▲*USP30*
by the formula:

$$▲50{,}000(C_P / W)(r_i / r_P)▲_{USP29}$$

in which C_P is the concentration, in mg per mL, of phthalic acid in the *Standard solution; W* is the amount, in mg, of Thalidomide taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_P is the phthalic acid peak response obtained from the *Standard solution:* not more than 0.1% of any individual impurity is found; and not more than 0.3% of total impurities is found.

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BRIEFING

Thimerosal, *USP 29* page 2126. On the basis of information received, it is proposed to revise the color of the precipitate formed in *Identification* test *B.*

(MD-AA: B. Davani) RTS—43211-1

Change to read:

Identification—
A: *Infrared Absorption* ⟨197K⟩.
B: To a solution (1 in 100) add a few drops of silver nitrate TS: a ~~white~~

▲pale yellow▲*USP30*
precipitate is formed.

BRIEFING

Tizanidine Tablets, page 456 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to add a test for *Dissolution* to this proposed new monograph. Minor editorial revisions are also being made.

(BPC: M. Marques) RTS—40316-4

Add the following:

▲Tizanidine Tablets

» Tizanidine Tablets contain Tizanidine Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of tizanidine ($C_9H_8ClN_5S$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩**—***USP Tizanidine Hydrochloride RS. USP Tizanidine Related Compound A RS. USP Tizanidine Related Compound B RS. USP Tizanidine Related Compound C RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩**—**

Medium: 0.1 N hydrochloric acid; 500 mL, degassed.

Apparatus 1: 100 rpm.

Time: 45 minutes.

Determine the amount of tizanidine hydrochloride ($C_9H_8ClN_5S \cdot HCl$) dissolved by employing the following method.

Phosphoric acid solution, Buffer solution, and *Mobile phase*—Proceed as directed in the *Assay.*

Standard stock solution—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS, and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a concentration of about 201 µg per mL.

Working standard solution—For Tablets labeled to contain 2 mg, transfer 4.0 mL of the *Standard stock solution* to a 200-mL volumetric flask, dilute with *Medium* to volume, and mix. For Tablets labeled to contain 4 mg, transfer 4.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with *Medium* to volume, and mix.

Test solution—Withdraw 10 mL of the solution under test. Pass through a suitable 0.45-µm filter, discarding the first 5 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column

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temperature is maintained at 50°. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in percentage, of $C_9H_8ClN_5S \cdot HCl$ dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times LC} \times \frac{253.71}{290.17}$$

in which r_U and r_S are the peak responses for the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in µg per mL, of the *Working standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; *LC* is the Tablet label claim, in mg; 253.71 is the molecular weight of tizanidine; and 290.17 is the molecular weight of tizanidine hydrochloride.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_9H_8ClN_5S \cdot HCl$ is dissolved in 45 minutes.

Related compounds—

Phosphoric acid solution, Buffer solution, Mobile phase, Tizanidine related compound A solution, Tizanidine related compound B solution, Tizanidine related compound C solution, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of tizanidine, to a 100-mL volumetric flask, add about 50 mL of *Buffer solution,* sonicate for about 15 minutes with occasional shaking, and shake by mechanical means for 15 minutes. Add 20 mL of acetonitrile, and mix. Allow to cool, dilute with *Buffer solution* to volume, and mix. Centrifuge a portion of this solution at 2000 rpm or higher for 10 minutes. Pass a portion of this solution through a filter having a 45-µm or finer porosity, and use the filtrate.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major analyte peaks, disregarding the peaks due to the solvent. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$(253.71/290.17)10{,}000(C/W)(A/D)F(r_i / r_S)$$

in which 253.71 and 290.17 are the molecular weights of tizanidine and tizanidine hydrochloride, respectively; *C* is the concentration, in mg per mL, of USP Tizanidine Hydrochloride RS in the *Standard solution; A* is the average weight, in mg, of each Tablet; *D* is the labeled dose, in

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mg, of tizanidine per Tablet; *W* is the weight, in mg, of sample taken to prepare the *Test solution; F* is the relative response factor and is given in *Table 1; r_i* is the peak area for each impurity obtained from the *Test solution;* and r_S is the peak area of tizanidine in the *Standard solution*. The limits for the impurities are specified in *Table 1.*

Table 1

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Tizanidine related compound C	about 0.8	1.0	0.2
Tizanidine	1.0	—	—
Tizanidine related compound B	about 1.4	0.9	0.2
Tizanidine Related compound A	about 10.2	0.9	0.2
Individual unknown	—	1.0	0.2
Total	—	—	0.5

Assay—

Phosphoric acid solution—Dilute 6 mL of phosphoric acid with water to make 50 mL of solution.

Buffer solution—Dissolve about 3.5 g of sodium 1-pentanesulfonate in 1000 mL of water. Adjust with *Phosphoric acid solution* or 1 N sodium hydroxide to a pH of 3.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Tizanidine related compound A solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound B solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound C solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound C RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Resolution solution—Transfer about 23 mg of USP Tizanidine Hydrochloride RS to a 100-mL volumetric flask, add 20 mL of *Mobile phase* and 10 mL each of *Tizanidine related compound A solution, Tizanidine related compound B solution,* and *Tizanidine related compound C solution.* Sonicate to dissolve the USP Tizanidine Hydrochloride RS, and dilute with *Mobile phase* to volume.

Standard preparation—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.046 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of tizanidine, to a 500-mL volumetric flask, add about 250 mL of *Buffer solution,* sonicate for about 15 minutes with occasional shaking,

and shake by mechanical means for 15 minutes. Add 100 mL of acetonitrile, and mix. Allow to cool, dilute with *Buffer solution* to volume, and mix. Centrifuge a portion of this solution at 2000 rpm or higher for 10 minutes. Pass a portion of this solution through a filter having a 45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are given in *Table 1;* the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 4.0, and the resolution, *R,* between tizanidine and tizanidine related compound B is not less than 4.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of tizanidine ($C_9H_8ClN_5S$) in the portion of Tablets taken by the formula:

$$(253.71/290.17)500C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Tizanidine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

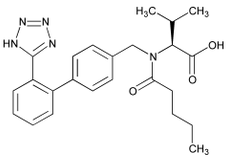
BRIEFING

Valsartan, page 1996 of *PF* 29(6) [Nov.–Dec. 2003]. This new *USP* monograph is presented again with additional changes. On the basis of comments received, it is proposed to remove the requirement for a 4-cm cell in the test for *Absorbance* and to revise the preparation of the *Standard solution* and the *System suitability solution* in *Test 1* under *Related compounds*.

(MD-CV: D. Bempong) RTS—43409-1

Add the following:

▲Valsartan



$C_{24}H_{29}N_5O_3$ ~~435.53~~ 435.52

L-Valine, *N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-.

N-[*p*-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine [*137862-53-4*].

» Valsartan contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{29}N_5O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in ~~well-closed containers~~ tight containers, and store at 25°, excursions permitted between 15° and 30°. Protect from moisture and heat.

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

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Identification—

A: *Infrared Absorption* ⟨197M⟩.

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

Absorbance: ~~not more than 0.070~~ 0.07, ~~determined at 420 nm, in a 4-cm cell, on a solution prepared by dissolving 1 g in 20 mL of methanol.~~ Prepare a 1 in 20 solution in methanol and determine the absorbance at 420 nm. The absorbance divided by the path length is not more than 0.02.

~~**Specific rotation** ⟨781S⟩**:** between −64° and −69° at 20°.~~

~~*Test solution:* 10 mg per mL, in methanol.~~

Water, *Method I* ⟨921⟩**:** not more than 2.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

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

Related compounds—

TEST 1 (LIMIT OF VALSARTAN RELATED COMPOUND A)—

~~*0.07 M Phosphate buffer solution*~~ ~~Dissolve 10.99 g of dibasic sodium phosphate and 3.81 g of monobasic potassium phosphate in water, dilute with water to 1000 mL, and mix.~~

Mobile phase—Prepare a ~~filtered and degassed~~ mixture of ~~*0.07 M Phosphate buffer solution* and isopropyl alcohol (98 : 2)~~ *n*-hexane, 2-propanol, and trifluoroacetic acid (85 : 15 : 0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Standard stock solution* Pipet 5.0 mL of *System suitability solution* into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Dissolve an accurately weighed quantity of USP Valsartan Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.003 mg of valsartan related compound A per mL. Transfer about 5 mg of USP Valsartan Related Compound A RS, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.~~

Standard solution— ~~Transfer 1.0 mL of *Standard stock solution* into a 10-mL volumetric flask, dilute with *Mobile phase,* and mix. Transfer 1.0 mL of this solution into a 10-mL volumetric flask, dilute with *Mobile phase,* and mix.~~ Dissolve an accurately weighed quantity of USP Valsartan Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.01 mg per mL.

System suitability solution— ~~Transfer about 30 mg of USP Valsartan Related Compound A, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Mobile phase* to volume. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume (*Solution 1*). Transfer about 15 mg of USP Valsartan RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in *Mobile phase*. Add, by pipetting, 10.0 mL of *Solution 1* to the same flask, dilute with *Mobile phase* to volume, and mix. Dissolve accurately weighed quantities of USP Valsartan RS and USP Valsartan Related Compound A RS in *Mobile phase,* serially diluting, if necessary, to obtain a solution having a known concentration of about 0.15 mg of valsartan per mL and about 0.003 mg of valsartan related compound A per mL. Transfer about 1 mg of Valsartan, accurately weighed, to a 20-mL 25-mL volumetric flask, add 10 mL of the *Standard stock solution,* and dissolve in and dilute with *Mobile phase* to volume.~~ Dissolve accurately weighed quantities of USP Valsartan RS and USP Valsartan Related Compound A RS in *Mobile phase* to obtain a solution having known concentrations of about 0.04 mg per mL each of valsartan and valsartan related compound A.

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Test solution— ~~Transfer about 100 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 5.0 mL of this solution into a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~ Transfer about 50 mg of Valsartan, accurately weighed, to a 50-mL volumetric flask, add about 40 mL of *Mobile phase,* and sonicate for 5 minutes. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a ~~227-nm 220-nm~~ 230-nm detector and a ~~4.0-mm × 10-cm~~ 4.6-mm × 25-cm column that contains 5-µm packing ~~L41~~ L40. The flow rate is about 0.8 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are 0.60 for valsartan related compound A and 1.0 for valsartan; the ratio of the height between the baseline and the lowest point between the valsartan and valsartan related compound A peaks to the height of the valsartan related compound A peak is not more than 0.4. and~~ the resolution, *R,* between valsartan related compound A and valsartan is not less than 2.0; ~~Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:*~~ and the relative standard deviation, determined from the valsartan related compound A peak, for replicate injections is not more than ~~15.0%~~ 5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the ~~heights~~ areas for the major peaks. Calculate the percentage of valsartan related compound A in the portion of Valsartan taken by the formula:

~~$100(r_u/r_s),$~~

~~in which r_u and r_s are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.5% is found.~~

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Valsartan Related Compound A RS in the *Standard solution;* C_U is the concentration, in mg per mL, of valsartan in the *Test solution;* and r_U and r_S are the peak responses for valsartan related compound A obtained from the *Test solution* and *Standard solution,* respectively: not more than ~~1.5%~~ 1.0% is found.

TEST 2 (LIMIT OF VALSARTAN RELATED COMPOUND B, VALSARTAN RELATED COMPOUND C, AND OTHER RELATED COMPOUNDS)—

~~*Diluent* and~~ *Mobile phase*—Proceed as directed in the *Assay.*

~~*Standard stock solution A*— Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase* to obtain a solution having a known concentration of about 5 mg per mL.~~

~~*Standard stock solution B*— Dissolve an accurately weighed quantity of USP Valsartan Related Compound B RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.05 mg per mL.~~

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~~*Standard stock solution C*—Dissolve an accurately weighed quantity of USP Valsartan Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.025 mg per mL.~~

Resolution solution—~~Pipet 10.0 mL of *Standard stock solution A,* 5.0 mL of *Standard stock solution B,* and 2.0 mL of *Standard stock solution C* into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~ Dissolve accurately weighed quantities of USP Valsartan RS, USP Valsartan Related Compound B RS, and USP Valsartan Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about ~~0.5 mg~~ 0.001 mg of valsartan per mL, ~~0.0025 mg~~ 0.001 mg of valsartan related compound B per mL, and ~~0.0005 mg~~ 0.001 mg of valsartan related compound C per mL.

Standard solution—~~Dilute an accurately measured volume of *Standard stock solution A* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.0005 mg per mL.~~ Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about ~~0.0005 mg~~ 0.001 mg of valsartan per mL.

Test solution—Transfer about 50 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay,* except to use a 225-nm detector. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are 0.73 for valsartan related compound B, 1.0 for valsartan, and 3.8 for valsartan related compound C;~~ the resolution, *R,* between valsartan related compound B and valsartan is not less than 1.8; the relative standard deviation, determined from the valsartan related compound B peaks, for replicate injections is not more than ~~5.0%~~ 10.0%; and the relative standard deviation, determined from the valsartan peaks, for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Resolution solution, Standard solution,* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of ~~each impurity~~ valsartan related compound B and valsartan related compound C in the portion of Valsartan taken by the formula:

~~$$100(Dr_i / r_s),$$~~

~~in which *D* is the factor due to the extent of dilution and is equal to 2.5 for valsartan related compound B, 0.5 for valsartan related compound C, and 0.05 for all other impurities; r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the peak response for valsartan related compound B or valsartan related compound C obtained from the *Resolution solution* or the valsartan peak response obtained from the *Standard solution,* as appropriate:~~

$$100(C_S / C_U)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of the appropriate USP Valsartan Related Compound RS in the *Resolution solution;* C_U is the concentration, in mg per mL, of valsartan in the *Test solution;* r_i is the peak response for the impurity obtained from the *Test solution;* and r_S is the peak response for the appropriate valsartan related compound ob-

tained from the *Resolution solution.* Calculate the percentage of each other impurity in the portion of Valsartan taken by the formula:

$$100(C_S / C_U)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Valsartan RS in the *Standard solution;* r_S is the peak response for valsartan obtained from the *Standard solution;* and the other terms are as defined above: not more than ~~0.5%~~ 0.2% of valsartan related compound B is found; not more than 0.1% of valsartan related compound C is found; not more than 0.1% of any other individual impurity, excluding valsartan related compound A, is found; ~~and not more than 0.5% of total impurities is found.~~ and not more than 0.3% of total impurities, excluding valsartan related compound A, is found.

Assay—

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

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and glacial acetic acid (500 : 500 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about ~~0.05 mg~~ 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. ~~Pipet 10.0 mL of this solution into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~230-nm 248-nm~~ 273-nm detector and a 3.0-mm × 12.5-cm column that contains 5-µm packing L1. The flow rate is about 0.4 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the tailing factor is between 0.8 and 1.5; and~~ the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{24}H_{29}N_5O_3$ in the portion of Valsartan taken by the formula:

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

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Valsartan RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Verapamil Hydrochloride Injection, *USP 29* page 2245; **Verapamil Hydrochloride Tablets,** *USP 29* page 2246. It is proposed to provide USP Reference Standards for the two related compounds in these monographs: 3,4-dimethoxybenzaldehyde and 3,4-dimethoxybenzyl alcohol are used in the preparation of the *Standard solution* in the test for *Related compounds.*

(MD-CV: D. Bempong) RTS—43398-1

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Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Verapamil Hydrochloride RS. USP Verapamil Related Compound A RS.*

▲*USP Verapamil Related Compound E RS. USP Verapamil Related Compound F RS.*▲USP30

Change to read:

Related compounds—

Aqueous solvent mixture, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed for *Chromatographic purity* under *Verapamil Hydrochloride.*

Standard solution—Dissolve accurately weighed quantities of USP Verapamil Hydrochloride RS, USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

▲USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS▲USP30
in *Mobile phase* to obtain a solution having known concentrations of about 2.5 mg of USP Verapamil Hydrochloride RS per mL and 0.0075 mg each of USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

▲USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS▲USP30
per mL.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than four times the retention time for verapamil hydrochloride. Record the chromatograms, and measure all of the peak responses. The retention times are about 0.4 for ~~3,4-dimethoxybenzyl alcohol~~

▲verapamil related compound F,▲USP30
0.5 for verapamil related compound A, 0.7 for ~~3,4-dimethoxybenzaldehyde~~

▲verapamil related compound E,▲USP30
and 1.0 for verapamil. Calculate the quantity, in mg, of each individual impurity in each mL of the Injection taken by the formula:

$$C(L/D)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of the appropriate impurity in the *Standard solution; L* is the labeled quantity, in mg per mL, of verapamil hydrochloride in the Injection; D is the concentration, in mg per mL, of verapamil hydrochloride in the *Test solution*, on the basis of the labeled quantity in each mL and the extent of dilution; and r_U and r_S are the peak responses of the appropriate impurity in the *Test solution* and the *Standard solution*, respectively: not more than 0.3% of any specified impurity is found, and the sum of all impurities is not greater than 1.0%.

BRIEFING

Verapamil Hydrochloride Oral Solution—See briefing under *Acetazolamide Oral Solution.*

(CRX: C. Okeke) RTS—42993-13

Add the following:

▲Verapamil Hydrochloride Oral Solution

» Verapamil Hydrochloride Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$). Prepare Verapamil Hydrochloride Oral Solution 50 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Verapamil Hydrochloride Oral Suspension*):

Verapamil Hydrochloride powder . .	5 g
Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

Dissolve Verapamil Hydrochloride powder in about 40 mL of Cherry Syrup in a mortar, and mix to a uniform paste. Add the Cherry Syrup in small portions almost to volume, and mix thoroughly after each addition. Transfer the contents of the mortar, stepwise and quantitatively, to a calibrated bottle. Add enough Cherry Syrup to bring to final volume, and mix well.

In-Process Revision

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

Labeling—Label it to indicate the beyond-use date.

USP Reference standards ⟨11⟩**—***USP Verapamil Hydrochloride RS.*

pH ⟨791⟩**:** between 3.0 and 3.8.

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Sodium acetate solution—Dissolve an accurately weighed quantity of sodium acetate in acetic acid having a concentration of 33 mL per L to obtain a solution having a 0.01 M sodium acetate concentration.

Mobile phase—Prepare a mixture of *Sodium acetate solution,* acetonitrile, and 2-aminoheptane (50 : 50 : 0.5), filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Verapamil Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 500 µg per mL.

Assay preparation—Agitate containers of Oral Solution for 30 minutes on a rotating mixer, remove a 5-mL sample, and store in a clear glass vial at –70° until analyzed. At the time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL into a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 0.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the retention time for verapamil hydrochloride is about 4.8 minutes, and the relative standard deviation for replicate injections is not more than 0.7%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in the volume of Oral Solution taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Verapamil Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Solution taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Verapamil Hydrochloride Oral Suspension, page 949 of *PF* 31(3) [May–June 2005]—See briefing under *Acetazolamide Oral Suspension.*

(CRX: C. Okeke) RTS—43131-23

In-Process Revision

Add the following:

▲Verapamil Hydrochloride Oral Suspension

» Verapamil Hydrochloride Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$). Prepare Verapamil Hydrochloride Oral Suspension 50 mg per mL as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. See also *Verapamil Hydrochloride Oral Solution*):

Verapamil Hydrochloride	5 g
Vehicle: a mixture of Vehicle for Oral Solution, *NF* (regular or sugar-free), and Vehicle for Oral Suspension, *NF* (1 : 1), or Cherry Syrup, *NF,* a sufficient quantity to make	100 mL

NOTE—~~If Cherry Syrup, *NF* is used, it becomes a solution.~~ If Tablets are used instead of bulk powder, the preparation becomes a suspension and should be labeled as such.If using Verapamil Hydrochloride Tablets, comminute to a fine powder using a suitable mortar, or add Verapamil Hydrochloride powder. Add about 40 mL of the Vehicle in small portions, and mix to obtain a uniform paste. Transfer the mortar contents, stepwise and quantitatively, to a calibrated bottle. Add the Vehicle in portions to rinse the mortar, add sufficient Vehicle to final volume, and mix well.

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

Labeling—Label it to state that it is to be well shaken before use, and to state the beyond-use date.

USP Reference standards ⟨11⟩—*USP Verapamil Hydrochloride RS.*

pH ⟨791⟩**:** between 3.8 and 4.8 (Vehicle for Oral Solution and Vehicle for Oral Suspension), and between 3.0 and 3.8 (Cherry Syrup).

Beyond-use date: 60 days after the day on which it was compounded.

Assay—

Mobile phase—Prepare a suitable filtered and degassed mixture of 0.01 M sodium acetate with a mixture of acetic acid having a concentration of 33 mL per L, acetonitrile, and 2-aminoheptane (50 : 50 : 0.5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve USP Verapamil Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of 500 µg per mL.

Assay preparation—Agitate the container of Oral Suspension for 30 minutes on a rotating mixer, remove a 5-mL sample, store in a clear glass vial at –70° until analyzed. At time of analysis, remove the sample from the freezer, allow it to reach room temperature, and mix on a vortex mixer for 30 seconds. Pipet 1.0 mL of the sample solution into a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 25-cm analytical column that contains 5-µm packing L1. The flow rate is about 0.5 mL per minute. Chromatograph the *Standard preparation,* and record the

peak responses as directed for *Procedure:* the retention time for verapamil hydrochloride is about 4.8 minutes, and the relative standard deviation for replicate injections is not more than 0.7%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in the volume of Oral Suspension taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Verapamil Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP30*

BRIEFING

Verapamil Hydrochloride Tablets, *USP 29* page 2246—See briefing under *Verapamil Hydrochloride Injection.*

(MD-CV: D. Bempong) RTS—43397-1

Change to read:

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

▲*USP Verapamil Related Compound E RS. USP Verapamil Related Compound F RS.*▲*USP30*

Change to read:

Related compounds—

Aqueous solvent mixture, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the test for *Chromatographic purity* under *Verapamil Hydrochloride.*

Standard solution—Dissolve accurately weighed quantities of USP Verapamil Hydrochloride RS, USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

▲USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS▲*USP30*
in *Mobile phase* to obtain a solution having known concentrations of about 1.6 mg of USP Verapamil Hydrochloride RS per mL and 0.0048 mg each of USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

▲USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS▲*USP30*
per mL.

Test solution—Use the *Assay preparation.*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than four times the retention time for verapamil. Record the chromatograms, and measure all of the peak responses. [NOTE—The retention times are about 0.4 for ~~3,4-dimethoxybenzyl alcohol~~

▲verapamil related compound F,▲*USP30*
0.5 for verapamil related compound A, 0.7 for ~~3,4-dimethoxybenzaldehyde~~

▲verapamil related compound E,▲*USP30*
and 1.0 for verapamil.] Calculate the quantity, in mg, of each individual impurity in each mL of the portion of Tablets taken by the formula:

$$25C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of the appropriate impurity in the *Standard solution;* and r_U and r_S are the peak responses of the appropriate impurity obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.3% of any specified impurity is found; and the sum of all impurities is not more than 1.0%.

BRIEFING

Zidovudine Tablets, *USP 29* page 2284. It is proposed to clarify the impurity levels in the test for *Related compounds* to be consistent with the terminology preferred in drug product application approvals and in the ICH Q3B (R) guideline. This proposed revision is intended to eliminate the possibility that a specified impurity controlled at levels higher than the present limit of 0.2% might be unintentionally restricted to the lower limit due to the way the limit is worded in the current monograph. In addition, the relative

In-Process Revision

response factor in the formula in the test for *Related compounds* has been reformatted in accordance with the recent USP policy as published on page 691 of *PF* 31(3) [May–June 2005].

(MD-AA: B. Davani) RTS—43062-1; 43080-1

Change to read:

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

▲*USP Zidovudine Related Compound B RS. USP Zidovudine Related Compound C RS.*▲*USP30*

Change to read:

Related compounds—

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

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

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

~~$100F(r_i / r_s)$~~

▲$100/F\ (r_i / r_S)$▲*USP30*

in which F is the relative response factor and is equal to ~~0.59~~

▲1.7▲*USP30*
for ~~any peak with a relative retention time of 0.17,~~

▲zidovudine related compound C,▲*USP30*
and is equal to 1.00 for all other peaks; r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for zidovudine obtained from the *Standard solution:* not more than 1.5% of ~~an impurity with a relative retention time of 0.17~~

▲zidovudine related compound C▲*USP30*
is found; not more than 0.2% of any other

▲individual unidentified▲*USP30*
impurity is found; and not more than 2.0% of total impurities is found.

Change to read:

Assay—

Mobile phase—Dissolve 3.0 g of sodium acetate and 1.3 g of sodium 1-octanesulfonate in 900 mL of water. Add 90 mL of methanol and 40 mL of acetonitrile, and mix. Adjust with glacial acetic acid to a pH of 5.3, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

▲*Zidovudine related compound B standard stock solution*—Dissolve an accurately weighed quantity of USP Zidovudine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Zidovudine related compound C standard stock solution—Dissolve by sonicating for about 15 minutes, an accurately weighed quantity of USP Zidovudine Related Compound C RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.2 mg per mL.▲*USP30*

Standard preparation—~~Dissolve an accurately weighed quantity of USP Zidovudine RS in a volume of methanol, equivalent to not more than 1.2% of the total flask volume, dilute with water to volume, and mix to obtain a final solution having a known concentration of about 0.12 mg per mL.~~

▲Transfer about 30 mg of USP Zidovudine RS, accurately weighed, to a 250-mL volumetric flask, and dissolve in 3.0 mL of methanol. Add 2.5 mL of *Zidovudine related compound B standard stock solution,* 5.0 mL of *Zidovudine related compound C standard stock solution,* and dilute with water to volume. This solution contains zidovudine, zidovudine related compound B, and zidovudine related compound C at concentrations of about 0.12 mg per mL, 0.001 mg per mL, and 0.004 mg per mL, respectively.▲*USP30*

Assay preparation—Transfer a counted number of Tablets, equivalent to 1500 mg of zidovudine, to a 500-mL volumetric flask. Add about 50 mL of water, and shake by mechanical means for 30 minutes to disperse the Tablets. Add about 150 mL of methanol, and sonicate for 10 minutes. Dilute with water to volume, and mix. Pipet 4.0 mL into a 100-mL volumetric flask, and dilute with water to volume. Mix, and pass a portion of the solution through a suitable nylon filter, discarding the first 2 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 265-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:*

▲the relative retention times are about 0.17 for zidovudine related compound C (thymine), 1.0 for zidovudine, and 1.2 for zidovudine related compound B;▲*USP30*
the resolution, *R,* between zidovudine and ~~a peak having a relative retention time of about 1.2~~

▲zidovudine related compound B▲*USP30*

is not less than 2.5; the tailing factor for the zidovudine peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of zidovudine ($C_{10}H_{13}N_5O_4$) in each Tablet taken by the formula:

$$12{,}500(C/N)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Zidovudine RS in the *Standard preparation; N* is the number of Tablets taken for the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Ginger, *USP 29* page 2331; **Powdered Ginger,** *USP 29* page 2332; **Ginger Capsules,** *USP 29* page 2333; **Ginger Tincture,** *USP 29* page 2333. Proposed revisions that affect this monograph and may affect its dosage forms include the following: adding a storage temperature to the *Packaging and storage* section; adding a new USP Reference Standard, which by cross reference is used in the *Identification, Alcohol soluble extractives,* and *Limit of shogaols* tests; making the microbial limits consistent with those in *Microbial Attributes of Nonsterile Nutritional and Dietary Supplements* ⟨2023⟩; and revising the *System suitability solution* and relevant subsections in the test for *Content of gingerols and gingerdiones* to include the new USP Reference Standard, USP Ginger Constituent Mixture RS. Minor editorial changes have also been made.

(DSB: M. Sharaf) RTS—43244-1

In-Process Revision

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light and moisture,

▲and store at room temperature.▲*USP30*

Change to read:

Labeling—The label states the Latin binominal ~~name~~

▲▲*USP30*

and, following the official name, the part of the plant contained in the article.

Change to read:

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

▲*USP Ginger Constituent Mixture RS.*▲*USP30*
USP Powdered Ginger RS.

Change to read:

Identification—

A: Pulverize about 5 g of Ginger. To about 1 g of the pulverized Ginger add 5 mL of dilute acetic acid, prepared by diluting 1 part of glacial acetic acid with 1 part of water, and shake for 15 minutes. Filter, and add a few drops of ammonium oxalate TS to the filtrate: not more than a slight turbidity is produced.

B: Dissolve about 50 mg of the residue obtained in the test for *Alcohol-soluble extractives* in 25 mL of water, and extract this solution with two 15-mL portions of ether. Combine the ether extracts, and evaporate in a porcelain dish. To the residue so obtained, add 5 mL of sulfuric acid solution (7.5 in 10.0) and about 5 mg of vanillin. Allow to stand for 15 minutes, and add an equal volume of water: the solution turns azure blue.

C: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—
Adsorbent: 0.50-mm layer of chromatographic silica gel mixture.

Test solution—Pulverize about 5 g of Ginger. Transfer about 0.2 g of pulverized sample to a test tube, add 5 mL of methanol, shake for 30 minutes, and centrifuge. Apply the supernatant to the plate.

~~*Standard solution*~~

▲*Standard solution 1*—▲*USP30*
Proceed as directed for the *Test solution,* except to use 0.2 g of USP Powdered Ginger RS.

▲*Standard solution 2*—Use the *System suitability solution,* prepared as directed in the test for *Content of gingerols and gingerdiones.*▲*USP30*
Application volume: 20 µL

▲for the *Test solution* and *Standard solution 1;* 40 µL for *Standard solution 2.*▲*USP30*
Developing solvent system: a mixture of ether and hexanes (7 : 3).

▲*Spray reagent*—Prepare a solution of 10% sulfuric acid in alcohol.▲*USP30*
Procedure—Proceed as directed in the chapter.

▲Examine the plate under UV light at 254 nm. Spray the plate with *Spray reagent,* heat between 100° and 105° for 10 minutes, and examine under daylight. The chromatogram of the *Test solution* exhibits a▲*USP30*
spot due to gingerols occurs at an R_F value of about 0.2 and a spot of shogaols may occur at an R_F value of about 0.4,

▲corresponding to those shown in the chromatogram from *Standard solution 2.*▲*USP30*

[NOTE—The chromatograms of the *Test solution* and ~~the *Standard solution*~~

▲*Standard solution 1*▲USP30
may exhibit other spots in the upper region and at the origin of the plate.]

Change to read:

Microbial enumeration ⟨2021⟩—The total bacterial count does not exceed ~~10,000 cfu per g. The total combined molds and yeasts count does not exceed 100 cfu per g, and it meets the requirements of the tests for absence of *Salmonella* species, *Escherichia coli*, and *Staphylococcus aureus*~~

▲10^5 cfu per g. The total combined molds and yeasts count does not exceed 10^3 cfu per g, the bile-tolerant Gram-negative bacteria count does not exceed 10^3 cfu per g, and it meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.▲USP30

Change to read:

Alcohol-soluble extractives, *Method 2* ⟨561⟩—~~Evaporate~~

▲Collect the filtrate in a 100-mL volumetric flask, dilute with alcohol to volume, and mix. Evaporate 50 mL of▲USP30
the filtrate at a temperature not exceeding 90°: not less than 4.5%

▲residue▲USP30
is found. Save the residue for use in *Identification* test *B* and

▲the remaining volume of the filtrate for▲USP30
the tests for *Limit of shogaols* and *Content of gingerols and gingerdiones*.

Change to read:

Limit of shogaols—From the chromatograms obtained in the test for *Content of gingerols and gingerdiones*, calculate the sum of the peak responses due to shogaols, occurring at about the following retention times, relative to 1.0 for capsaicin: ~~1.86 for 6-shogaol, 4.22 for 8-shogaol and 5.76 for 10-shogaol. Calculate the percentage of shogaols, *B*, in the portion of the residue from the test for *Alcohol-soluble extractives* taken for the *Test preparation* in the test for *Content of gingerols and gingerdiones*~~

▲1.9 for 6-shogaol, 4.2 for 8-shogaol, and 5.8 for 10-shogaol. Calculate the percentage of shogaols▲USP30
by the formula:

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

▲$10(C/W)(r_U/r_S)$▲USP30

in which C is the concentration, in mg per mL, of USP Capsaicin RS in the *Standard preparation,* prepared as directed in the test for *Content of gingerols and gingerdiones; W* is the weight, ~~in mg, of the residue from the test for *Alcohol-soluble extractives* taken for the *Test preparation*~~

▲in g, of Ginger used in the test for *Alcohol-soluble extractives;*▲USP30
r_U is the sum of the peak responses due to shogaols as calculated above; and r_S is the peak response due to capsaicin obtained from the *Standard preparation:* ~~not more than 4.0% is found. Calculate the percentage of shogaols in the Ginger rhizome by the formula:~~

~~$EB/100$~~

~~in which *E* is the percentage of alcohol-soluble extractive found in the test for *Alcohol-soluble extractives;* and *B* is as defined above:~~

▲▲USP30
not more than 0.18% of shogaols is found.

Change to read:

Content of gingerols and gingerdiones—

▲*Solution A*—Prepare a filtered and degassed mixture of acetonitrile, dilute phosphoric acid (1 in 1000), and methanol (55 : 44 : 1).

Solution B—Use filtered and degassed acetonitrile.▲USP30
Mobile phase— ~~Prepare a filtered and degassed mixture of acetonitrile, dilute phosphoric acid (1 in 1000), and methanol (55 : 44 : 1).~~

▲Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.*▲USP30
Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard preparation—Dissolve an accurately weighed quantity of USP Capsaicin RS in methanol to obtain a solution having a known concentration of about ~~0.25 mg per mL.~~

▲0.1 mg per mL.▲USP30
Test preparation— ~~Transfer about 50 mg, accurately weighed, of the residue (equivalent to about 9 mg of gingerols) retained from the test for *Alcohol-soluble extractives*. to a 10-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.~~

▲Use the filtrate retained from the test for *Alcohol-soluble extractives.*▲USP30
System suitability solution— ~~Mix 1.0 mL of the *Standard preparation* with 1.0 mL of the *Test preparation.*~~

▲Reconstitute the content of 1 vial of USP Ginger Constituent Mixture RS in 1 mL of the *Standard preparation.*▲USP30

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 282-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute.

In-Process Revision

▲The chromatograph is programmed as follows.

Time	*Solution A* (%)	*Solution B* (%)	Elution
Not less than seven times the retention of capsaicin	100	0	isocratic
2 minutes	0	100	linear gradient
10 minutes	0	100	isocratic
2 minutes	100	0	linear gradient
15 minutes	100	0	isocratic

▲*USP30*
Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for 6-gingerol, 1.0 for capsaicin, ~~1.51 for 8-gingerol A, 2.21 for 8-gingerol B, 2.46 for 6-gingerdiol, 2.60 for 6-gingerdione, 3.35 for 10-gingerol, and 5.16 for 8-gingerdione; and the resolution, *R,* between 6-gingerol and capsaicin is not less than 1.0.~~

▲and 1.9 for 6-shogaol; the resolution, *R,* between the 6-gingerol and the capsaicin peaks is not less than 3.0 and between the capsaicin and 6-shogaol peaks is not less than 10.0; and the tailing factors for the 6-gingerol, the capsaicin, and the 6-shogaol peaks are not more than 2.0.▲*USP30*
Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes ~~(about 10 µL)~~

▲(about 25 µL)▲*USP30*
of the *Standard preparation,*

▲the *System suitability solution,*▲*USP30*
and the *Test preparation* into the chromatograph, ~~and allow the *Test preparation* to elute for not less than seven times the retention time of capsaicin. Record the chromatograms, and measure all of the peak responses.~~

▲and proceed as directed for *Chromatographic system.* Record the chromatograms, and measure all of the peak responses. Calculate the sum of the peak responses due to gingerols and gingerdiones, occurring at about the following retention times, relative to 1.0 for capsaicin: 0.8 for 6-gingerol, 1.5 for 8-gingerol A, 2.2 for 8-gingerol B, 2.5 for 6-gingerdiol, 2.6 for 6-gingerdione, 3.4 for 10-gingerol, and 5.2 for 8-gingerdione.▲*USP30*

Calculate the percentage of gingerols and gingerdiones ~~*A* in the portion of the residue from the test for *Alcohol-soluble extractives* taken for the *Test preparation* by the formula:~~

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

▲by the formula:

$$10(C / W)(r_U / r_S)_{▲USP30}$$

in which *C* is the concentration, in mg per mL, of USP Capsaicin RS in the *Standard preparation; W* is the weight, ~~in mg, of the residue from the test for *Alcohol-soluble extractives* taken for the *Test preparation;*~~

▲in g, of Ginger used in the test for *Alcohol-soluble extractives;*▲*USP30*
r_U is the sum of the peak responses due to gingerols and gingerdiones as calculated above; and r_S is the capsaicin peak response obtained from the *Standard preparation:* ~~not less than 18% of gingerols and gingerdiones is found. Calculate the percentage of gingerols and gingerdiones in the Ginger rhizome by the formula:~~

~~$EA / 100$,~~

~~in which *E* is the percentage of alcohol-soluble extractives obtained in the test for *Alcohol-soluble extractives;* and *A* is as defined above:~~

▲▲*USP30*
not less than 0.8% is found.

BRIEFING

Powdered Ginger, *USP 29* page 2332—See briefing under *Ginger.*

(DSB: M. Sharaf) RTS—43244-2

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light and moisture,

▲and store at controlled room temperature.▲*USP30*

Change to read:

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

▲*USP Ginger Constituent Mixture RS.*▲*USP30*
USP Powdered Ginger RS.

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BRIEFING

Ginger Capsules, *USP 29* page 2333—See briefing under *Ginger.*

(DSB: M. Sharaf) RTS—43244-3

Change to read:

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

▲*USP Ginger Constituent Mixture RS.*▲*USP30*
USP Powdered Ginger RS.

Change to read:

Content of gingerols, gingerdiones, and shogaols—

Mobile phase, Standard preparation, System suitability solution, and *Chromatographic system*—Proceed as directed in the test for *Content of gingerols and gingerdiones* under *Ginger.*

Test preparation— ~~Carefully open not fewer than 20 Capsules, and transfer about 1.0 g of the powder, accurately weighed,~~

▲Mix and finely powder the content of not fewer than 20 Capsules, and transfer an accurately weighed amount of the powder, equivalent to about 2.0 g of powdered ginger,▲*USP30*
to a glass-stoppered conical flask. Add 50 mL of alcohol, insert a stopper into the flask, and macerate for 24 hours, shaking frequently during the first 8 hours, and then allowing to stand for 18 hours. Filter, and ~~evaporate the solvent to dryness in a vacuum. Quantitatively transfer the contents with the aid of methanol to a 10-mL volumetric flask, add methanol to volume, and mix.~~

▲use the filtrate.▲*USP30*

Procedure—Proceed as directed in the test for *Content of gingerols and gingerdiones* under *Ginger.* Calculate the amounts, in mg, of gingerols, gingerdiones, and shogaols in the portion of the Capsules taken by the formula:

~~$10C(r_U/r_S)$~~

▲$50C(r_U/r_S)$▲*USP30*

in which C is the concentration, in mg per mL, of USP Capsaicin RS in the *Standard preparation;* r_U is the sum of peak responses for gingerols, gingerdiones, and shogaols; and r_S is the peak response for capsaicin obtained from the *Standard preparation.* Calculate the amount ~~in mg, of 6-gingerol in the portion of Capsules taken by the formula:~~

~~$10C(r_U/r_S)$~~

▲(G_0), in mg, of 6-gingerol in each Capsule by the formula:

$$50C/W(r_U/r_S)A_{▲USP30}$$

in which r_U is the peak response for 6-gingerol obtained from the *Test preparation;*

▲W is the weight of powdered ginger, in g, used in the *Test preparation; A* is the average Capsule fill weight, in g;▲*USP30* and the other terms are as defined above.

BRIEFING

Ginger Tincture, *USP 29* page 2333—See briefing under *Ginger.*

(DSB: M. Sharaf) RTS—43377-1

Change to read:

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

▲*USP Ginger Constituent Mixture RS.*▲*USP30*

Change to read:

Thin-layer chromatographic identification test ⟨201⟩—

Test solution—Use the Tincture.

Developing solvent system: a mixture of ethyl ether and ~~solvent hexane~~

▲hexanes▲*USP30*
(7 : 3).

Procedure—Proceed as directed ~~in the chapter, except to use the *Test solution* only: the chromatogram obtained for the *Test solution* exhibits two clearly separated, intense spots from the gingerols at R_F values of about 0.2 and 0.4.~~

▲in *Identification* test *C* under *Ginger.*▲*USP30*

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Change to read:

Microbial enumeration ⟨2021⟩—~~It meets the requirements of the tests for absence of *Salmonella* species, *Escherichia coli,* and *Staphylococcus aureus*. The total aerobic microbial count does not exceed 300 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.~~

▲The total aerobic microbial count does not exceed 10^4 cfu per g, and the total combined molds and yeasts count does not exceed 10^3 cfu per g.▲*USP30*

Change to read:

Content of gingerols—
Mobile phase, Standard preparation, ~~and~~

▲▲*USP30*
System suitability solution,

▲and*Chromatographic system*▲*USP30*
—Proceed as directed for the *Content of gingerols and gingerdiones* test under *Ginger*.
Test preparation—Use the Tincture.
~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—Proceed as directed for the *Content of gingerols and gingerdiones* test under *Ginger*. , except that the relative retention times are about 0.8 for 6-gingerol, 1.0 for capsaicin, 1.64 for 8-gingerol, 2.04 for 6-shogaol, and 3.95 for 10-gingerol; and the resolution, *R,* between 6-gingerol and capsaicin is not less than 5.0.~~

▲▲*USP30*
Procedure—Proceed as directed for the *Content of gingerols and gingerdiones* test under *Ginger*. Calculate the percentage of gingerols in the Tincture by the formula:

$$0.1C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Capsaicin RS in the *Standard preparation;* r_U is the sum of the peak responses for gingerols obtained from the *Test preparation;* and r_S is the capsaicin peak response obtained from the *Standard preparation*.

BRIEFING

Ginkgo, *USP 29* page 2334. It is proposed to make the following revisions: (1) in the *Definition,* to delete ginkgolide J because of the difficulty of its identification in sample chromatograms; (2) in *Packaging and storage,* to add storage conditions; and (3) in *Identification* test *A,* to replace chlorogenic acid with USP Chlorogenic Acid RS. In the test for *Microbial enumeration,* it is proposed to (1) revise microbial limits on the basis of the limits specified in USP general information chapter ⟨2023⟩, (2) add a test for bile-tolerant Gram-negative bacteria, and (3) delete the test for absence of *Staphylococcus aureus.* Also, in the test for *Content of terpene lactones* it is proposed to (1) revise the procedure for the preparation of the *Standard solutions,* (2) add a clean-up step to the preparation of the *Test solution* to remove interferences due to other components in the plant material, and (3) revise the elution table in the *Chromatographic system.* In addition, editorial style changes have been made.

(DSB: M. Sharaf) RTS—43416-1

Change to read:

» Ginkgo consists of the dried leaf of *Ginkgo biloba* Linné (Fam. Ginkgoaceae). It contains not less than 0.5 percent of flavonoids, calculated as flavonol glycosides, with a mean molecular mass of 756.7; and not less than 0.1 percent of terpene lactones, calculated as the sum of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$),

▲and▲*USP30*
ginkgolide C ($C_{20}H_{24}O_{11}$), ~~and ginkgolide J ($C_{20}H_{24}O_{10}$),~~

▲▲*USP30*
both on the dried basis.

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light and moisture,

▲and store at room temperature.▲*USP30*

Change to read:

USP Reference standards ⟨11⟩—

▲*USP Chlorogenic Acid RS.*▲*USP30*
USP Ginkgo Terpene Lactones RS. USP Quercetin RS. USP Rutin RS.

Change to read:

Thin-layer chromatographic identification test ⟨201⟩

TEST FOR FLAVONOIDS—
Test solution—Transfer 0.2 g of finely powdered Ginkgo to a test tube, add 10 mL of methanol, and heat on a water bath at 65° for 10 minutes. Shake the mixture frequently during the heating. Allow to cool to room temperature, filter, concentrate the filtrate on a hot water bath at 60° to half its volume, and cool.
Standard solution: a solution of USP Rutin RS and ~~chlorogenic acid~~

▲USP Chlorogenic Acid RS▲*USP30*
in methanol containing about 0.6 mg per mL and 0.2 mg per mL, respectively.
Developing solvent system: a mixture of ethyl acetate, water, anhydrous formic acid, and glacial acetic acid (67.5 : 17.5 : 7.5 : 7.5).
Spray reagent 1: a solution of diphenyl boryloxyethylamine in methanol containing 10 mg per mL.
Spray reagent 2: a solution of polyethylene glycol 400 in alcohol containing 50 mg per mL.

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Procedure— Apply separately, as bands, 20 µL each of the *Test solution* and the *Standard solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel, and allow the bands to dry. Develop the chromatograms in the *Developing solvent system* until the solvent front has moved about 10 cm from the origin. Remove the plate from the chromatographic chamber, and dry it in a circulating air oven at 100° to 105°. Immediately spray the hot plate with *Spray reagent 1,* and then spray with *Spray reagent 2.* Allow the plate to cool for 30 minutes, and examine it under long-wavelength UV light. The chromatogram of the *Standard solution* shows in its middle part, with increasing R_F values, the yellowish-brown fluorescent zone due to rutin and a light blue fluorescent zone due to chlorogenic acid. The presence of flavonol glycosides in the *Test solution* is shown by three yellowish-brown to green fluorescent zones, and slightly above a blue to green fluorescent zone below the zone due to rutin, a light blue fluorescent zone appears in the same location as that due to chlorogenic acid, as well as two greenish-brown to yellow fluorescent zones, located above. Other, less intense zones may be seen in the chromatogram of the *Test solution*.

TEST FOR TERPENE LACTONES—

Adsorbent: a 0.50-mm layer of chromatographic silica gel.

Test solution—Transfer 0.8 g of the dried test specimen retained from the test for *Loss on drying* to a suitable flask fitted with a reflux condenser, add 5 mL of a mixture of methanol and water (1 in 10), and heat under reflux for 15 minutes. While still hot, filter the contents of the flask with the aid of a vacuum. Rinse the flask and the test specimen with 2 mL of a mixture of methanol and water (2 in 100), and transfer the rinsings to the filter with the aid of a vacuum. Return the powdered Ginkgo to the flask, add 4 mL of a mixture of methanol and water (1 in 10), and repeat the extraction. After filtration, wash the residue of powdered Ginkgo twice with 1.5 mL of a mixture of methanol and water (2 in 100). Combine the filtrates, and transfer the combined filtrates (about 12 mL) to a solid-phase extraction column containing L1 packing with a sorbent mass-to-column volume ratio of 1000 mg per 3 mL or equivalent. [NOTE—Initially pass 10 mL of methanol and then 10 mL of a mixture of methanol and water (2 in 100) through the column to condition it. Do not allow the column to dry.] Collect the eluate at the rate of 1 drop per second. Evaporate the eluate to dryness, and dissolve the residue in 2 mL of methanol.

Developing solvent system: a mixture of ethyl acetate and methyl acetate (1 : 1).

Procedure—Prepare a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with *Adsorbent* as follows. Immerse the plate for 20 seconds in a solution of sodium acetate in methanol containing 1 g per 10 mL. Allow the excess coating liquid to drip from the plate, and dry in a forced-air oven at 70° for 30 minutes. Cool in a desiccator. Separately apply several 10-µL spots of the test solution to the impregnated plate, and allow the spots to air-dry. Develop the plate in the *Developing solvent system* in a chromatographic chamber without filter paper attached to the walls until the solvent front travels about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and dry in an oven at 105° for 15 minutes. Spray the plate with acetic anhydride, and heat in an oven at 140° for 25 minutes. Cool, and examine the plate under short- and long-wavelength UV light. [NOTE—The compounds present in high concentrations may be visible in daylight as light brown spots.] The presence of terpene lactones in the test solution is shown by the following spots detected in the chromatogram at both the short and long wavelengths: bilobalide (R_F about 0.75), ginkgolide A (R_F about 0.68), ginkgolide B (R_F about 0.52), ginkgolide J (R_F about 0.39), and ginkgolide C (R_F about 0.27). Other spots of varying intensities also may be seen.

Change to read:

Microbial enumeration ⟨2021⟩—It meets the requirements of the tests for absence of *Salmonella* species

▲and▲*USP30*
Escherichia coli. ~~and *Staphylococcus aureus.*~~

▲▲*USP30*
The total aerobic bacterial count does not exceed ~~10,000~~

▲10^5▲*USP30*
cfu per g, the total combined molds and yeasts count does not exceed ~~100~~

▲10^3▲*USP30*
cfu per g,

▲and the bile-tolerant Gram-negative bacteria does not exceed 10^3 cfu per g.▲*USP30*

Change to read:

Content of terpene lactones~~—~~

Solvent—Prepare a mixture of methanol and water (9 : 1).

▲*Buffer solution*—Dissolve 1.19 g of dibasic sodium phosphate and 8.25 g of monobasic potassium phosphate in 1000 mL of water, and adjust to a pH of about 5.8.

Diluent—prepare a mixture of methanol and water (1 : 1).▲*USP30*

Solution A—Use filtered and degassed water.

Solution B—Use filtered and degassed methanol.

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

Standard solutions—Dissolve accurately weighed quantities of USP Ginkgo Terpene Lactones RS in ~~methanol~~

▲*Diluent,*▲*USP30*
sonicating for a few minutes, and dilute with ~~methanol~~

▲*Diluent*▲*USP30*
to obtain solutions having known concentrations of about ~~0.5, 1, 2, 4, and 8~~

▲0.25, 0.5, 1.0, 2.0, and 4.0▲*USP30*
mg per mL. Pass through a filter having a 0.45-µm or finer porosity.

Test solution—Transfer about 2.5 g of Ginkgo, accurately weighed, to a 30-mL glass

▲centrifuge▲*USP30*
tube with screw cap and PTFE gasket. Add 10.0 mL of *Solvent*, seal the tube, and mix well on a vortex mixer. Heat in a water bath at 90° for 30 minutes. Mix the hot suspension on a vortex mixer, and repeat the heating at 90° for 30 minutes. ~~Allow to cool to room temperature, and pass through a filter having a 0.45-µm or finer porosity.~~

▲Cool, centrifuge, transfer the supernatant to a flask, and return the residue to the glass tube. Repeat the extraction two more times, each time using 10.0 mL of *Solvent.* Combine

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the extracts, allow them to cool to room temperature, and evaporate to dryness under vacuum on a water bath maintained at 50°. Add 10 mL of *Buffer solution* to the residue, and sonicate for 5 minutes. Quantitatively transfer the solution to a glass chromatographic tube filled with chromatographic siliceous earth capable of holding 20 mL of aqueous phase.* Rinse the beaker with two 5-mL portions of *Buffer solution,* and transfer the washings to the column. [NOTE—Do not exceed 20 mL of total aqueous phase or the holding capacity of the chromatographic tube.] Allow the *Buffer solution* to be absorbed into the column. After 15 minutes, elute the column with 100 mL of ethyl acetate, collect the ethyl acetate solution, and evaporate to dryness under vacuum on a water bath maintained at 50°. Dissolve the residue in 10.0 mL of *Diluent.*▲*USP30*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with an evaporative light-scattering detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 25 ± 1°. [NOTE—The parameters of the detector are adjusted to achieve the best signal-to-noise ratio, ▲according to manufacturer recommendations.]▲*USP30* The chromatograph is programmed as follows. Chromatograph the *Standard solutions,* and record the peak responses as directed for *Procedure:* the chromatograms obtained are similar to the Reference Chromatogram provided with USP Ginkgo Terpene Lactones RS; and the relative standard deviation determined from the bilobalide peak for replicate injections is not more than 2.0%.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–23	75→52	25→48	linear gradient
~~23–25~~	~~52→25~~	~~48→75~~	~~linear gradient~~
▲23–28▲*USP30*	▲52▲*USP30*	▲48▲*USP30*	▲isocratic▲*USP30*
~~25–30~~	~~25~~	~~75~~	~~isocratic~~
▲28–30▲*USP30*	▲52→25▲*USP30*	▲48→75▲*USP30*	▲linear gradient▲*USP30*
30–35	25→10	75→90	linear gradient
35–40	10→75	90→25	linear gradient
40–50	75	25	isocratic

Procedure—Separately inject equal volumes (about 15 µL) of each of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and identify the peaks of the relevant analytes in the chromatogram of the *Standard solution* by comparison with the Reference Chromatogram. Measure the areas of the analyte peaks. Plot the logarithms of the relevant peak responses versus logarithms of concentrations, in mg per mL, of each analyte obtained from the *Standard solutions*, and determine the regression line using a least-squares analysis. The correlation coefficient for the regression line is not less than 0.995. From the graphs so obtained, determine the concentration, *C*, in mg per mL, of the relevant analyte in the *Test solution*. Separately calculate the percentages of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), ▲and▲*USP30* ginkgolide C ($C_{20}H_{24}O_{11}$)~~, and ginkgolide J ($C_{20}H_{24}O_{10}$)~~ ▲▲*USP30* in the portion of Ginkgo taken by the formula:

$$1000(C/W)$$

in which *W* is the weight, in mg, of Ginkgo taken to prepare the *Test solution.* Calculate the total percentage of terpene lactones in the portion of Ginkgo taken by adding the percentages calculated for each analyte.

* Suitable commercially available material is Extrelut® NT 20 from E Merck Science.

BRIEFING

Powdered Ginkgo Extract, page 2233 of *PF* 27(2) [Mar.–Apr. 2001]; **Gingko Capsules,** page 2238 of *PF* 27(2) [Mar.–Apr. 2001]; **Gingko Tablets,** page 2240 of *PF* 27(2) [Mar.–Apr. 2001]. In accordance with the recommendations of the USP AMB Expert Committee, it is proposed to add a limit for *Microbial enumeration.* It is also proposed to add storage conditions to *Packing and storage,* to add an *Identification* test *B,* and to revise the test for *Limit of ginkgolic acids* as follows: decrease the concentration of the *Standard solution* to correspond to the expected *Test solution* concentration; use a shorter column with smaller particle size (Zorbax XBD-C8, 4.6 mm × 5.0 cm, 3.5 µm) to increase the peak efficiency; shorten the *Mobile phase* gradient proportionally to the column length, which leads to a shorter run time; replace trifluoroacetic acid with phosphoric acid in preparation of *Solution A* and *Solution B* to decrease baseline noise; change the extraction solvent used in preparation of the *Test solution* from 100% methanol to a mixture of methanol and water (8 : 2) to reduce the solvent effect; and increase the injection volume in the *Procedure* to increase peak height. Also, in the *Chromatographic system* section, it is proposed to increase the column temperature to 35° and to add a *Note* recommending washing of the column if peak shape deterioration is observed with multiple injections. In the test for *Content of terpene lactones* it is proposed to add a clean-up step in the

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preparation of the *Test solution* to remove interferences due to other components in the extract. In addition, other revisions have been proposed, and editorial style changes have been made.

(DSB: M. Sharaf) RTS—43433-1

Add the following:

▲Powdered Ginkgo Extract

» Powdered Ginkgo Extract is prepared from dried and comminuted leaves of Ginkgo extracted with an acetone–water mixture or other suitable solvents. The ratio of the crude plant material to Powdered Extract is between 35 : 1 and 67 : 1. It contains not less than 22.0 percent and not more than 27.0 percent of ~~flavonoids, calculated as flavonol glycosides, with a mean molecular weight of 756.7, calculated as the sum of quercetin, kaempferol, and isorhamnetin glycosides.~~ flavonoids, calculated as flavonol glycosides, with a mean molecular mass of 756.7. It contains not less than ~~5.4 6.0~~ 5.4 percent and not more than ~~6.6~~ 12.0 percent of terpene lactones, consisting of between ~~2.6 2.9~~ 2.6 percent and ~~3.2~~ 5.8 percent of bilobalide ($C_{15}H_{18}O_8$) and between ~~2.8 3.0~~ 2.8 percent and ~~3.4~~ 6.2 percent of ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), ~~and~~ and ginkgolide C ($C_{20}H_{24}O_{11}$).~~, and ginkgolide J ($C_{20}H_{24}O_{10}$).~~

Packaging and storage—Preserve in tight, light-resistant containers, protected from moisture, and store at controlled room temperature.

Labeling—The label states the Latin binomial ~~name~~ and, following the official name, the part of the plant from which the article was prepared. The label also indicates the content of flavonol glycosides and of terpene lactones, the extracting solvent used for preparation, and the ratio of the starting crude plant material to the Powdered Extract.

USP Reference standards ⟨11⟩— *USP Chlorogenic Acid RS. USP Ginkgo Terpene Lactones RS. USP Ginkgolic Acids RS.* ~~*USP Isorhamnetin RS. USP Kaempferol RS.*~~ *USP Quercetin RS. USP Rutin RS.*

~~**Thin-layer chromatographic identification test —**~~**Identification—**

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

Adsorbent: 0.5-mm layer of chromatographic silica gel mixture.

Test solution—Dissolve about 50 mg of Powdered Extract, accurately weighed, in 10 mL of a mixture of methanol and water (8 : 2). Apply 20 µL.

Standard solution—Prepare a solution of USP Rutin RS and ~~chlorogenic acid~~ USP Chlorogenic Acid RS in methanol containing 0.3 mg per mL and 0.1 mg per mL, respectively. Apply 10 µL.

Developing solvent system: a mixture of ethyl acetate, water, glacial acetic acid, and anhydrous formic acid (67.5 : 17.5 : 7.5 : 7.5).

Spray reagent 1—Prepare a solution of 2-aminoethyl diphenylborinate in methanol containing 10 mg per mL.

Spray reagent 2—Prepare a solution of polyethylene glycol 4000 in methanol containing 50 mg per mL.

Procedure—Proceed as directed in the chapter, except to dry the plate between 100° and 105°, spray with *Spray reagent 1* while the plate is still warm, and then spray with *Spray reagent 2*. After about 30 minutes, examine the plate under UV light at 365 nm: the chromatogram of the *Stan-*

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dard solution exhibits a yellow-brown fluorescent zone due to rutin in the lower section and a light blue fluorescent zone due to chlorogenic acid in the middle section. The chromatogram of the *Test solution* exhibits three yellow-brown to greenish fluorescent zones at R_F values below that for the rutin zone in the chromatogram of the *Standard solution;* a green-blue fluorescent zone at an R_F value just above that for the rutin zone in the chromatogram of the *Standard solution;* an intense, light blue fluorescent zone at an R_F value about equal to that of the chlorogenic acid zone in the chromatogram of the *Standard solution;* and two yellow-brown to greenish fluorescent zones in the upper third of the plate. Other, less intense zones may be observed in the chromatogram of the *Test solution.*

B: Proceed as directed in the test for *Content of flavonol glycosides:* the retention times of the peaks for quercetin, isorhamnetin, and kaempferol in the chromatogram of the *Test solution* correspond to those in the chromatogram of the *Standard solution;* the peak for kaempferol is between 0.8 and 1.2 times the size of the quercetin peak; and the peak for isorhamnetin is not less than 0.1 times the size of the quercetin peak.

Microbial enumeration ⟨2021⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic bacterial count does not exceed 10^4 cfu per g, and the total combined molds and yeasts count does not exceed 10^3 cfu per g.

Loss on drying ⟨731⟩—Dry about 1.0 g of Powdered Extract, accurately weighed, at 105° for 2 hours: it loses not more than 5.0% of its weight.

Pesticide residues ⟨561⟩: meets the requirements.

Limit of ginkgolic acids—

Solution A—~~Prepare a mixture of water, acetonitrile, and phosphoric acid (70 : 30 : 0.3), and trifluoroacetic acid (1000 : 1).~~ Prepare a solution of 0.01% phosphoric acid in water.

Solution B—~~Prepare a mixture of acetonitrile and phosphoric acid (100 : 0.3), trifluoroacetic acid (1000 : 1).~~ Prepare a solution of 0.01% phosphoric acid in acetonitrile.

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

Standard solution—Dissolve an accurately weighed quantity of USP Ginkgolic Acids RS in methanol, and dilute quantitatively, and stepwise if necessary, with ~~methanol~~ water to obtain a solution having a known concentration of about ~~2.5 µg/0.5 µg~~ 0.25 µg per mL of ginkgolic acids.

Test solution—Transfer about ~~1.0 g~~ 0.5 g of Powdered Extract, accurately weighed, to a ~~suitable beaker, add 10 mL of water, and stir the mixture for 5 minutes. Quantitatively transfer the mixture to a separatory funnel, and rinse the beaker with 5 mL of water, adding the washings to the separatory funnel. Extract with four 10-mL portions of ethyl acetate. Combine the extracts, wash with two 5-mL portions of water, and discard the aqueous layer. Filter the organic phase, and evaporate to dryness in vacuum, on a water bath maintained at 50°. Dissolve the residue in 2.0 mL of methanol.~~ 10-mL volumetric flask, add ~~5~~ 8 mL of methanol to dissolve, and dilute with ~~methanol~~ water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~310-nm~~ 210-nm detector and a ~~4.0-mm × 12.5-cm~~ 4.6-mm × ~~25-cm~~ 5-cm column that contains base-deactivated packing ~~L1.~~ L7.

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The column temperature is maintained at 35°. The flow rate is about ~~1.2~~ 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
~~0~~	~~100~~	~~0~~	~~equilibration~~
~~0–20~~	~~100→0~~	~~0→100~~	~~linear gradient~~
~~20–35~~	~~0~~	~~100~~	~~isocratic~~
~~35–36~~	~~0→100~~	~~100→0~~	~~linear gradient~~
~~36–41~~	~~100~~	~~0~~	~~isocratic~~
~~0–30~~ 0–6	25→10	75→90	linear gradient
~~30–35~~ 6–7	10	90	isocratic
~~35–36~~ 7–8	10→25	90→75	linear gradient
~~36–45~~ 8–10	25	75	isocratic

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* ~~the retention times of peaks for ginkgolic acids are about 30 and 32 minutes;~~ the chromatogram obtained is similar to the Reference Chromatogram provided with USP Ginkgolic Acids RS; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than ~~3.0%~~ 2.0%.[NOTE—If deterioration of peak shapes is observed, wash the column using a mixture of methanol and water (9 : 1) for 30 minutes.]

Procedure—Separately inject equal volumes (about ~~200 µL 50 µL~~ 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, identify the peaks of the relevant analytes by comparison with the Reference Chromatogram, and measure the areas for the major peaks. ~~the sum of the peak areas due to ginkgolic acids obtained from the *Test solution* is not more than that obtained from the *Standard solution* (5 µg per g).~~ Calculate the concentration, in µg per g, of each ginkgolic acid in the portion of Powdered Extract taken by the formula:

$$10P(C/W)(r_U / r_S)$$

in which P is the content, in µg per g, of the relevant ginkgolic acid in USP Ginkgolic Acids RS; C is the concentration, in mg per mL, of USP Ginkgolic Acids RS in the *Standard solution; W* is the weight, in mg, of Powdered Extract taken to prepare the *Test solution;* and r_U and r_S are the peak areas for the relevant analyte obtained from the *Test solution* and the *Standard solution*, respectively. Calculate the total amount of ginkgolic acids by adding the individual contents: the limit is 5 µg per g.

Content of flavonol glycosides—

~~*Hydrochloric acid solution*—Transfer 16.0 mL of hydrochloric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Mobile phase*—Prepare a mixture of citric acid solution (0.6 in 100), acetonitrile, and isopropyl alcohol (100 : 47 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard solution*—Dissolve an accurately weighed quantity of USP Quercetin RS in a mixture of methanol, *Hydrochloric acid solution*, and water (6 : 3 : 1) to obtain a solution having a known concentration of about 0.2 mg per mL.~~

~~*Test solution*—Transfer about 200 mg of Powdered Extract, accurately weighed, to a 50-mL volumetric flask, add 20 mL of methanol, and shake well to dissolve. Add 15 mL of *Hydrochloric acid solution* and 5 mL of water, dilute with methanol to volume, and mix. Transfer 10.0 mL of this solution to a 10-mL amber glass flask, seal the flask with a rubber seal and an aluminum cap, and heat in a hot water bath for 25 minutes. Cool the flask to room temperature.~~

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~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 370-nm detector and a 4.0-mm × 12.5-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Test solution*, and record the peak responses as directed for *Procedure:* the relative retention times for the flavonol glycosides of interest are about 1.0 for quercetin, 1.58 for kaempferol, and 1.7 for isorhamnetin. [NOTE—Isorhamnetin sometimes co-elutes with kaempferol.]~~

~~*Procedure*—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of flavonol glycosides, as *3-O*-(*2-O*-[*6-O*-(*p*-hydroxy-*trans*-cinnamoyl-RS-*β*-D-glucosyl]-α-L-rhamnosyl)-quercetin with a mean molecular weight of 756.7, in the portion of Powdered Extract taken by the formula:~~

$$2.51 \times 50CP(r_U/r_S)$$

~~in which 2.51 is the mean molecular weight conversion factor; *C* is the concentration, in mg per mL, of USP Quercetin RS in the *Standard solution; P* is the designated purity, in percentage, of USP Quercetin RS; r_U is the sum of the peak areas for quercetin, kaempferol, and isorhamnetin obtained from the chromatogram of the *Test solution;* and r_S is the peak area for quercetin obtained from the chromatogram of the *Standard solution*.~~

Extraction solvent, Mobile phase, and *Chromatographic system*—Proceed as directed in the test for *Content of flavonol glycosides* under *Ginkgo*.

Standard solutions—Transfer accurately weighed quantities of USP Quercetin RS, kaempferol, and isorhamnetin to separate volumetric flasks, dissolve each in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain *Standard solutions 1*, *2*, and *3* having known concentrations of 0.125 mg per mL, 0.125 mg per mL, and 0.03 mg per mL, respectively.

Test solution—Transfer about 0.300 g of Powdered Extract, accurately weighed, to a 250-mL flask fitted with a reflux condenser. Add 78 mL of *Extraction solvent*, and reflux on a hot water bath for 135 minutes. [NOTE—The solution will turn deep red. The color of the solution is not a definitive indication of reaction completeness.] Allow to cool at room temperature. Transfer to a 100-mL volumetric flask, add water to volume, and mix.

Procedure—Proceed as directed in the test for *Content of flavonol glycosides* under *Ginkgo*. Calculate the percentage of each flavonol glycoside in the portion of Powdered Extract taken by the formula:

~~$10M(C/W)(r_U/r_S)$~~

$$10(2.51)(C/W)(r_U/r_S)$$

in which *W* is the weight, in g, of Powdered Extract taken to prepare the *Test solution;* and the other terms are as defined therein. Calculate the total percentage of flavonol glycosides by adding the individual percentages calculated.

Content of terpene lactones—

~~*Buffer solution*—Dissolve 1.19 g of dibasic sodium phosphate and 8.25 g of monobasic potassium phosphate in 1000 mL of water, and adjust to a pH of about 5.8.~~

~~*Mobile phase*—Prepare a mixture of water, methanol, and tetrahydrofuran (70 : 20 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

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~~*Standard solution*—Dilute benzyl alcohol with *Mobile phase* to obtain a solution having a known concentration of about 0.3 mg per mL.~~

~~*Test solution*—Transfer about 120 mg of Powdered Extract, accurately weighed, to a 25-mL beaker, add 10 mL of *Buffer solution*, and dissolve by stirring. Quantitatively transfer the solution to a 30- × 150-mm glass chromatographic tube filled with 15 g of chromatographic siliceous earth. Rinse the beaker with two 5-mL portions of *Buffer solution*, and transfer the washings to the column. Allow the *Buffer solution* to drain off the column. After 15 minutes elute the column with 100 mL of ethyl acetate, collect the ethyl acetate solution, and evaporate to dryness under vacuum, on a water bath maintained at 50°. Remove the last traces of the solvent with the aid of a current of air at room temperature. Dissolve the residue in 2.5 mL of *Mobile phase*.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector, maintained at a temperature of 35°, and a 4.0-mm × 25-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution* and the *Test solution*, and record the chromatograms as directed for *Procedure*: the retention time for benzyl alcohol is between 5 and 12 minutes; the relative retention times are about 1.0 for benzyl alcohol, 1.1 for ginkgolide C, 1.3 for bilobalide, 1.6 for ginkgolide A, and 2.2 for ginkgolide B; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the quantities, in mg, of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), and ginkgolide C ($C_{20}H_{24}O_{11}$) in the portion of Powdered Extract taken by the formula:~~

~~$$2.5FCP(r_u/r_s)$$~~

~~in which F is the response factor for the relevant analyte (namely, 1.20 for bilobalide, 1.22 for ginkgolide A, 1.19 for ginkgolide B, and 1.27 for ginkgolide C, relative to 1.0 for benzyl alcohol); C is the concentration, in mg per mL, of benzyl alcohol in the *Standard solution*; P is the designated purity, in percentage, of benzyl alcohol used in the *Standard solution*; r_u is the peak area for the corresponding analyte obtained from the *Test solution*; and r_s is the peak area for benzyl alcohol obtained from the *Standard solution*. Calculate the content of total terpene lactones, in mg, in the portion of Powdered Extract taken by adding all of the quantities calculated for individual analytes.~~

~~*Solvent,*~~ *Solution A, Solution B, Mobile phase, Standard solutions, Buffer solution, Diluent,* and *Chromatographic system*—Proceed as directed in the test for *Content of terpene lactones* under *Ginkgo*.

Test solution—~~Transfer 400 mg of Powdered Extract, accurately weighed, to a round-bottom 50-mL volumetric flask, add 40.0 mL of *Solvent*, sonicate in a bath at 60° for 20 for a few minutes, allow to cool, dilute with *Solvent* to volume, and filter through a membrane having a 0.45 µm or finer porosity.~~ Transfer about 120 mg of Powdered Extract, accurately weighed, to a 25-mL beaker, and proceed as directed for *Test solution* in the test for *Content of terpene lactones* under *Ginkgo,* starting with "add 10 mL of *Buffer solution*", except to dissolve the residue in 20.0 mL of *Diluent.*

Procedure—Proceed as directed in the test for *Content of terpene lactones* under *Ginkgo*. ~~except that the correlation coefficient for the regression line is not less than 0.999.~~ Se-

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parately calculate the percentages of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), and ginkgolide C ($C_{20}H_{24}O_{11}$) ~~and ginkgolide J ($C_{20}H_{24}O_{10}$)~~ in the portion of Powdered Extract taken by the formula:

~~4000(*C/W*)~~

~~5000(*C/W*)~~

2000(*C/W*)

in which *C* is the concentration, in mg per mL, of the relevant analyte in the *Test solution;* and *W* is the weight, in mg, of Powdered Extract taken to prepare the *Test solution.* Calculate the total percentage of terpene lactones in the portion of Powdered Extract taken by adding the percentages calculated for each analyte.

Other requirements—It meets the requirements for *Residue on Evaporation, Residual Solvents,* and *Heavy Metals* under *Botanical Extracts* ⟨565⟩.▲*USP30*

BRIEFING

Ginkgo Capsules, page 2238 of *PF* 27(2) [Mar.–Apr. 2001]. It is proposed to add storage conditions to *Packaging and storage.* In the test for *Disintegration and Dissolution,* it is proposed to change the index component used in the *Procedure* from ginkgolide A to ginkgolide B, to correspond to the component used in the *Ginkgo Tablets* monograph and because ginkgolide B is less polar than ginkgolide A. See also briefing under *Powdered Ginkgo Extract.*

(DSB: M. Sharaf) RTS—43478-1

Add the following:

▲Ginkgo Capsules

» Ginkgo Capsules are prepared with Powdered Ginkgo Extract and contain, in the labeled amount of Powdered Extract, not less than ~~20.0~~ 22.0 percent and not more than ~~30.0~~ 27.0 percent of flavonol glycosides and not less than 5.4 percent and not more than ~~13.2~~ 12.0 percent of terpene lactones, calculated as the sum of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), and ginkgolide C ($C_{20}H_{24}O_{11}$). ~~and ginkgolide J ($C_{20}H_{24}O_{10}$).~~

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

Labeling—The label states the Latin binomial ~~name~~ and, following the official name, the article used to prepare the Capsules. Label the Capsules to indicate the amount, in mg, of Powdered Ginkgo Extract per Capsule.

USP Reference standards ⟨11⟩—*USP Ginkgo Terpene Lactones RS.* ~~*USP Isorhamnetin RS. USP Kaempferol RS.*~~ *USP Quercetin RS.* ~~*USP Rutin RS.*~~

Identification—

A: ~~The retention times of the peaks for quercetin, isorhamnetin, and kaempferol in the chromatogram of the *Test solution* correspond to those in the chromatogram of the appropriate *Standard solution,* as obtained in the test for *Content of flavonol glycosides.*~~ It meets the requirements of *Identification* test *B* under *Powdered Ginkgo Extract.*

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B: The retention times of the peaks for bilobalide, ginkgolide A, ginkgolide B, and ginkgolide C in the chromatogram of the *Test solution* correspond to those in the chromatogram of the *Standard solutions,* as obtained in the test for *Content of terpene lactones.*

Disintegration and dissolution ⟨2040⟩**:** meet the requirements for *Dissolution.*

Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Standard solutions—Proceed as directed in the test for *Content of terpene lactones* under *Ginkgo*.

Test solution—Combine 25-mL portions of the solution under test from each one of the six dissolution vessels in a separation funnel. Extract with four 50-mL portions of ethyl acetate. Combine the extracts, and evaporate in vacuum to dryness. Dissolve the residue with sonication in 5.0 mL of a mixture of water and methanol ~~(7 : 3)~~ (1 : 1).

Procedure—Proceed as directed in the test for *Content of terpene lactones* to determine the concentration, *C*, in mg per mL, of ginkgolide ~~A~~ B in the *Test solution.* Calculate the percentage of ginkgolide ~~A~~ B dissolved by the formula:

$$5000C/3G$$

in which *C* is as obtained above; and *G* is the content, in mg per Capsule, of ginkgolide ~~A~~ B as determined in the test for *Content of terpene lactones.*

Tolerances—Not less than 75% of the content of ginkgolide ~~A~~ B is dissolved in 45 minutes.

Weight variation ⟨2091⟩**:** meet the requirements.

Content of flavonol glycosides—

Mobile phase and *Chromatographic system*—Proceed as directed in the test for *Content of flavonol glycosides* under *Ginkgo*.

Standard solutions—Proceed as directed in the test for *Content of flavonol glycosides* under *Ginkgo,* except to obtain solutions having known concentrations of 0.2 mg per mL, 0.2 mg per mL, and 0.05 mg per mL, respectively.

Test solution—Weigh and finely powder the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 48 mg of flavonol glycosides, to a 50-mL volumetric flask. Add 20 mL of methanol, and sonicate for about 3 minutes. Add 20 mL of 1.5 N hydrochloric acid, and sonicate again for about 10 minutes. Allow to cool to room temperature, and dilute with methanol to volume. Centrifuge, and transfer a portion of the clear supernatant to a rubber-capped, low-actinic glass vial. Heat in a steam bath for 25 minutes, and cool to room temperature in an ice bath.

Procedure—Separately inject equal volumes (about 10 µL) of each of the *Standard solutions* and the *Test solution* into the chromatograph; record the chromatograms; identify the peaks for quercetin, kaempferol, and isorhamnetin by comparison with the chromatogram obtained from the corresponding *Standard solution;* and measure the responses for those peaks. Separately calculate the quantities, in mg, of quercetin, kaempferol, and isorhamnetin glycosides in the portion of Capsules taken by the formula:

~~$50CM(r_U/r_S)$~~

$$50(2.51)C(r_U/r_S)$$

in which 2.51 is the mean molecular mass factor to convert each analyte into a flavonol glycoside with a mean molecular mass of 756.7; *C* is the concentration, in mg per mL, of ~~the relevant~~ USP ~~Reference Standard~~ Quercetin RS in ~~each~~ *Standard solution 1;* ~~*M* is the factor to convert each analyte into its respective glycoside and it is 2.504 for quercetin,~~

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~~2.588 for kaempferol, and 2.437 for isorhamnetin; r_U and r_S are~~ r_U is the peak response for the relevant analytes obtained from the *Test solution;* and r_S is the peak response of USP Quercetin RS in ~~the corresponding~~ *Standard solution 1.* ~~, respectively~~.

Content of terpene lactones—

Solution A, Solution B, Mobile phase, Standard solutions, Buffer solution, Diluent, Solvent, and *Chromatographic system*—Proceed as directed in the test for *Content of terpene lactones* under *Ginkgo*.

Test solution—Weigh and finely powder the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about ~~18 mg of terpene lactones, to a 50-mL volumetric flask, add about 40 mL of methanol, and sonicate for about 15 minutes. Allow to cool to room temperature, dilute with methanol to volume, mix, and centrifuge.~~ 120 mg of ginkgo extract, to a 30-mL tube with screw cap and PTFE gasket, and proceed as directed in the *Test solution* in the test for *Content of terpene lactones* under *Ginkgo,* starting with "Add 10.0 mL of *Solvent*", except to dissolve the final residue in 20.0 mL of *Diluent*.

Procedure—Proceed as directed in the test for *Content of terpene lactones* under *Ginkgo*. Separately calculate the quantities, in mg, of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), and ginkgolide C ($C_{20}H_{24}O_{11}$)~~, and ginkgolide J ($C_{20}H_{24}O_{10}$)~~ in the portion of Capsules taken by the formula:

$$\frac{\text{~~50}C\text{~~}}{20C}$$

in which C is as defined therein. Calculate the total quantity, in mg, of terpene lactones in the portion of Capsules taken by adding the individual quantities calculated.▲*USP30*

BRIEFING

Ginkgo Tablets, page 2240 of *PF* 27(2) [Mar.–Apr. 2001]. It is proposed to add storage conditions in *Packaging and storage.* In the test for *Content of terpene lactones,* it is proposed to revise the preparation of the *Test solution* and also to revise the formula used for the calculation in the *Procedure*. See also briefing under *Powdered Gingko Extract.*

(DSB: M. Sharaf) RTS—43478-2

Add the following:

▲Ginkgo Tablets

» Ginkgo Tablets are prepared from Powdered Ginkgo Extract and contain, in the labeled amount of Powdered Extract, not less than ~~90.0 20.0~~ 22.0 percent and not more than ~~110.0 30.0~~ 27.0 percent ~~of the labeled amount~~ of flavonol glycosides and not less than ~~90.0~~ 5.4 percent and not more than ~~110.0 13.2~~ 12.0 percent ~~of the labeled amount~~ of terpene lactones, consisting of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), ~~and~~ and ginkgolide C ($C_{20}H_{24}O_{11}$). ~~, and ginkgolide J ($C_{20}H_{24}O_{10}$).~~

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

Labeling—The label states the Latin binomial ~~name,~~ and following the official name, the article used to prepare the Tablets. Label the Tablets to indicate the ~~amount,~~ content, in mg, of ~~total flavonol glycosides and total terpene lactones per Tablet.~~ Powdered Ginkgo Extract per Tablet.

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USP Reference standards ⟨11⟩—~~*USP Powdered Ginkgo Extract RS.*~~ *USP Ginkgo Terpene Lactones RS.* ~~*USP Isorhamnetin RS. USP Kaempferol RS.*~~ *USP Quercetin RS.*

Identification—

A: ~~The retention times of the peaks for quercetin, isorhamnetin, and kaempferol in the chromatogram of the *Test solution* correspond to those in the chromatogram of the appropriate *Standard solution*, as obtained in the test for *Content of flavonol glycosides.*~~ It meets the requirements of *Identification* test *B* under *Powdered Ginkgo Extract*.

B: The retention times of the peaks for bilobalide, ginkgolide A, ginkgolide B, and ginkgolide C in the chromatogram of the *Test solution* correspond to those in the chromatogram of the *Standard solutions,* as obtained in the test for *Content of terpene lactones.*

Disintegration and dissolution ⟨2040⟩: meet the requirements for *Dissolution.*

Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Standard solutions—Proceed as directed in the test for *Content of terpene lactones* under *Ginkgo.*

Test solution—Combine 25-mL portions of the solution under test from each one of the six dissolution vessels in a separation funnel. Extract with four 50-mL portions of ethyl acetate. Combine the extracts, and evaporate in vacuum to dryness. Dissolve the residue with sonication in 5.0 mL of a mixture of water and methanol ~~(7 : 3)~~ (1 : 1).

Procedure—Proceed as directed in the test for *Content of terpene lactones* to determine the concentration, *C*, in mg per mL, of ginkgolide B in the *Test solution.* Calculate the percentage of ginkgolide B dissolved by the formula:

$$5000C/3G$$

in which *C* is as obtained above; and *G* is the content, in mg per Tablet, of ginkgolide B as determined in the test for *Content of terpene lactones.*

Tolerances—Not less than 75% of the content of ginkgolide B is dissolved in 45 minutes.

Weight variation ⟨2091⟩: meet the requirements.

Content of flavonol glycosides—

Mobile phase—Proceed as directed in the test for *Content of flavonol glycosides* under *Ginkgo.*

Solvent—Transfer 20 mL of 1.5 N hydrochloric acid to a 50-mL volumetric flask, dilute with methanol to volume, and mix.

Standard solutions—~~Dissolve an accurately weighed quantity of USP Powdered Ginkgo Extract RS in *Solvent* to obtain a solution having a known concentration of about 1 mg of flavonol glycosides per mL. Transfer a portion of this solution to a rubber-capped, low-actinic glass vial, heat in a steam bath for 25 minutes, and then cool to room temperature in an ice bath.~~ Proceed as directed for *Standard solutions* in the test for *Content of flavonol glycosides* under *Ginkgo,* except to obtain solutions having known concentrations of 0.2 mg per mL, 0.2 mg per mL, and 0.05 mg per mL, respectively.

Test solution—Weigh and ~~using a mortar and pestle,~~ finely powder not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about 50 mg of flavonol glycosides, to a 50-mL volumetric flask.

Add 20 mL of methanol, and sonicate for about 3 minutes. Add 20 mL of 1.5 N hydrochloric acid, and sonicate again for about 10 minutes. Allow to cool to room temperature, and dilute with methanol to volume. Centrifuge, and transfer a portion of the clear supernatant to a rubber-capped, low-actinic glass vial. Heat in a steam bath for 25 minutes, and cool to room temperature in an ice bath.

Chromatographic system—Prepare as directed in the test for *Content of flavonol glycosides* under *Ginkgo*. ~~Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the chromatogram obtained from the *Standard solution* is similar to the Reference Chromatogram for flavonol glycosides provided with USP Powdered Ginkgo Extract RS.~~

Procedure—Separately inject equal volumes (about 10 µL) of each of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, identify the peaks for quercetin, isorhamnetin, and kaempferol by comparison with the chromatogram obtained from the corresponding *Standard solution*, and measure the responses for those peaks. Separately calculate the quantities, in mg, of quercetin, isorhamnetin, and kaempferol glycosides in the portion of Tablets taken by the formula:

~~$0.5CP(r_U/r_S)$~~

~~$50CM(r_U/r_S)$~~

$$50(2.51)C(r_U/r_S)$$

in which 2.51 is the mean molecular mass factor to convert each analyte into a flavonol glycoside with a mean molecular mass of 756.7; C is the concentration, in mg per mL, of ~~USP Powdered Ginkgo Extract RS the relevant~~ USP ~~Reference Standard~~ Quercetin RS in ~~each~~ *Standard solution 1;* ~~P is the designated percentage of the relevant glycoside in USP Powdered Ginkgo Extract RS; M is the factor to convert each analyte into its respective glycoside and it is 2.504 for quercetin, 2.588 for kaempferol, and 2.437 for isorhamnetin;~~ r_U ~~and r_S are~~ is the peak response for the relevant analytes obtained from the *Test solution;* and r_S is the peak response of USP Quercetin RS in ~~corresponding~~ *Standard solution 1.* ~~respectively.~~ Calculate the total quantity, in mg, of flavonol glycosides in the portion of Tablets taken by adding the individual quantities calculated.

Content of terpene lactones—

~~*Buffer solution*—Dissolve 1.19 g of dibasic sodium phosphate and 8.25 g of monobasic potassium phosphate in 1000 mL of water, and adjust to a pH of about 5.8.~~

~~*Mobile phase*—Prepare a mixture of water, methanol, and tetrahydrofuran (70 : 20 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard solution*—Dissolve an accurately weighed quantity of USP Powdered Ginkgo Extract RS in *Buffer solution* to obtain a solution having a known concentration of about 0.4 mg of terpene lactones per mL. Transfer 20.0 mL of this solution to a 30 × 150 mm glass chromatographic tube filled with 15 g of chromatographic siliceous earth. Allow the *Buffer solution* to drain off the column. After 15 minutes elute the column with 100 mL of ethyl acetate, collect the eluate, and evaporate to dryness in vacuum on a water bath maintained at 50°. Remove the last traces of solvent with the aid of a current of air at room temperature. Dissolve the residue in 2.5 mL of *Mobile phase*.~~

Solvent, Buffer solution, Diluent, Solution A, Solution B, Mobile phase, Standard solutions, and *Chromatographic system*—Proceed as directed in the test for *Content of terpene lactones* under *Ginkgo.*

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Test solution—Weigh and finely powder~~, using a mortar and pestle,~~ not fewer than 20 Tablets. Transfer an accurately weighed quantity of the powder, equivalent to about ~~18 mg of terpene lactones, to a 50-mL volumetric flask, add about 35 mL of *Buffer solution*, 40 mL of *Solvent*, and sonicate for about 15 minutes with occasional shaking. Allow to cool to room temperature, and dilute with *Buffer solution* *Solvent* to volume, and mix, and centrifuge. Use the supernatant as the *Test solution*. and transfer 20.0 mL of the clear supernatant to a 30- × 150-mm glass chromatographic tube filled with 15 g of chromatographic siliceous earth. Proceed as directed for the *Standard solution,* beginning with "Allow the *Buffer solution* to drain off...".~~ 120 mg of ginkgo extract, to a 30-mL tube with a cap and PTFE gasket, and proceed as directed in the *Test solution* in the test for *Content of terpene lactones* under *Ginkgo,* starting with ''Add 10.0 mL of Solvent,'' except to dissolve the final residue in 20.0 mL of *Diluent*.

~~*Chromatographic system* (see *Chromatography* ⟨621⟩) — The liquid chromatograph is equipped with a refractive index detector and a 4.0-mm × 25-cm column that contains packing L7. The column temperature is maintained at 35°. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution* and the *Test solution*, and record the chromatograms as directed for *Procedure*: the relative standard deviation for replicate injections of bilobalide is not more than 2.0%; and the chromatogram obtained from the *Standard solution* is similar to the Reference Chromatogram for terpene lactones provided with USP Powdered Ginkgo Extract RS.~~

Procedure— ~~Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution*, record the chromatograms, and measure the areas of the major peaks.~~ Proceed as directed for *Content of terpene lactones* under *Ginkgo*. Separately calculate the quantities, in mg, of bilobalide ($C_{15}H_{18}O_8$), ginkgolide A ($C_{20}H_{24}O_9$), ginkgolide B ($C_{20}H_{24}O_{10}$), ~~and~~ and ginkgolide C ($C_{20}H_{24}O_{11}$)~~, and ginkgolide J ($C_{20}H_{24}O_{10}$)~~ in the portion of Tablets taken by the formula:

~~$0.025CP(r_U/r_S)$,~~

~~$50C$~~

$20C$

in which C is as ~~the concentration, in mg per mL, of USP Powdered Ginkgo Extract RS in the *Standard solution; P* is the designated percentage of the relevant analyte in USP Powdered Ginkgo Extract RS; and r_U and r_S are the areas for the relevant peaks obtained from the *Test solution* and the *Standard solution*, respectively~~ defined therein. Calculate the total quantity, in mg, of terpene lactones in the portion of Tablets taken by adding the individual quantities calculated. ▲*USP30*

MONOGRAPHS (NF)

BRIEFING

Acetyltributyl Citrate, *NF 24* page 3266; **Acetyltriethyl Citrate,** *NF 24* page 3266; **Tributyl Citrate,** *NF 24* page 3450; **Triethyl Citrate,** *NF 24* page 3451. On the basis of several comments received, it is proposed to revert to the previous assay method requiring the use of an on-column temperature programmable injector. The current method employs the use of a split injection system, and reports have indicated that this system fails to separate acetyl-

tributyl citrate, tributyl citrate, triethyl citrate, and acetyltriethyl citrate peaks. In addition, minor editorial style changes have been made.

(EM1: C. Sheehan) RTS—43050-1

Change to read:

Assay—

System suitability solution—Prepare a solution in toluene containing about 30 mg each of USP Acetyltributyl Citrate RS and USP Tributyl Citrate RS per mL.

Assay preparation—Transfer about 300 mg of Acetyltributyl Citrate, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with

▲an on-column, temperature-programmable injector,▲*NF25* a flame-ionization detector maintained at about 275°, ~~a split injection system with a split ratio of about 30 : 1,~~

▲▲*NF25* and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed as follows. Initially the temperature of the column is maintained at about 80° for 0.5 minute, then increased at a rate of 20° per minute to about 220°, and maintained at about 220° for 10 minutes. The injection port temperature is ~~maintained at about 85°.~~

▲programmed as follows. Initially the temperature is maintained at about 85° for 0.5 minute, then increased at a rate of 20° per minute to about 225°, and maintained at about 225° for 10 minutes.▲*NF25*

The carrier gas is helium, flowing at a rate of about 2.3 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for tributyl citrate and 1.0 for acetyltributyl citrate; the resolution, *R,* between tributyl citrate and acetyltributyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the tributyl citrate and acetyltributyl citrate peaks, based on area percent calculation.

Procedure—Inject 1 µL of the *Assay preparation* into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $C_{20}H_{34}O_8$ in the portion of Acetyltributyl Citrate taken by the formula:

$$100(A/B)$$

in which *A* is the acetyltributyl citrate peak area response; and *B* is the sum of the area responses of all the peaks.

BRIEFING

Acetyltriethyl Citrate, *NF 24* page 3266—See briefing under *Acetyltributyl Citrate*.

(EM1: C. Sheehan) RTS—43050-2

Change to read:

Assay—

System suitability solution—Prepare a solution in toluene containing about 30 mg each of USP Acetyltriethyl Citrate RS and USP Triethyl Citrate RS per mL.

Assay preparation—Transfer about 300 mg of Acetyltriethyl Citrate, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with

▲an on-column, temperature-programmable injector,▲*NF25* a flame-ionization detector maintained at about 275°, ~~a split injection system with a split ratio of about 30 : 1,~~

▲▲*NF25* and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed as follows. Initially the temperature of the column is maintained at about 80° for 0.5 minute, then increased at a rate of 20° per minute to about 220°, and maintained at about 220° for 10 minutes. The injection port temperature is ~~maintained at about 85°.~~

▲programmed as follows. Initially the temperature is maintained at about 85° for 0.5 minute, then increased at a rate of 20° per minute to about 225°, and maintained at about 225° for 10 minutes.▲*NF25*

The carrier gas is helium, flowing at a rate of about 2.3 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for triethyl citrate and 1.0 for acetyltriethyl citrate; the resolution, *R,* between triethyl citrate and acetyltriethyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the triethyl citrate and acetyltriethyl citrate peaks, based on area percent calculation.

Procedure—Inject 1 µL of the *Assay preparation* into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $C_{14}H_{22}O_8$ in the portion of Acetyltriethyl Citrate taken by the formula:

$$100(A/B)$$

in which *A* is the acetyltriethyl citrate peak area response; and *B* is the sum of the area responses of all the peaks.

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BRIEFING

Cellacefate, *NF 24* page 3306. In accordance with the implemented name change to the reference standard, from USP Cellulose Acetate Phthalate RS to USP Cellacefate RS, it is proposed to make the corresponding change in the *USP Reference standards* ⟨11⟩ section of the monograph.

(EM2: C. Sheehan) RTS—43534-1

Change to read:

USP Reference standards ⟨11⟩ ~~*USP Cellulose Acetate Phthalate RS.*~~

▲*USP Cellacefate RS.*▲*NF25*

BRIEFING

Strawberry Syrup. Because there is no existing *NF* monograph for this syrup, the following new monograph is proposed.

(CRX: C. Okeke) RTS—43128-1

Add the following:

▲Strawberry Syrup

» Prepare Strawberry Syrup as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Strawberry juice	475 mL
Sucrose	800 g
Alcohol	20 mL
Purified Water, a sufficient quantity to make	1000 mL

Dissolve Sucrose in Strawberry juice by gently heating on a steam bath, cool, and remove the foam and floating solids. Add Alcohol and sufficient Purified Water to make 1000 mL, and mix.

Packaging and storage—Preserve in tight, light-resistant containers, and prevent exposure to excessive heat.

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

Alcohol content, *Method I* ⟨611⟩**:** between 1.0% and 2.0% of C_2H_5OH is found.▲*NF25*

BRIEFING

Tributyl Citrate, *NF 24* page 3450—See briefing under *Acetyltributyl Citrate*.

(EM1: C. Sheehan) RTS—43050-3

In-Process Revision

Change to read:

Assay—

System suitability solution—Prepare a solution in toluene containing about 30 mg each of USP Tributyl Citrate RS and USP Acetyltributyl Citrate RS per mL.

Assay preparation—Transfer about 300 mg of Tributyl Citrate, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with

▲an on-column, temperature-programmable injector,▲*NF25* a flame-ionization detector maintained at about 275°, ~~a split injection system with a split ratio of about 30 : 1~~

▲▲*NF25* and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed as follows. Initially the temperature is maintained at about 80° for 0.5 minute, then increased at a rate of 20° per minute to about 220°, and maintained at about 220° for 10 minutes. The injection port temperature is ~~maintained at about 85°.~~

▲programmed as follows. Initially the temperature is maintained at about 85° for 0.5 minute, then increased at a rate of 20° per minute to about 225°, and maintained at about 225° for 10 minutes.▲*NF25*

The carrier gas is helium, flowing at a rate of about 2.3 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for tributyl citrate and 1.0 for acetyltributyl citrate; the resolution, *R,* between tributyl citrate and acetyltributyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the tributyl citrate and acetyltributyl citrate peaks, based on area percent calculation.

Procedure—Inject 1 µL of the *Assay preparation* into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $C_{18}H_{32}O_7$ in the portion of Tributyl Citrate taken by the formula:

$$100(A/B)$$

in which A is the tributyl citrate peak area response; and B is the sum of the area responses of all the peaks.

BRIEFING

Triethyl Citrate, *NF 24* page 3451—See briefing under *Acetyltributyl Citrate*.

(EM1: C. Sheehan) RTS—43050-4

Change to read:

Assay—

System suitability solution—Prepare a solution in toluene containing about 30 mg each of USP Triethyl Citrate RS and USP Acetyltriethyl Citrate RS per mL.

Assay preparation—Transfer about 300 mg of Triethyl Citrate, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with toluene to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with ~~a split injection system with a split ratio of about 30 : 1,~~

▲an on-column, temperature-programmable injector,▲*NF25* a flame-ionization detector maintained at about 275°, and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed as follows. Initially the temperature is maintained at about 80° for 0.5 minute, then increased at a rate of 20° per minute to about 220°, and maintained at about 220° for 10 minutes. The injection port temperature is ~~maintained at about 85°.~~

▲programmed as follows. Initially the temperature is maintained at about 85° for 0.5 minute, then increased at a rate of 20° per minute to about 225°, and maintained at about 225° for 10 minutes.▲*NF25*

The carrier gas is helium, flowing at a rate of about 2.3 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for triethyl citrate and 1.0 for acetyltriethyl citrate; the resolution, *R,* between triethyl citrate and acetyltriethyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the triethyl citrate and acetyltriethyl citrate peaks, based on area percent calculation.

Procedure—Inject 1 µL of the *Assay preparation* into the chromatograph, record the chromatogram, and measure all of the peak areas, excluding the solvent peak. Calculate the percentage of $C_{12}H_{20}O_7$ in the portion of Triethyl Citrate taken by the formula:

$$100(A/B)$$

in which A is the triethyl citrate peak area response; and B is the sum of the area responses of all the peaks.

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**11**〉 **USP Reference Standards,** *USP 29* page 2458, page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], page 1154 of *PF* 31(4) [July–Aug. 2005], page 1433 of *PF* 31(5) [Sept.–Oct. 2005], and page 1680 of *PF* 31(6) [Nov.–Dec. 2005].

(HDQ) RTS—40261-1; 41820-2; 42064-3; 42064-4; 42064-5; 42064-6; 43244-1; 43398-1; 43538-1; 43560-1; 43561-1

Add the following:

▲**USP Carbamazepine Related Compound A RS** **[**10, 11-dihydrocarbamazepine**]**—[To come.]▲*USP30*

Add the following:

▲**USP Carbamazepine Related Compound B RS** **[**iminostilbene**]**—[To come.]▲*USP30*

Add the following:

▲**USP Cilostazol RS**—[To come.]▲*USP30*

Add the following:

▲**USP Cilostazol Related Compound A RS** **[**6-hydroxy-3,4-dihydro-1*H*-quinolin-2-one**]** ($C_9H_9NO_2$ ✧ 163.17)—[To come.]▲*USP30*

Add the following:

▲**USP Cilostazol Related Compound B RS** **[**6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one**]** ($C_{20}H_{25}N_5O_2$ ✧ 367.45)—[To come.]▲*USP30*

Add the following:

▲**USP Cilostazol Related Compound C RS** **[**1,6-bis-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one**]** ($C_{31}H_{43}N_9O_3$ ✧ 589.73)—[To come.]▲*USP30*

Add the following:

▲**USP *exo*-Tetrahydrocannabinol RS** **[**(6a*R,* 10a*R*)-6,6-dimethyl-9-methylene-3-pentyl-6a,7,8,9,10,10a-hexahydro-6*H*-benzo[*c*]chromen-1-ol**]** ($C_{21}H_{30}O_2$ ✧ 314.46)—[To come.]▲*USP30*

Add the following:

▲**USP Flumazenil Related Compound C RS** **[***N,N*-dimethylformamide diethyl acetal**]**—[To come.]▲*USP30*

Add the following:

▲**USP Formoterol Fumarate RS**—[To come.]▲*USP30*

Add the following:

▲**USP Formoterol Related Compound I RS** **[***N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[(1*SR*)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide fumarate salt (2 : 1)(diastereoisomer)**]**—[To come.]▲*USP30*

Add the following:

▲**USP Formoterol Fumarate System Suitability Mixture RS** —It is a mixture of USP Formoterol Fumarate RS and formoterol related compounds A, B, C, D, E, F, G, and H.

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Formoterol related compound A [1-(3-amino-4-hydroxyphenyl)-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethanol].

Formoterol related compound B [*N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]formamide].

Formoterol related compound C [*N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]acetamide].

Formoterol related compound D [*N*-[2-hydroxy-5-[1-hydroxy-2-[methyl[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide].

Formoterol related compound E [*N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-3-methylphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide].

Formoterol related compound F [*N*-[2-hydroxy-5-[1-[[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]amino]-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide].

Formoterol related compound G [(2*RS*)-1-(4-methoxyphenyl)propan-2-amine].

Formoterol related compound H [*N*-[5-[(1*RS*)-2-[benzyl[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]formamide (monobenzyl analogue)].▲*USP30*

Add the following:

▲**USP Ginger Constituent Mixture RS**—[To come.]▲*USP30*

Change to read:

USP Polyoxyl 35 Castor Oil RS—

▲Do not dry. After opening, store in a tightly closed container. Protect from light.▲*USP30*

Add the following:

▲**USP Verapamil Related Compound E RS** [3,4-dimethoxybenzaldehyde]—[To come.]▲*USP30*

Add the following:

▲**USP Verapamil Related Compound F RS** [(3,4-dimethoxyphenyl)methanol]—[To come.]▲*USP30*

Chemical Tests and Assays

LIMIT TESTS

BRIEFING

⟨**231**⟩ **Heavy Metals,** *USP 29* page 2556 and page 1435 of *PF* 31(5) [Sept.–Oct. 2005]. On the basis of comments received, *Method II* is being revised to add a *Blank Preparation* and to address issues related to sample size and pH adjustment. The *Standard Preparation* has also been revised to ensure that the *Standard Preparation, Test Preparation,* and *Blank Preparation* are treated the same way for valid comparison.

(GC: K. Zaidi) RTS—43620-1

Change to read:

METHOD II

NOTE—This method does not recover mercury.

▲**Blank Preparation—**Prepare as directed under *Standard Preparation,* using 2 mL of water instead of the *Standard Lead Solution.*▲*USP30*

pH 3.5 Acetate Buffer—Prepare as directed under *Method I.*

Standard Preparation— ~~Pipet 4 mL of the *Standard Lead Solution* into a suitable test tube, and add 10 mL of 6 N hydrochloric acid.~~

▲Pipet 2 mL of the *Standard Lead Solution* into a suitable crucible and evaporate on a steam bath to dryness. Add sufficient sulfuric acid to wet the surface, and carefully ignite at low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved.

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Ignite, preferably in a muffle furnace, at 500° to 600°, until the carbon is completely burned off (no longer than 2 hours). If carbon remains, allow the residue to cool, add a few drops of sulfuric acid, evaporate, and ignite again. Cool, add 5 mL of 6 N hydrochloric acid, cover, and digest on a steam bath for 10 minutes. Cool, and quantitatively transfer the solution to a test tube. Rinse the crucible with a second 5-mL portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube.▲*USP30*

Test Preparation—Use a quantity, in g, of the substance to be tested as calculated by the formula:

~~4.0/(1000*L*)~~

▲2.0/(1000*L*)▲*USP30*

in which *L* is the *Heavy metals* limit, as a percentage.

▲[NOTE—If the sample is liquid, first evaporate to dryness on a steam bath.]▲*USP30*
Transfer the weighed quantity of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at 500° to 600°, until the carbon is completely burned off (no longer than 2 hours). If carbon remains, allow the residue to cool, add a few drops of sulfuric acid, evaporate, and ignite again. Cool, add 5 mL of 6 N hydrochloric acid, cover, and digest on a steam bath for 10 minutes. Cool, and quantitatively transfer the solution to a test tube

▲or a beaker.▲*USP30*
Rinse the crucible with a second 5-mL portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube

▲or a beaker.▲*USP30*

~~**Monitor Preparation**—Pipet 4 mL of the *Standard Lead Solution* into a crucible identical to that used for the *Test Preparation* and containing a quantity of the substance under test that is equal to 10% of the amount required for the *Test Preparation*. Evaporate on a steam bath to dryness. Ignite at the same time, in the same muffle furnace, and under the same conditions used for the *Test Preparation*. Cool, add 5 mL of 6 N hydrochloric acid, cover, and digest on a steam bath for 10 minutes. Cool, and quantitatively transfer to a test tube. Rinse the crucible with a second 5-mL portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube.~~

■■2S (*USP29*)

Procedure—

▲[NOTE—When adjusting the pH, a water bath can be used to keep the preparations near room temperature. Stir well during pH adjustment.]▲*USP30*
Adjust the solution in each of the tubes containing the *Standard Preparation*

■and■2S (*USP29*)
the *Test Preparation* ~~and the *Monitor Preparation*~~

■■2S (*USP29*)
with ammonium hydroxide, added cautiously and dropwise, to a pH of ~~9~~

▲8.5.▲*USP30*

■Thoroughly mix the solution after each addition of ammonium hydroxide.■2S (*USP29*)
Cool, and adjust with glacial acetic acid, added dropwise, to a pH of 8, then add 0.5 mL in excess. Using a pH meter, ~~or short range pH indicator paper as external indicator, check the pH,and adjust,~~

■check and adjust the pH,■2S (*USP29*)
if necessary, with

▲glacial acetic acid,▲*USP30*
1 N acetic acid, or 6 N ammonium hydroxide to a pH between 3.0 and 4.0. Filter, if necessary, washing the filter with a few mL of water, into a 50-mL color-comparison tube, and then dilute with water to 40 mL. Add 2 mL of *pH 3.5 Acetate Buffer,* then add 1.2 mL of thioacetamide–glycerin base TS, dilute with water to 50 mL, mix, allow to stand for 2 minutes, and view downward over a white surface*: the color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation.*

▲[NOTE—If the color of the solution from the *Standard Preparation* is not distinguishable from the *Blank Preparation,* the *Test Preparation* is not evaluated.]▲*USP30*
~~and the color of the solution from the *Monitor Preparation* is equal to or darker than that of the solution from the *Standard Preparation*. [NOTE—If the color of the solution from the *Monitor Preparation* is lighter than that of the solution from the *Standard Preparation,* proceed as directed for *Method III* for the substance being tested.]~~

■■2S (*USP29*)

* In those countries or jurisdictions where thioacetamide cannot be used, add 10 mL of freshly prepared hydrogen sulfide TS to each of the tubes, mix, allow to stand for 5 minutes, and view downward over a white surface.

DIETARY SUPPLEMENTS

General Chapters—General Information

BRIEFING

⟨2040⟩ Disintegration and Dissolution of Dietary Supplements, *USP 29* page 3089. This revision of general chapter ⟨2040⟩, which previously appeared in *Pharmacopeial Previews* on page 1673 of *PF* 28(5) [Sept.–Oct. 2002], is now forwarded to *In-Process Revision.* Having received no comments regarding this proposal to use a *Rupture* test in lieu of a *Disintegration* test for soft gelatin capsules, the text is published here with minor editorial changes. The previewed revision was based on comments stating that performance characteristics for dietary supplements in soft gelatin capsules are not appropriately measured by the *Disintegration* test. This problem seems to be worse for some preparations containing botanical extracts, where the gelatin cross-linking process is reported to be exacerbated over time. Complete disintegration of the gelatin mass formed from placing the capsule in a disintegration medium requires a significantly longer time than that for other dosage forms. Although the gelatin capsule may rupture and release its contents, the gelatin shell requires a longer period of time to disintegrate. Therefore, a *Disintegration* test for soft gelatin capsules would be measuring the disintegration of gelatin which may not be representative of the availability of the dietary ingredient. For these reasons, in several monographs, USP has adopted a *Rupture* test in lieu of a test for *Disintegration*. A *Rupture* test seems to be a more appropriate test for soft gelatin capsules filled with liquids. The DS-BA Expert Committee decided to move this proposal forward to *In-Process Revision* and encourages interested parties to submit their comments and pertinent data.

(DS-BA: D. Cairatti) RTS—43551-1

In-Process Revision

Change to read:

DISINTEGRATION

This test is provided to determine compliance with the limits on *Disintegration* stated below or in the individual class monographs on dietary supplements, including botanical dosage forms. This test applies to uncoated and plain coated tablets and to hard gelatin and soft gelatin capsules. It does not apply to tablets or capsules designed to liberate vitamin or mineral content over an extended period or where the label states that the dosage form is to be chewed. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell remaining on the screen of the test apparatus, is a soft mass having no palpably firm core.

Apparatus

Apparatus A—Use the *Apparatus* described under *Disintegration* ⟨701⟩ for tablets or capsules that are not greater than 18-mm long. For larger tablets or capsules, use *Apparatus B.*

Apparatus B—The apparatus* consists of a basket-rack assembly, a 1000-mL, low-form beaker for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly—The basket-rack assembly consists of three open-ended transparent tubes, each 7.95- ± 0.05-cm long and having an inside diameter of approximately 33.3 mm and a wall approximately 2.4 mm thick; the tubes are held in a vertical position by two plastic plates, each about 9.7 cm in diameter and 9.5 mm in thickness, with three holes, each about 39 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is 10-mesh No. 23 (0.025-inch) W. and M. gauge woven stainless-steel wire cloth having a plain square weave. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks—Each tube is provided with a perforated cylindrical disk 15.3- ± 0.15-mm thick and 31.4 ± 0.13 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Seven 3.2-mm holes extend between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it equally spaced on a 6-mm radius from it. All surfaces of the disk are smooth.

Procedure

VITAMIN–MINERAL DOSAGE FORMS

Uncoated Tablets and Film-Coated Tablets—Place 1 tablet in each of the tubes of the basket, add a disk to each tube, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid. At the end of 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or

* An apparatus and disks meeting these specifications are available from VanKel Technology Group, 13000 Weston Parkway, Cary, NC 27513, or from laboratory supply houses.

2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets (Other Than Film-Coated Tablets)—Place 1 tablet in each of the tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then add a disk to each tube, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid. After 45 minutes of operation in water, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets,* using 0.05 M acetate buffer, prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain 1000 mL of solution having a pH of 4.50 ± 0.05, maintained at 37 ± 2° as the immersion fluid. At the end of 45 minutes, lift the basket from the fluid, and observe the capsules: all of the capsules disintegrate except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under ~~*Hard Gelatin Capsules.*~~

▲*Rupture Test for Soft Gelatin Capsules.*▲*USP30*

BOTANICAL DOSAGE FORMS

Uncoated Tablets and Film-Coated Tablets—[NOTE—Omit the use of disks unless otherwise specified in the individual monograph.] Place 1 tablet in each of the tubes of the basket, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid. At the end of 20 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets (other than Film-Coated Tablets)—[NOTE—Omit the use of disks, unless otherwise specified in the individual monograph.] Place 1 tablet in each of the tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Operate the apparatus using water maintained at 37 ± 2° as the immersion fluid. After 20 minutes of operation in water, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 of the tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Delayed-Release (Enteric-Coated) Tablets—Place 1 tablet in each of the six tubes of the basket, and if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS, maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*, using 0.05 M acetate buffer, prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain 1000 mL of solution having a pH of 4.50 ± 0.05, maintained at 37 ± 2° as the immersion fluid. At the end of 20 minutes, lift the basket from the fluid, and observe the capsules: all of the capsules disintegrate except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under ~~*Hard Gelatin Capsules.*~~

▲*Rupture Test for Soft Gelatin Capsules.*▲*USP30*

Add the following:

▲RUPTURE TEST FOR SOFT GELATIN CAPSULES

Medium: water; 500 mL.

Apparatus—Use *Apparatus 2* as described under *Dissolution* ⟨711⟩, operating at 50 rpm.

Time: 15 minutes.

Procedure—Place 1 capsule in each vessel, and allow the capsule to sink to the bottom of the vessel before starting rotation of the blade. Observe the capsules, and record the time taken for each capsule shell to rupture.

Tolerances—The requirements are met if all of the capsules tested rupture in not more than 15 minutes. If 1 or 2 of the capsules rupture in more than 15 but not more than 30 minutes, repeat the test on 12 additional capsules: not more than 2 of the total of 18 capsules tested rupture in more than 15 but not more than 30 minutes.▲*USP30*

In-Process Revision\

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Dextran, High Molecular Weight, *USP 29* page 3123. It is proposed to update information on a possible supplier for this reagent.

(HDQ: M. Marques) RTS—43738-1

Change to read:

Dextran, High Molecular Weight—A dextran molecular weight standard having a weight-average molecular weight, M_W, of 1 to 2×10^6 Da and a weight-average molecular weight to number-average molecular weight ratio, M_W / M_N, of 1.0 to 1.8.

[NOTE—A suitable grade is available from ~~Sigma-Aldrich, www.sigma-aldrich.com.~~]

▲American Polymer Standards Corporation, www.ampolymer.com.]▲*USP30*

BRIEFING

Hydrazine Hydrate, 85% in Water, *USP 29* page 3133. In the *Assay* it is proposed to correct the quantity of hydrazine hydrate equivalent to each mL of 0.1 N iodine used.

(HDQ: M. Marques) RTS—43473-1

Change to read:

Hydrazine Hydrate, 85% in Water, $(NH_2)_2 \cdot H_2O$—**50.06**—Colorless liquid.

Assay—Transfer 600 mg, accurately weighed, to a 100-mL volumetric flask. Dilute with water to volume, and mix. Pipet 10 mL into a suitable beaker, and add 1.0 g of sodium bicarbonate and 50.0 mL of 0.1 N iodine VS. Titrate the excess iodine with 0.1 N sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N iodine is equivalent to ~~12.52 mg~~ ▲1.252 mg▲*USP30* of $(NH_2)_2 \cdot H_2O$. Not less than 83% is found.

BRIEFING

1-Naphthol, *USP 29* page 3140. It is proposed to update the specifications for this reagent.

(HDQ: M. Marques) RTS—43725-1

Change to read:

1-Naphthol (*Alphanaphthol*), $C_{10}H_7OH$—**144.17**—Colorless or slightly pinkish crystals or crystalline powder. ▲▲*USP29* ~~Insoluble in water; soluble in alcohol, in benzene, and in ether.~~

~~*Melting range* ⟨741⟩: between 95° and 97°.~~

~~*Solubility*—Separate 1-g portions dissolve in alcohol and in benzene to yield solutions that are clear and colorless or nearly colorless.~~

~~*Acidity*—Shake 1 g with 50 mL of water occasionally during 15 minutes, and filter: the filtrate is neutral to litmus.~~

~~*Residue on ignition* (Reagent test): not more than 0.05%.~~

▲Use a suitable grade with a content of not less than 99%.▲*USP30*

BRIEFING

***p*-Toluenesulfonyl-L-arginine Methyl Ester Hydrochloride,** *USP 29* page 3160. It is proposed to add the synonyms and CAS number to this reagent to facilitate its procurement.

(HDQ: M. Marques) RTS—43229-1

Change to read:

***p*-Toluenesulfonyl-L-arginine Methyl Ester Hydrochloride**

▲*(N_α-p-Tosyl-L-arginine methyl ester hydrochloride; TAME)*,▲*USP30*

$C_{14}H_{22}N_4O_4S \cdot HCl$—**378.88**

▲[*1784-03-8*]▲*USP30*

—Determine its suitability as directed in the test for *Trypsin* under *Chymotrypsin* (USP monograph).

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 29* page 3164 and page 1702 of *PF* 31(6) [Nov.–Dec. 2005].

(HDQ) RTS—43361-1

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Add the following:	
▲Benazepril Hydrochloride Tablets	W ▲*USP30*
Add the following:	
■Citalopram ~~Hydrobromide~~ Tablets	W ■1S (*USP29*)
Add the following:	
■Black Cohosh Tablets	T, LR ■1S (*USP29*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W ■1S (*USP29*)
Add the following:	
■Diclofenac Potassium Tablets	T, LR ■2S (*USP29*)
Add the following:	
■Didanosine Tablets	T ■2S (*USP29*)
Add the following:	
▲Estradiol Vaginal Tablets	T ▲*USP30*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W ■1S (*USP29*)
Add the following:	
■Fexofenadine Hydrochloride Tablets	W ■1S (*USP29*)
Add the following:	
■Fosinopril Sodium Tablets	T ■1S (*USP29*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T ■1S (*USP29*)
Add the following:	
■Ginkgo Capsules	T, LR ■1S (*USP29*)
Add the following:	
■Ginkgo Tablets	T, LR ■1S (*USP29*)
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ■ ■1S (*USP29*)
Add the following:	
▲Glipizide and Metformin Hydrochloride Tablets	W ▲*USP30*
Add the following:	
■Glyburide and Metformin Hydrochloride Tablets	T, LR ■1S (*USP29*)
Add the following:	
■Irbesartan Tablets	W ■1S (*USP29*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W ■1S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Isosorbide Mononitrate Tablets	T■1S (*USP29*)
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■1S (*USP29*)
Add the following:	
■Ketoprofen Capsules, Extended-Release	T■2S (*USP29*)
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■1S (*USP29*)
Add the following:	
■Modafinil Tablets	T■1S (*USP29*)
Add the following:	
■Nefazodone Hydrochloride Tablets	T■2S (*USP29*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■1S (*USP29*)
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	T, LR■2S (*USP29*)
Add the following:	
■Quinapril Tablets	W■1S (*USP29*)
Add the following:	
■Tizanidine Tablets	T■1S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Valerian Capsules	T, LR■1S (*USP29*)
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■1S (*USP29*)

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 29* page 3191, page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 812 of *PF* 29(3) [May–June 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 2057 of *PF* 29(6) [Nov.–Dec. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], page 1193 of *PF* 31(4) [July–Aug. 2005], page 1491 of *PF* 31(5) [Sept.–Oct. 2005], and page 1703 of *PF* 31(6) [Nov.–Dec. 2005].

(HDQ) RTS—41820-3; 41982-3; 42064-2; 43069-3; 43535-1

Add the following:

▲**Cilostazol:** White to off-white crystals. Freely soluble in chloroform; slightly soluble in methanol and in ethanol; practically insoluble in water.▲*USP30*

In-Process Revision

Add the following:

▲**Dronabinol:** Light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. Insoluble in water.▲*USP30*

Add the following:

▲**Formoterol Fumarate Dihydrate:** White or almost white or slightly yellow powder. Freely soluble in dimethyl sulfoxide and in acetic acid; soluble in methanol; slightly soluble in water and in 2-propanol; practically insoluble in acetonitrile and in diethyl ether.▲*USP30*

Add the following:

▲**Mono- and Di-glycerides:** Vary in consistency from yellow liquids, through ivory-colored plastics, to ivory white-colored solids (bead or flake forms). Insoluble in water, but soluble in alcohol, in ethyl acetate, in chloroform, and in other chlorinated hydrocarbons. *NF category:* Emulsifying and/or solubilizing agent.▲*NF25*

Add the following:

▲**Pancuronium Bromide:** White, yellowish-white, or slightly pink crystalline powder, hygroscopic. Freely soluble in water, in methylene chloride, and in alcohol.▲*USP30*

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF.* For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 31(1) through 31(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF.*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
General Notices—*Tests and Assays—Foreign Substances and Impurities; Preservation, Packaging, Storage, and Labeling—Storage Temperature and Humidity; Repackaging Instructions; Guidelines for Packaging and Storage Statements in USP–NF Monographs* (*Controlled Cold Temperature*-added)	31	3	718
<u>*USP Monographs*</u>			
Acetaminophen—*Packaging and storage*	31	4	1024
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Medical Air—*Definition, Packaging and storage*	31	4	1024
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albumin Human—*Definition, Packaging and storage, Expiration date, Labeling, USP Reference standards* (add), *Identification A, B* (add), *Bacterial endotoxins* (add), *Safety* (add), *Sterility* (add), *pH* (add), *Molecular size distribution* (add), *Heat stability* (add), *Incubation* (add) *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add)	31	5	1338
Albuterol Tablets—*Dissolution, Assay*	31	3	726
Alendronate Sodium—*Packaging and storage*	31	5	1344
Allopurinol—*USP Reference standards, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	28	5	1386
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Amantadine Hydrochloride—*Chromatographic purity*	31	5	1344

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—*Dissolution*	31	4	1025
Amitriptyline Hydrochloride—*USP Reference standards, Identification, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	31	6	1606
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water* (delete)	31	4	1026
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Aspartic Acid—*Chloride*	31	5	1345
Aspirin Boluses—*Dissolution*	31	4	1026
Atenolol—*Assay*	31	5	1345
Aztreonam for Injection—*Assay*	31	3	737
Benazepril Hydrochloride (new)	31	4	1027
Benazepril Hydrochloride Tablets (new)	29	3	606
Betamethasone Oral Solution—*Thin-layer chromatographic identification test*	31	4	1032
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	31	3	741
Bromocriptine Mesylate—*Chromatographic purity*	31	5	1346
Budesonide (new)	30	6	1978
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butorphanol Tartrate Nasal Solution (new)	31	5	1346
Calcitonin Salmon (new)	31	4	1036
Calcitonin Salmon Nasal Solution (new)	30	4	1178
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	29	5	1433
Calcitriol Injection (new)	29	5	1434
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate—*USP Reference standards* (add), *Identification*	31	6	1608
Calcium Lactate Tablets—*Identification, Dissolution*	31	6	1609
Camphor—*Water*	31	3	742
Carbamazepine Tablets—*Dissolution*	31	4	1044
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium—*Heavy metals*	31	5	1349
Carboxymethylcellulose Sodium Paste—*Heavy metals*	31	5	1349
Cefaclor Tablets (new)	29	6	1858
Cefadroxil for Oral Suspension—*Water*	31	4	1045
Citalopram Hydrobromide (new)	31	3	742
Citalopram Tablets (new)	31	4	1046
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid (delayed implementation to January 1, 2009)*	31	2	394
Cladribine (new)	31	2	395
Cladribine—*Specific rotation, Related compounds, Limit of residual solvents*	31	6	1609
Clindamycin Hydrochloride Oral Solution—*pH*	31	5	1350

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Cloxacillin Benzathine—*Assay*	31	4	1050
Cloxacillin Benzathine Intramammary Infusion—*Assay*	31	4	1051
Cyanocobalamin—*Pseudo cyanocobalamin*	31	5	1350
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Diclofenac Potassium (new)	31	5	1350
Diclofenac Potassium Tablets (new)	31	5	1352
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Didanosine (new)	31	5	1355
Didanosine for Oral Solution (new)	31	5	1357
Didanosine Tablets (new)	31	5	1359
Digoxin Oral Solution—*Assay*	31	5	1361
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1612
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1614
Diphtheria Toxin for Schick Test (delete)	31	6	1616
Divalproex Sodium (new)	31	5	1362
Docusate Calcium—*Limit of bis(2-ethylhexyl)maleate*	31	3	752
Docusate Potassium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Docusate Sodium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Drospirenone (new)	31	3	754
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Ensulizole—*USP Reference standards, Assay*	31	6	1617
Estradiol and Norethindrone Acetate Tablets (new)	31	5	1364
Estradiol Transdermal System (new)	31	4	1063
Estradiol Vaginal Tablets (new)	31	6	1617
Conjugated Estrogens—*Definition*	30	3	840
Synthetic Conjugated Estrogens (new)	31	6	1620
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add), *Related compounds*	31	4	1067
Ethyl Chloride—*Alcohol* (delete)	31	5	1368
Etidronate Disodium—*Limit of phosphite*	31	6	1625
Fenofibrate (new)	31	3	763
Fentanyl (new)	31	6	1626
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Fluconazole—*Definition, Labeling* (add), *USP Reference standards, Melting range* (delete), *Related compounds*	31	5	1368
Flumazenil—*USP Reference standards, Related compounds, Assay*	31	6	1628
Fluorometholone Acetate (new)	31	5	1371
Flurazepam Hydrochloride—*Identification*	31	3	766
Flurbiprofen—*Identification*	31	4	1069
Fluticasone Propianate—*Chemical information, Definition, Assay*	31	4	1070
Fluticasone Propianate Nasal Spray (new)	31	4	1071
Fluvoxamine Maleate Tablets (new)	30	5	1622
Fosinopril Sodium (new)	30	6	2001
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Gemcitabine for Injection—*USP Reference standards, Chromatographic purity*	31	6	1630
Glipizide and Metformin Hydrochloride Tablets (new)	31	6	1631
Glucagon—*Assay*	31	6	1635
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Dissolution*	29	2	418
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Glycopyrrolate Tablets—*Identification, Dissolution*	31	4	1077
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	31	6	1637
Helium—*USP Reference standards* and *Assay* (postponed indefinitely)	31	4	1014
Helium—*Definition, Packaging and storage*	31	4	1077
Hepatitis B Virus Vaccine Inactivated (delete)	31	6	1641
Hydrocodone Bitartrate—*USP Reference standards Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hyoscyamine Sulfate—*USP Reference standards, Identification, Melting temperature* (delete), *Loss on drying* (delete), *Water* (add), *Residue on ignition, Other alkaloids* (delete), *Readily carbonizable substances* (delete), *Chromatographic purity* (add), *Assay*	31	4	1078
Hyoscyamine Sulfate Elixir—*Identification*	31	5	1372
Hyoscyamine Sulfate Injection—*Identification*	31	5	1373
Hyoscyamine Sulfate Oral Solution—*Identification*	31	5	1373
Hyoscyamine Sulfate Tablets—*Identification*	31	5	1374
Hypromellose Ophthalmic Solution—*Identification*	31	3	771
Ibuprofen—*Assay*	31	5	1374
Insulin—*USP Reference standards*	31	5	1375
Insulin Human—*USP Reference standards*	31	5	1375
Sodium Iodide I 123 Capsules—*Definition*	31	6	1642
Sodium Iodide I 123 Solution—*Definition, Radionuclidic purity, Bacterial endotoxins, pH*	31	6	1642
Sodium Iodide I 131 Solution—*pH*	31	6	1643
Irbesartan Tablets (new)	31	4	1080
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isopropyl Alcohol—*USP Reference standards* (add), *Identification*	31	5	1375
Isosorbide Dinitrate Tablets—*Dissolution, Assay*	31	5	1375
Isosorbide Dinitrate Chewable Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Extended-Release Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Sublingual Tablets—*Dissolution, Assay*	31	5	1377
Diluted Isosorbide Mononitrate—*USP Reference standards, Identification, pH* (delete), *Water* (delete), *Residue on ignition* (delete), *Related compounds, Assay*	31	6	1643
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082

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Ivermectin—*Specific rotation, Limit of alcohol and formamide*	31	6	1645
Ketoprofen—*Assay*	31	3	772
Ketoprofen Extended-Release Capsules (new)	31	5	1378
Leflunomide (new)	31	5	1380
Leflunomide Tablets (new)	31	5	1383
Leuprolide Acetate (new)	30	3	882
Levocabastine Hydrochloride (new)	31	6	1647
Lidocaine and Prilocaine Cream (new)	31	4	1087
Lindane—*Definition, Assay*	31	6	1648
Lipid Injectable Emulsion (new)	31	2	416
Lisinopril Tablets—*Dissolution*	31	4	1090
Lithium Carbonate Extended-Release Tablets—*Dissolution*	31	5	1385
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	419
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	31	5	1386
Magnesium Chloride—*Identification*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	421
Magnesium Oxide—*Labeling, Bulk density* (add)	31	4	1091
Mangafodipir Trisodium—*Limit of residual solvents*	31	6	1650
Megestrol Acetate Oral Suspension—*Dissolution*	31	5	1387
Meloxicam (new)	31	1	57
Metformin Hydrochloride—*Related compounds*	31	4	1092
Metformin Hydrochloride Tablets—*Identification, Related compounds*	31	4	1093
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
Methoxyflurane—*Foreign odor* (delete)	31	5	1388
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Miconazole Nitrate Vaginal Suppositories—*Assay*	31	5	1389
Mirtazapine—*Heavy metals*	31	6	1650
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage*	30	4	1264
Nefazodone Hydrochloride (new)	31	4	1094
Nefazodone Hydrochloride Tablets (new)	31	4	1096
Nitrous Oxide—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1014
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate—*USP Reference standards, Limit of residual solvents, Chromatographic purity, Assay*	31	5	1390
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole—*Chromatographic purity*	31	4	1100

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Omeprazole Delayed-Release Capsules—*Identification, Chromatographic purity*	31	5	1392
Ondansetron Injection—*Chromatographic purity*	31	6	1651
Ondansetron Oral Solution—*Packaging and storage*	30	3	905
Ondansetron Orally Disintegrating Tablets (new)	31	4	1101
Orphenadrine Citrate Injection—*Assay*	31	6	1651
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete), *Related compounds* (add), *Assay*	31	1	64
Oxaprozin—*Packaging and storage*	29	4	1059
Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new)	31	6	1652
Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxygen—*Definition, Packaging and storage*	31	4	1107
Oxygen 93 Percent—*Definition, Packaging and storage*	31	4	1107
Pamidronate Disodium (new)	31	4	1108
Pamidronate Disodium for Injection (new)	31	4	1111
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital Sodium—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
PEG 3350 and Electrolytes for Oral Solution—*Title* (name change—*delayed implementation to February 1, 2009*), *Definition, Assay for potassium and sodium*	31	5	1393
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay (delayed implementation to January 1, 2009)*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Pravastatin Sodium (new)	31	5	1394
Prednicarbate (new)	31	5	1398
Prednicarbate Cream (new)	31	6	1655
Prednicarbate Ointment (new)	31	6	1657
Quinapril Tablets—*Packaging and storage*	29	4	1071
Ramipril—*Definition, Assay*	31	3	787
Ranitidine Hydrochloride—*USP Reference standards, Chromatographic purity, Assay*	30	6	2033
Oral Rehydration Salts—*USP Reference standards* (add), *Identification F* (delete), *Assay for citrate (delayed implementation to January 1, 2009)*	31	5	1399
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Risperidone (new)	31	6	1659
Ritonavir (new)	31	3	788
Rubella and Mumps Virus Vaccine Live (delete)	31	6	1662
Saccharin Calcium (new)—*Harmonization*	31	2	607

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Saccharin Sodium (new)—*Harmonization*	31	4	1225
Saquinavir Mesylate—*Identification*	31	5	1400
Schick Test Control (delete)	31	6	1662
Sevoflurane (new)	30	1	178
Simvastatin—*Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	31	3	792
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	31	3	795
Sodium Bicarbonate Injection—*Packaging and storage*	31	5	1401
Sodium Chloride—*Identification, Loss on drying, Limit of phosphates, Limit of potassium*	31	5	1401
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate (delayed implementation to April 1, 2009)*	31	3	797
Sodium Lactate Injection—*Identification B* (delete)	31	5	1402
Sodium Phosphates Rectal Solution—*Assay*	31	5	1403
Sodium Salicylate Tablets—*USP Reference standards* (add)	31	4	1116
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Stavudine Capsules—*Assay*	31	5	1403
Succinylcholine Chloride—*Limit of ammonium salts* (delete), *Chromatographic purity*	31	5	1404
Sulfamethazine Granulated—*Assay*	31	3	797
Talc—*Packaging and storage* (new), *Limit of iron, Limit of calcium, Limit of aluminum*	31	6	1662
Tazobactam (new)	31	4	1116
Technetium Tc 99m Fanolesomab Injection (new)—*Packaging and storage* (add)	31	5	1405
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thioridazine Hydrochloride—*Identification*	31	3	798
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Titanium Dioxide—*Definition, Packaging and storage, Labeling, Loss on ignition, Water-soluble substances, Acid-soluble substances, Limit of lead* (add), *Limit of antimony* (add), *Limit of mercury* (add), *Organic volatile impurities* (delete), *Assay*	30	4	1301
Tizanidine Tablets (new)	31	2	456
Tolazamide—*Chromatographic purity*	31	4	1118
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Travoprost (new)	31	4	1119
Travoprost Ophthalmic Solution (new)	31	4	1121
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800
Tricitrates Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	465
Triclosan—*USP Reference standards; Limit of monochlorophenols and 2,4-dichlorophenol; Limit of 1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran; Assay*	31	5	1408
Trimethoprim—*Packaging and storage*	31	5	1409
Tryptophan—*Chloride, Sulfate*	31	5	1410
Tylosin Tartrate (new)	31	5	1410
Ursodiol Capsules—*Dissolution*	31	3	800
Valsartan (new)	29	6	1996
Valsartan and Hydrochlorothiazide Tablets (new)	31	4	1123
Valproic Acid Injection (new)—*Title (delayed implementation to October 1, 2007)*	31	5	1412
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add)	30	6	2055

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Vasopressin—*Identification*	31	4	1127
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins*	31	2	468
Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Sterile Purified Water—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Dietary Supplements Monographs			
Ademetionine Disulfate Tosylate (new)	31	2	469
Acesulfame Potassium—*Packaging and storage* (add), *Limit of fluoride*	31	3	811
Black Cohosh (new)	28	5	1455
Powdered Black Cohosh (new)	28	5	1460
Powdered Black Cohosh Extract (new)	28	5	1461
Black Cohosh Tablets (new)	28	5	1462
Ethylcellulose Aqueous Dispersion—*Identification*	31	3	811
Ethylparaben—*Identification*	31	3	812
Gamma Cyclodextrin (new)	31	3	812
Powdered Ginkgo Extract (new)	27	2	2233
Lutein—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1133
Lutein Preparation—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1134
Tomato Extract Containing Lycopene—*Microbial enumeration, Limit of aflatoxins*	30	2	578
Maleic Acid—*Identification*	31	3	815
Maltose—*Water*	31	3	815
Fish Oil Containing Omega-3 Acids (new)	31	2	474
Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481
Olive Oil—*Definition, Labeling* (add), *Teaseed oil*	31	3	815
Phenoxyethanol—*Chromatographic purity, Assay*	31	3	816
Polyethylene Glycol (new)—*Harmonization*	31	3	897
Polyoxyl 10 Oleyl Ether—*Free ethylene oxide*	31	3	816
Polyoxyl 20 Oleyl Cetostearyl Ether—*Free ethylene oxide*	31	3	817
Pygeum Extract—*Packaging and storage*	30	3	956
Sodium Benzoate—*USP Reference standards* (add), *Identification*	31	3	818
Sucrose (new)—*Harmonization*	31	3	902
Sugar Spheres—*Identification, Specific rotation*	31	3	819
Tagatose (new)	31	3	819
Thymol—*USP Reference standards* (add), *Identification*	31	3	821
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Xanthan Gum—*Assay*	31	3	821
USP General Test Chapters			
⟨1⟩ Injections—*Labels and Labeling, Packaging*	31	5	1428

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⟨1⟩ Injections—*Packaging—Printing on Ferrules and Cap Overseals* (postponed indefinitely)	31	6	1599
⟨1⟩ Injections *(Harmonization)—Packaging*	31	1	192
⟨11⟩ USP Reference Standards—	26	4	1101
	27	1	1832
	27	6	3348
	28	2	433
	28	3	839
	28	5	1468
	29	3	710
	29	5	1601
	29	6	2022
	30	2	613
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
	31	3	822
	31	4	1154
	31	5	1433
	31	6	1680
⟨41⟩ Weights and Balances—*Introduction, Weights, Balances*	31	2	508
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests *(Harmonization)—Title, Introduction, General Procedures, Enumeration Methods, Growth Promotion Test and Suitability of the Counting Method, Testing of Products*	29	5	1714
⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) *(Harmonization)—Title, Introduction, General Proce dures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
⟨121⟩ Insulin Assays—*Appendix* (add)	30	5	1675
⟨231⟩ Heavy Metals—*Method II*	31	5	1435
⟨267⟩ Porosimetry by Mercury Intrusion (new)—*Harmonization*	31	3	905
⟨281⟩ Residue on Ignition—*Harmonization*	31	5	1526
⟨345⟩ Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514
⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures (delayed implementation to January 1, 2006)*	30	1	220
⟨401⟩ Fats and Fixed Oils—*Acid Value (Free Fatty Acids)*	31	4	1157
⟨429⟩ Light Diffraction Measure of Particle Size (new)—*Harmonization*	31	4	1234
⟨467⟩ Organic Volatile Impurities—*Title (delayed implementation to January 1, 2007); Residual Solvents Limits; Identification, Control, and Quantification of Residual Solvents; Other Analytical Procedures* (delete); *Appendix 1*	31	5	1435
⟨616⟩ Bulk Density and Tapped Density—*Harmonization*	31	3	909
⟨621⟩ Chromatography—*Interpretation of Chromatograms, System Suitability, Glossary of Symbols, Chromatographic reagents*	31	6	1681
⟨644⟩ Conductivity (new)	31	3	841
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490

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⟨699⟩ Density of Solids (new)—*Harmonization*	31	3	912
⟨711⟩ Dissolution—*Introduction, Procedure, Interpretation*	31	6	1691
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	31	5	1448
⟨730⟩ Inductively-Coupled Plasma—*References* (add)	30	3	1022
⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	31	3	845
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *(Harmonization)*	31	1	228
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
⟨941⟩ X-Ray Diffraction (new)—*Harmonization*	31	4	1241
General Information Chapters			
⟨1058⟩ Analytical Instrument Qualification (new)	31	5	1453
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	30	5	1706
⟨1072⟩ Disinfectants and Antiseptics (new)	30	6	2108
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients—*Background* (delete), *General Guidance* (delete), *Excipient Quality Systems* (delete), *Appendix 1* (delete), *Appendix* (delete), *Background* (add), *General Guidance* (add), *Quality Management System—Excipient Quality Systems* (add), *Management Responsibility* (add), *Resource Management* (add), *Product Realization* (add), *Measurement, Analysis, and Improvement* (add), *Appendix 1* (add), *Appendix 2* (add)	28	5	1504
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	31	4	1167
⟨1082⟩ Genotoxicity Testing (new)	30	1	264
⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1092⟩ The Dissolution Procedure: Development and Validation (new)	31	5	1463
⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products—*Introduction (Tables 1 and 2)*	29	5	1733
⟨1112⟩ Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new)	30	5	1709

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⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add),*Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding—*Basic Pharmaceutical Calculations*	31	3	847
⟨1184⟩ Sensitization Testing (new)	30	1	289
⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)	31	4	1180
⟨1208⟩ Sterility Testing—Validation of Isolator Systems—*Introduction, Isolator Design and Construction, Validation of the Isolator System, Package Integrity Verification, Maintenance of Asepsis Within the Isolator Environment, Interpretation of Sterility Test Results, Training and Safety*	30	6	2162
⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1217⟩ Tablet Breaking Force (new)	31	6	1695
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1223⟩ Validation of Alternative Microbiological Methods (new)	31	5	1475
⟨1225⟩ Validation of Compendial Methods—*Title, Introduction, Submissions to the Compendia, Validation*	31	2	549
⟨1226⟩ Verification of Compendial Procedures (new)	31	2	555
⟨1230⟩ Water for Health Applications—*Microbial Considerations*	31	5	1486
⟨1232⟩ Instrumentation for Analysis of High Purity PharmaceuticalWaters (new)	30	5	1806
⟨2030⟩ Supplemental Information for Articles of Botanical Origin (new)	31	2	555
Reagent Specifications			
2-Aminophenol	31	5	1487
3-Aminopropionic Acid	31	4	1189
3-Aminosalicylic Acid	31	5	1487
Anion-Exchange Resin, Strong, Lightly Cross-Linked, in the Chloride Form	31	3	858

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L-Arabinitol (delete)	31	5	1487
Bacterial Alkaline Protease Preparation	30	2	644
Barbituric Acid (new)	29	1	265
Benzaldehyde	31	2	574
1-Butaneboronic Acid (delete)	31	4	1189
Butyl Methacrylate (new)	31	4	1189
n-Butylboronic Acid	31	4	1189
Deuterated Methanol (new)	29	6	2054
2,8-Dichlorodibenzo-*p*-dioxin (delete)	30	6	2168
2,8-Dichlorodibenzofuran (delete)	30	6	2168
2,4-Dichlorophenol (delete)	30	6	2168
Dicyclohexyl	31	3	858
DEAE-Agarose (new)	29	1	265
2-Dimethylaminoethyl Methacrylate (new)	31	4	1190
N,N-Dimethyldodecylamine-*N*-oxide (new)	27	4	2837
Docusate Sodium (new)	31	4	1190
Dodecyltrimethylammonium Bromide (new)	31	3	859
Erythritol (delete)	31	5	1487
Ethylene Oxide in Methylene Chloride (50 mg/mL) (new)	31	3	859
Furfural	31	4	1190
Galactitol (delete)	31	5	1488
Geneticin (new)	31	6	1700
Hexadimethrine Bromide (new)	29	1	265
Hydroxypropyl-β-cyclodextrin (new)	31	6	1701
Isoferulic Acid (new)	27	4	2837
Isopropyl Iodide	31	6	1701
Lead Standard Solution (new)	31	5	1488
Magnesium Matrix Modifier (new)	31	5	1488
Nitric Acid, 65 Percent (new)	31	5	1488
Palladium Matrix Modifier (new)	31	5	1488
Anion-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Cation-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Thrombin Human (new)	29	6	2055
2,4,8-Trichlorodibenzofuran (delete)	30	6	2169
1,3,7-Trichlorodibenzo-*p*-dioxin (delete)	30	6	2169
Saccharin Calcium	31	2	607
Saccharin Calcium—*Harmonization*	31	2	609
Saccharin Sodium	31	2	612
Saccharin Sodium—*Harmonization*	31	2	613
Sodium Carbonate, Monohydrate (new)	31	6	1701
1-Vinyl-2-pyrrolidone	31	6	1701
Zinc Sulfate Heptahydrate (new)	26	2	504
Test Solutions			
Phenol TS (new)	31	3	859
Sodium Citrate TS, Alkaline (new)	31	3	859
Sodium Tetraphenylboron TS	31	5	1489
Volumetric Solutions			
Iodine, Hundreth-Normal (0.01 N)	31	5	1489
Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)	31	5	1490
Reference Tables			
Container Specifications for Capsules and Tablets	31	6	1702
Excipients, USP and NF Excipients, Listed by Category	31	6	1664
Description and Solubility	25	4	8589
	25	6	9254
	26	4	1135
	27	1	1908
	28	2	554
	28	6	1953
	29	1	266
	29	3	812

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
	29	5	1684
	30	4	1405
	30	5	1822
	31	1	122
	31	2	591
	31	3	861
	31	4	1193
	31	5	1491
	31	6	1703
NF Monographs			
Amino Methacrylate Copolymer (new)	31	4	1137
Calcium Silicate—*Definition, USP Reference standards* (add), *pH, Lead* (delete), *Limit of lead* (add), *Limit of fluoride, Assay for silicon dioxide, Assay for calcium oxide, Ratio of silicon dioxide to calcium oxide*	31	5	1417
Canola Oil (new)	31	6	1667
Carboxymethylcellulose Calcium—*Heavy metals*	31	5	1420
Carboxymethylcellulose Sodium 12—*Labeling, Viscosity, Heavy metals*	31	5	1420
Cellaburate—*Packaging and storage* (add)	31	5	1420
Microcrystalline Cellulose—*Labeling, Identification, Particle size distribution estimation by analytical sieving*	31	5	1421
Powdered Cellulose—*Identification B*	31	5	1421
Corn Syrup (new)	28	2	403
High Fructose Corn Syrup (new)	28	2	408
Corn Syrup Solids (new)	28	6	1894
Crospovidone—*Monograph*	28	4	1257
Cyclomethicone—*Identification*	31	4	1140
Dibutyl Sebacate—*Saponification value*	31	4	1140
Diethanolamine—*USP Reference standards* (add), *Identification*	31	5	1422
Diisopropanolamine (new)	31	4	1140
Erythritol (new)	31	5	1422
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion (new)	31	4	1141
Ethylcellulose Aqueous Dispersion—*Labeling, Identification*	31	6	1668
Glyceryl Monostearate—*Labeling, USP Reference standards* (delete), *Assay for monoglycerides*	31	6	1669
Hydroxyethyl Cellulose (new)—*Harmonization*	30	2	709
Hydroxypropyl Cellulose—*USP Reference standards* (add), *Identification*	31	5	1425
Low-Substituted Hydroxypropyl Cellulose—*Harmonization*	30	1	338
Isobutane—*Limit of sulfur compounds* (delete)	31	5	1425
Lactitol—*Related compounds*	31	4	1143
Magnesium Stearate—*Microbial limits*	29	6	2018
Magnesium Stearate—*Harmonization*	30	1	340
Maltitol (new)	31	4	1143
Maltol—*Packaging and storage*	31	5	1425
Monoethanolamine—*USP Reference standards* (add), *Identification* (add)	31	5	1425
Nitrogen—*Definition, Packaging and storage, Assay*	31	4	1145
Nitrogen 97 Percent—*Definition, Packaging and storage, Assay*	31	4	1146
Oleyl Oleate (new)	31	6	1670
Paraffin—*Readily carbonizable substances*	31	5	1426
Polacrilin Potassium—*CAS number, Chemical name*	31	6	1671
Polyethylene Glycol—*Harmonization*	31	3	897
Polyoxyl 35 Castor Oil—*Viscosity*	31	6	1671
Potassium Alginate (new)	31	5	1426
Saccharin	31	2	616
Saccharin (new)—*Harmonization*	31	2	618

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Sesame Oil—*USP Reference standards* (add), *Triglyceride composition*	30	5	1668
Silicon Dioxide (new)—*Harmonization*	31	4	1229
Colloidal Silicon Dioxide (new)—*Harmonization*	31	4	1233
Sodium Starch Glycolate—*Harmonization*	31	5	1523
Sodium Sulfite—*Identification*	31	4	1146
Sorbitol Sorbitan Solution—*Title statement*	31	6	1671
Rice Starch (new)—*Harmonization*	30	2	721
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706
Sucralose—*Limit of hydrolysis products*	31	4	1146
Sucrose—*Harmonization*	31	3	902
Compressible Sugar—*Loss on drying*	31	4	1147
Confectioner's Sugar—*Identification*	31	4	1147
Tagatose (new)	30	5	1672
Tetrafluoroethane (new)	31	6	1672
Trolamine—*USP Reference standards* (add), *Identification*	31	5	1427
Xylitol—*USP Reference standards, Limit of other polyols, Assay*	31	4	1147

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[*PF* 32(1)–*PF* 32(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
USP Monographs			
†Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
†Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
†Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
†Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
†Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
†Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
†Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
†Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
†Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
†Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albuterol Tablets—			
†*Dissolution*	30	1	50
†*Dissolution*	31	1	40
†Alprazolam Tablets—*Dissolution*	30	5	1582
†Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
†Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
†Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
†Ampicillin Capsules—*Dissolution*	30	1	55
†Ampicillin Tablets—*Dissolution*	30	1	56
†Ascorbic Acid Tablets—*Dissolution*	30	1	60
†Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
†Baclofen Tablets—*Dissolution*	30	1	61
†Betamethasone Tablets—*Dissolution*	30	1	62
†Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
†Calcium Lactate Tablets—*Dissolution*	30	1	81
†Calcium Pantothenate Tablets—*Dissolution*	30	1	81
†Carboxymethylcellulose Sodium Suspension (entire submission)	30	3	812
†Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
†Colchicine Tablets—*Dissolution*	30	1	91
†Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
†Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
†Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
†Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
†Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add)	29	6	1870
†Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
†Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
†Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
†Estradiol Transdermal System (new)—*Drug release*	30	4	1201
†Ethinyl Estradiol Tablets—*Related compounds*	31	2	402
†Ethosuximide Capsules—*Dissolution*	30	1	102
†Fluticasone Propionate—*Content of acetone (Procedure)*	31	4	1070
†Gabapentin Capsules (new) (entire submission)	28	2	298
†Glycopyrrolate Tablets—*Dissolution*	30	1	105
†Guaifenesin Capsules—*Dissolution*	30	1	106

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
†Guaifenesin Tablets—*Dissolution*	30	1	107
†Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
†Indocyanine Green—*Definition, Assay*	29	6	1905
†Irbesartan Tablets (new)—*Dissolution*	29	4	1035
†Isosorbide Dinitrate Sublingual Tablets—*Dissolution*	30	1	113
†Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
†Levothyroxine Sodium Oral Solution (new)—*Preview*	31	3	938
†Lisinopril Tablets—*Dissolution*	30	1	121
†Loperamide Hydrochloride Tablets—*Dissolution*	30	5	1633
†Magnesium Oxide—*Bulk density* (add)	29	4	1047
†Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
†Meprobamate Tablets—*Dissolution*	30	1	129
†Methenamine Tablets—*Dissolution*	30	1	130
†Methocarbamol Tablets—*Dissolution*	30	1	130
†Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
†Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
†Neostigmine Bromide Tablets—*Dissolution*	30	1	133
†Niacinamide Tablets—*Dissolution*	30	1	139
†Ondansetron Orally Disintegrating Tablets (new)—*Disintegration, Dissolution*	30	6	2024
†Oxybutynin Chloride Extended-Release Tablets (new) (entire submission)	30	4	1276
†Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
†Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
†Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
†Penicillamine Capsules—*Dissolution*	30	1	153
†Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
†Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
†Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
†Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
†Pimozide Tablets—*Dissolution*	30	1	164
†Pindolol Tablets—*Dissolution*	30	1	165
†Piperazine Citrate Tablets—*Dissolution*	30	1	165
†Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
†Propantheline Bromide Tablets—*Dissolution*	30	1	170
†Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
†Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
†Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
†Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
†Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036
†Spironolactone Oral Suspension (new) (entire submission)	30	3	929
†Spironolactone and Hydrochlorothiazide Oral Suspension (new) (entire submission)	30	3	930
†Terbutaline Sulfate Tablets—*Dissolution*	31	1	76
†Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
†Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
†Timolol Maleate Tablets—*Dissolution*	30	1	191
†Titanium Dioxide (new) (entire submission)	30	4	1304
†Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
†Vecuronium Bromide for Injection (new)—*Preview*	25	4	8449
Dietary Supplements Monographs			
†Ginkgo Capsules (new)—*Disintegration and dissolution*	27	2	2238
†Ginkgo Tablets (new)—*Disintegration and dissolution*	27	2	2240
†Asian Ginseng Capsules (new)—*Dissolution*	30	2	571
†American Ginseng Capsules (new)—*Dissolution*	30	2	565

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
†American Ginseng Tablets—*Dissolution*	30	2	567
†Valerian Capsules (new)—*Disintegration and dissolution*	27	1	1825
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
†*USP Fluvastatin for System Suitability RS* (add)	31	1	99
†*USP Polyoxyl 35 Castor Oil RS*	30	5	1674
†⟨386⟩ Environmentally Sensitive Preparations (new) (entire submission)	30	5	1680
†⟨429⟩ Light Diffraction Measure of Particle Size (new) (entire submission)	28	3	895
†⟨621⟩ Chromatography—*System Suitability (All revisions after the first two paragraphs, through the end up to Glossary)*	30	6	2094
†⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets* (delete), *Interpretation*	30	1	234
USP General Information Chapters			
†⟨1089⟩ In Vitro, Absorption-Indicating Cell Culture System (new)—*Preview*	25	5	8733
Reagents, Indicators, and Solutions			
†1,4-Butanediol (added)—*Preview*	25	5	8747
†1-Vinyl-2-pyrrolidone	31	1	108
Reference Tables			
Container Specifications			
†Citalopram Hydrobromide Tablets (added)	31	3	859
Description and Relative Solubility			
†Magnesium Oxide	29	4	1262
†Titanium Dioxide (added)	30	4	1405
NF Monographs			
†Alfadex—*Packaging and storage*	30	1	202
†Sodium Caprylate—*Packaging and storage*	30	3	990

†New cancellations in *PF* 32(1).

In-Process Revision

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled

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[*PF* 32(1)–*PF* 32(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
USP Monographs			
†Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
†Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
†Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
†Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
†Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
†Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
†Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
†Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
†Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
†Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albuterol Tablets—			
†*Dissolution*	30	1	50
†*Dissolution*	31	1	40
†Alprazolam Tablets—*Dissolution*	30	5	1582
†Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
†Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
†Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
†Ampicillin Capsules—*Dissolution*	30	1	55
†Ampicillin Tablets—*Dissolution*	30	1	56
†Ascorbic Acid Tablets—*Dissolution*	30	1	60
†Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
†Baclofen Tablets—*Dissolution*	30	1	61
†Betamethasone Tablets—*Dissolution*	30	1	62
†Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
†Calcium Lactate Tablets—*Dissolution*	30	1	81
†Calcium Pantothenate Tablets—*Dissolution*	30	1	81
†Carboxymethylcellulose Sodium Suspension (entire submission)	30	3	812
†Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
†Colchicine Tablets—*Dissolution*	30	1	91
†Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
†Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
†Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
†Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
†Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add)	29	6	1870
†Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
†Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
†Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
†Estradiol Transdermal System (new)—*Drug release*	30	4	1201
†Ethinyl Estradiol Tablets—*Related compounds*	31	2	402
†Ethosuximide Capsules—*Dissolution*	30	1	102
†Fluticasone Propionate—*Content of acetone (Procedure)*	31	4	1070
†Gabapentin Capsules (new) (entire submission)	28	2	298
†Glycopyrrolate Tablets—*Dissolution*	30	1	105
†Guaifenesin Capsules—*Dissolution*	30	1	106

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals*		
	Vol.	*No.*	*Page(s)*
†Guaifenesin Tablets—*Dissolution*	30	1	107
†Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
†Indocyanine Green—*Definition, Assay*	29	6	1905
†Irbesartan Tablets (new)—*Dissolution*	29	4	1035
†Isosorbide Dinitrate Sublingual Tablets—*Dissolution*	30	1	113
†Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
†Levothyroxine Sodium Oral Solution (new)—*Preview*	31	3	938
†Lisinopril Tablets—*Dissolution*	30	1	121
†Loperamide Hydrochloride Tablets—*Dissolution*	30	5	1633
†Magnesium Oxide—*Bulk density* (add)	29	4	1047
†Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
†Meprobamate Tablets—*Dissolution*	30	1	129
†Methenamine Tablets—*Dissolution*	30	1	130
†Methocarbamol Tablets—*Dissolution*	30	1	130
†Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
†Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
†Neostigmine Bromide Tablets—*Dissolution*	30	1	133
†Niacinamide Tablets—*Dissolution*	30	1	139
†Ondansetron Orally Disintegrating Tablets (new)—*Disintegration, Dissolution*	30	6	2024
†Oxybutynin Chloride Extended-Release Tablets (new) (entire submission)	30	4	1276
†Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
†Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
†Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
†Penicillamine Capsules—*Dissolution*	30	1	153
†Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
†Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
†Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
†Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
†Pimozide Tablets—*Dissolution*	30	1	164
†Pindolol Tablets—*Dissolution*	30	1	165
†Piperazine Citrate Tablets—*Dissolution*	30	1	165
†Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
†Propantheline Bromide Tablets—*Dissolution*	30	1	170
†Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
†Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
†Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
†Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
†Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036
†Spironolactone Oral Suspension (new) (entire submission)	30	3	929
†Spironolactone and Hydrochlorothiazide Oral Suspension (new) (entire submission)	30	3	930
†Terbutaline Sulfate Tablets—*Dissolution*	31	1	76
†Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
†Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
†Timolol Maleate Tablets—*Dissolution*	30	1	191
†Titanium Dioxide (new) (entire submission)	30	4	1304
†Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
†Vecuronium Bromide for Injection (new)—*Preview*	25	4	8449
Dietary Supplements Monographs			
†Ginkgo Capsules (new)—*Disintegration and dissolution*	27	2	2238
†Ginkgo Tablets (new)—*Disintegration and dissolution*	27	2	2240
†Asian Ginseng Capsules (new)—*Dissolution*	30	2	571
†American Ginseng Capsules (new)—*Dissolution*	30	2	565

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
†American Ginseng Tablets—*Dissolution*	30	2	567
†Valerian Capsules (new)—*Disintegration and dissolution*	27	1	1825
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
†*USP Fluvastatin for System Suitability RS* (add)	31	1	99
†*USP Polyoxyl 35 Castor Oil RS*	30	5	1674
†⟨386⟩ Environmentally Sensitive Preparations (new) (entire submission)	30	5	1680
†⟨429⟩ Light Diffraction Measure of Particle Size (new) (entire submission)	28	3	895
†⟨621⟩ Chromatography—*System Suitability (All revisions after the first two paragraphs, through the end up to Glossary)*	30	6	2094
†⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets* (delete), *Interpretation*	30	1	234
USP General Information Chapters			
†⟨1089⟩ In Vitro, Absorption-Indicating Cell Culture System (new)—*Preview*	25	5	8733
Reagents, Indicators, and Solutions			
†1,4-Butanediol (added)—*Preview*	25	5	8747
†1-Vinyl-2-pyrrolidone	31	1	108
Reference Tables			
Container Specifications			
†Citalopram Hydrobromide Tablets (added)	31	3	859
Description and Relative Solubility			
†Magnesium Oxide	29	4	1262
†Titanium Dioxide (added)	30	4	1405
NF Monographs			
†Alfadex—*Packaging and storage*	30	1	202
†Sodium Caprylate—*Packaging and storage*	30	3	990

†New cancellations in *PF* 32(1).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

Harmonization

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

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

BRIEFING

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

(DSN: L. Evans) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

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Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in the *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

All manuscripts are subject to review by USP headquarters staff, Committee members, or qualified outside referees, and if accepted for publication will be subject to editing by USP staff. Accepted manuscripts become the property of the USP Convention (USPC) and may not be published elsewhere without written permission from the USPC. Authors are also responsible for obtaining permission for reprinting any illustrations that have been published elsewhere.

Abstract—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

References—Consult a current copy of the *Pharmacopeial Forum* and the *ACS Style Guide* for assistance with reference style.

Copyright—Copyright transfer documents will be sent to authors after manuscripts have been accepted for publication.

Contact Person—When submitting a manuscript, designate one author of the article as correspondent and include that author's full address, telephone number, fax number, and e-mail address.

Submission Instructions—Manuscripts must be submitted both as an electronic file and as a printed copy of the electronic file. Submit the text in Microsoft® Word or another current word-processing application. The preferred format for graphics submitted electronically is tagged image file format (TIFF). Graphics that cannot be submitted electronically must be camera-ready, of easily reproducible quality and size, and clearly labeled. Photocopies are not acceptable. Manuscripts submitted for publication should be addressed to:

Pharmacopeial Forum
Executive Secretariat, USP
12601 Twinbrook Pkwy.
Rockville, MD 20852

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

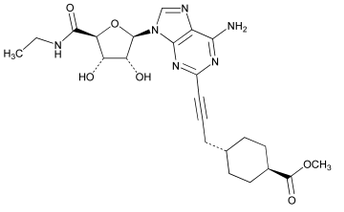
USP Dictionary of USAN and International Drug Names
2005 USP DICTIONARY SUPPLEMENT 5

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2005 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2005) edition will be included in the next complete edition of the Dictionary.

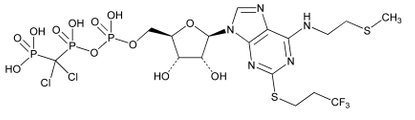
Newly Approved United States Adopted Names (USAN), Released for Publication

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

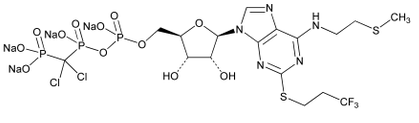
Apadenoson [*2005*] (a pa den′ oh son). $C_{23}H_{30}N_6O_6$. 486.50. (1) Cyclohexanecarboxylic acid, 4-[3-[6-amino-9-(*N*-ethyl-β-D-ribofuranuronamidosyl)-9*H*-purin-2-yl]-2-propynyl]-, methyl ester, *trans*-; (2) Methyl *trans*-4-[3-[6-amino-9-(*N*-ethyl-β-D-ribofuranosyluronamide)-9*H*-purin-2-yl]prop-2-ynyl]cyclohexanecarboxylate. *CAS-250386-15-3*. *Adjunct to nuclear myocardial perfusion imaging in patients unable to exercise adequately.* (Bristol-Myers Squibb) ✧*BMS068645*



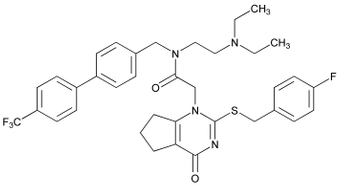
Cangrelor [*2005*] (kan′ grel or). $C_{17}H_{25}Cl_2F_3N_5O_{12}P_3S_2$. 776.36. (1) 5′-Adenylic acid, *N*-[2-(methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio]-, monoanhydride with (dichloromethylene)bis[phosphonic acid]; (2) (Dichloromethylene)diphosphonic *N*-[2-(methylsulfanyl)ethyl]-2-[(3,3,3-trifluoropropyl)sulfanyl-5′-adenylic monoanhydride. *CAS-163706-06-7*. INN; BAN. *Anti-platelet agent.* (Medical Arts) ✧*AR-C69931XX*



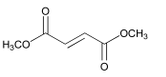
Cangrelor Tetrasodium [*2005*] (kan′ grel or). $C_{17}H_{21}Cl_2F_3N_5Na_4O_{12}P_3S_2$. 864.30. (1) 5′-Adenylic acid, *N*-[2-(methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio]-, monoanhydride with (dichloromethylene)bis[phosphonic acid], tetrasodium salt; (2) *N*-[2-(Methylthio)ethyl]-2-[(3,3,3-trifluoropropyl)thio]-5′-adenylic acid, monoanhydride with (dichloromethylene)diphosphonic acid tetrasodium salt. *CAS-163706-36-3*. *Antiplatelet agent.* (Medical Arts) ✧*AR-C69931MX*



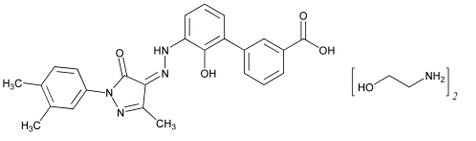
Darapladib [*2005*] (dar ap′ la lib). $C_{36}H_{38}F_4N_4O_2S$. 666.80. (1) 1*H*-Cyclopentapyrimidine-1-acetamide, *N*-[2-(diethylamino)ethyl]-2-[[(4-fluorophenyl)methyl]thio]-4,5,6,7-tetrahydro-4-oxo-*N*-[[4′-(trifluoromethyl)[1,1′-biphenyl]-4-yl]-methyl]-; (2) *N*-[2-(Diethylamino)ethyl]-2-[2-[(4-fluorobenzyl)sulfanyl]-4-oxo-4,5,6,7-tetrahydro-1*H*-cyclopentapyrimidin-1-yl]-*N*-[[4′-(trifluoromethyl)biphenyl-4-yl]-methyl]acetamide. *CAS-356057-34-6*. *Treatment of atherosclerosis.* (GlaxoSmithKline) ✧*SB-480848*



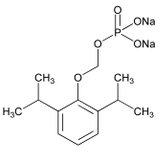
Dimethyl Fumarate [*2005*] (dye meth′ il fue′ ma rate). $C_6H_8O_4$. 144.10. (1) 2-Butenedioic acid, (2*E*)-, dimethyl ester; (2) Dimethyl (2*E*)-but-2-enedioate. *CAS-624-49-7*. *Immunomodulator.* (Biogen Idec) ✧*AZL O 211089*



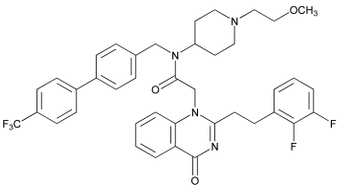
Eltrombopag Olamine [*2005*] (el trom′ boe pag). $C_{25}H_{22}N_4O_4 \cdot 2(C_2H_7NO)$. 564.60. (1) [1,1′-Biphenyl]-3-carboxylic acid, 3′-[(2*Z*)-[1-(3,4-dimethylphenyl)-1,5-dihydro-3-methyl-5-oxo-4*H*-pyrazol-4-ylidene]hydrazino]-2′-hydroxy-, compound with 2-aminoethanol (1:2); (2) 3′-[(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]diazanyl]-2′-hydroxybiphenyl-3-carboxylic acid compound with 2-aminoethanol (1:2). *CAS-496775-62-3*. *Treatment of chemotherapy-induced thrombocytopenia and treatment of immune thrombocytopenic purpura.* (GlaxoSmithKline) ✧*SB-497115-GR*



Fospropofol Disodium [*2005*] (fos proe poe′ fol). $C_{13}H_{19}Na_2O_5P$. 332.20. (1) Methanol, [2,6-bis(1-methylethyl)phenoxy]-, dihydrogen phosphate, disodium salt; (2) [2,6-Bis(1-methylethyl)phenoxy]methyl disodium phosphate; (3) 2,6-Diisopropylphenoxymethyl phosphate, disodium salt. *CAS-258516-87-9*. *Procedural sedation.* Aquavan (Guilford)

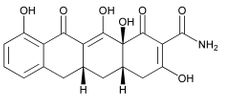


Goxalapladib [*2005*] (gox a lap′ la dib). $C_{40}H_{39}F_5N_4O_3$. 718.80. (1) 1,8-Naphthyridine-1(4*H*)-acetamide, 2-[2-(2,3-difluorophenyl)ethyl]-*N*-[1-(2-methoxyethyl)-4-piperidinyl]-4-oxo-*N*-[[4′-(trifluoromethyl)[1,1′-biphenyl]-4-yl]methyl]-; (2) 2-[2-[2-(2,3-Difluorophenyl)ethyl]-4-oxo-1,8-naphthyridin-1(4*H*)-yl]-*N*-[1-(2-methoxyethyl)piperidin-4-yl]-*N*-[[4′-(trifluoromethyl)biphenyl-4-yl]methyl]acetamide; (3) 2-{2-[2-(2,3-Difluorophenyl)ethyl]-4-oxo-1,8-naphthyridin-1(4*H*)-yl}-*N*-{1-(2-methoxyethyl)piperidin-4-yl]-*N*-[[4′-(trifluoromethyl)-1,1′-biphenyl-4-yl]methyl}acetamide. *CAS-412950-27-7*. *Treatment of atherosclerosis.* (GlaxoSmithKline)



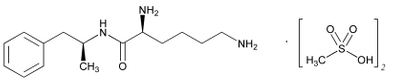
Inalimarev (CEA, MUC-1, Vaccinia virus) [*2005*] (in a lim′ a rev). PANVAC-V. The genome size is approximately 290,000 ± 50,000. *CAS-685563-13-7*. *Treatment of pancreatic cancer, CEA-bearing tumors.* Panvac (Therion Biologics)

Incyclinide [*2005*] (in sye′ kli nide). $C_{19}H_{17}NO_7$. 371.30. (1) 2-Naphthacenecarboxamide, 1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-tetrahydroxy-1,11-dioxo-, (4a*S*,5a*R*,12a*S*)-; (2) (4a*S*,5a*R*,12a*S*)-3,10,12,12a-Tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide. *CAS-15866-90-7*. *Treatment of acne, rosacea, and acute respiratory distress syndrome.* Metastat (CollaGenex) ✧*COL-3*

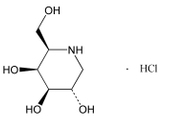


Iratumumab [*2005*] (ir″ a toom′ ue mab). Immunoglobulin G1, anti-(human CD30 (antigen)) (human monoclonal MDX-060 heavy chain), disulfide with human monoclonal MDX-060 light chain, dimer. Molecular weight is approximately 170,000 daltons. *CAS-640735-09-7*. *Oncological diseases; treatment of relapsed or refractory CD30 positive lymphoma including Hodgkin's Disease.* (Medarex) ✧*MDX-060*

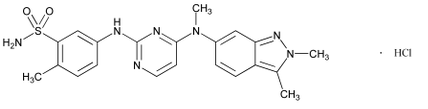
Lisdexamfetamine Dimesylate [*2005*] (lis dex″ am fet′ a meen). $C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2$. 455.60. (1) Hexanamide, 2,6-diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]-, (2S)-, dimethanesulfonate; (2) (2S)-2,6-Diamino-*N*-[(1*S*)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate. *CAS-608137-33-3*. *Treatment of attention deficit hyperactivity disorder (ADHD).* (New River) ✧*NRP104*



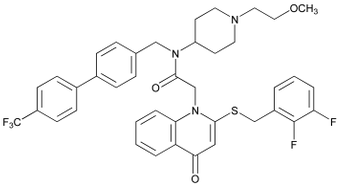
Migalastat Hydrochloride [*2005*] (mi gal′ a stat). $C_6H_{13}NO_4 \cdot HCl$. 199.63. (1) 3,4,5-Piperidinetriol, 2-(hydroxymethyl)-, hydrochloride, (2*R*,3*S*,4*R*,5*S*)-; (2) (+)-(2*R*,3*S*,4*R*,5*S*)-2-(Hydroxymethyl)piperidine-3,4,5-triol hydrochloride; (3) 1,5-Dideoxy-1,5-imino-D-galactitol hydrochloride. *CAS-75172-81-5*. *Treatment of Fabry disease.* (Amicus Therapeutics)



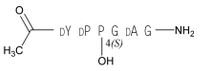
Pazopanib Hydrochloride [*2005*] (paz oh′ pa nib). $C_{21}H_{23}N_7O_2S \cdot HCl$. 474.00. (1) Benzenesulfonamide, 5-[[4-[(2,3-dimethyl-2*H*-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-, monohydrochloride; (2) 5-[[4-[(2,3-Dimethyl-2*H*-indazol-6-yl)methylamino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide monohydrochloride. *CAS-635702-64-6*. *Antineoplastic agent, a potent and selective inhibitor of VEGFR-1, -2, and -3 tyrosine kinases, blocking angiogenesis.* (GlaxoSmithKline) ✧*GW786034B*



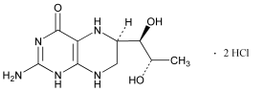
Rilapladib [*2005*] (ri lap′ la dib). $C_{40}H_{39}F_5N_3O_3S$. 735.80. (1) 1(4*H*)-Quinolineacetamide, 2-[[(2,3-difluorophenyl)-methyl]thio]-*N*-[1-(2-methoxyethyl)-4-piperidinyl]-4-oxo-*N*-[[4′-(trifluoromethyl)[1,1′-biphenyl]-4-yl]methyl]-; (2) 2-[2-[(2,3-Difluorobenzyl)sulfanyl]-4-oxoquinolin-1(4*H*)-yl]-*N*-[1-(2-methoxyethyl)piperidin-4-yl]-*N*-[[4′-(trifluoromethyl)-biphenyl-4-yl]methyl]acetamide.*CAS-412950-08-4*. *Treatment of atherosclerosis.* (GlaxoSmithKline) ✧*SB-659032*



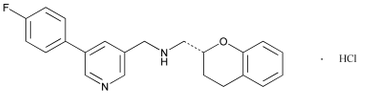
Rotigaptide [*2005*] (roe ti gap′ tide). $C_{28}H_{39}N_7O_9$. 617.70. (1) Glycinamide, *N*-acetyl-D-tyrosyl-D-prolyl-(4*S*)-4-hydroxy-D-prolylglycyl-D-alanyl-; (2) *N*-Acetyl-D-tyrosyl-D-prolyl-(4*S*)-4-hydroxy-D-prolylglycyl-D-alanylglycinamide. *CAS-355151-12-1. Treatment of ventricular tachycardia or ventricular fibrillation.* (Wyeth/Zealand) ✧*GAP (Wyeth); ZP-123 (Zealand)*



Sapropterin Dihydrochloride [*2005*] (sap″ roe ter′ in). $C_9H_{15}N_5O_3 \cdot 2HCl$. 314.20. [Sapropterin is INN.] (1) 4(1*H*)-Pteridinone, 2-amino-6-[(1*R*,2*S*)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-, dihydrochloride, (6*R*)-; (2) (6*R*)-2-Amino-6-[(1*R*,2*S*)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(1*H*)-pteridinone dihydrochloride. *CAS-69056-38-8; CAS-62989-33-7* [sapropterin]. *Treatment of mild-to-moderate phenylketonuria (PKU).* (BioMarin) ✧*T1401 (BioMarin); SUN-0588 (Shiratori)*

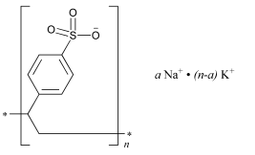


Sarizotan Hydrochloride [*2005*] (sar i zoe′ tan). $C_{22}H_{21}FN_2O \cdot HCl$. 384.90. [Sarizotan is INN.] (1) 3-Pyridinemethanamine, *N*-[[(2*R*)-3,4-dihydro-2*H*-1-benzopyran-2-yl]methyl]-5-(4-fluorophenyl)-, monohydrochloride; (2) (–)-*N*-[[(2*R*)-3,4-Dihydro-2*H*-1-benzopyran-2-yl)methyl]-5-(4-fluorophenyl)pyridine-3-yl]methanamine monohydrochloride. *CAS-195068-07-6; CAS-177975-08-5* [sarizotan]. *Treatment-associated dyskinesia in Parkinson's disease.* (EMD) ✧*EMD 128130*

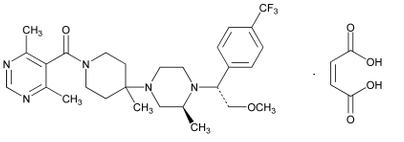


Stamulumab [*2005*] (sta mul′ ue mab). Immunoglobulin G1, anti-(human growth differentiation factor 8) (human MYO-029 heavy chain), disulfide with human MYO-029 λ-chain, dimer. *CAS-705287-60-1. Treatment of muscular dystrophy and age-related sarcopenia or frailty.* (Wyeth) ✧*MYO-029*

Tolevamer Potassium Sodium [*2005*] (tol ev′ am er). $(C_8H_7O_3S)_n \cdot K_{(n-a)} \cdot Na_a$. (1) Benzenesulfonic acid, 4-ethenyl-, potassium salt, polymer with sodium 4-ethenylbenzenesulfonate; (2) Poly[1-(4-sulfophenyl)ethylene], potassium sodium salt. Molecular weight is greater than 400,000 daltons. *CAS-81998-90-5. Treatment of Clostridium difficle associated diarrhea.* (Genzyme) ✧*GT267-004*



Vicriviroc Maleate [*2005*] (vi″ kri vir′ ok). $C_{28}H_{38}F_3N_5O_2 \cdot C_4H_4O_4$. 649.70. (1) Piperidine, 1-[(4,6-dimethyl-5-pyrimidinyl)-carbonyl]-4-[(3*S*)-4-[(1*R*)-2-methoxy-1-[4-(trifluoromethyl)-phenyl]ethyl]-3-methyl-1-piperazinyl]-4-methyl-, (2*Z*)-2-butenedioate (1:1); (2) 1-[(4,6-Dimethylpyrimidin-5-yl)carbonyl]-4-[(3*S*)-4-[(1*R*)-2-methoxy-1-[4-(trifluoromethyl)phenyl]ethyl]-3-methylpiperazin-1-yl]-4-methylpiperidine (2*Z*)-but-2-enedioate. *CAS-599179-03-0. Antiviral, CCR5 antagonist, treatment of autoimmune conditions.* (Schering-Plough Research) ✧*SCH 417690*



Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO).

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

Recommended International Nonproprietary Names

The following 58 nonproprietary names have been selected by the World Health Organization (WHO) as Recommended International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information,* Vol. 19, No. 3, 2005.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Ancriviroc	Deferitrin	Inotuzumab Ozogamicin	Raxibacumab
Aplindore	Delmitide	Isalmadol	Rimeporide
Atilmotin	Deutolperisone	Ispinesib	Salclobuzic Acid
Avanafil	Efipladib	Levotofisopam	Saxagliptin
Balicatib	Elomotecan	Linaprazan	Seliciclib
Becatecarin	Embeconazole	Morphine Glucuronide	Sugammadex
Becocalcidiol	Epoetin Zeta	Naveglitazar	Talabostat
Bemotrizinol	Eritoran	Omocianine	Talactoferrin Alfa
Besilesomab	Etalocib	Peliglitazar	Talaglumetad
Bisoctrizole	Farampator	Pemaglitazar	Tanogitran
Canfosfamide	Forodesine	Perflisobutane	Tefibazumab
Ceftobiprole	Galsulfase	Piclozotan	Temsirolimus
Ceftobiprole Medocaril	Glucarpidase	Pralatrexate	Tetomilast
Cintredekin Besudotox	Iboctadekin	Radotermin	Thrombomodulin Alfa
Davasaicin	Icomucret		

Nomenclature

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This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

[*Note—This index covers Vol. 32 No. 1, pp. 1–223*]

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REAGENTS, INDICATORS, AND SOLUTIONS

REFERENCE TABLES

GENERAL SUBJECTS

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PHARMACOPEIAL FORUM VOL. 32 NO. 2 **MAR.–APR. 2006**

* The *USP–NF* (*USP 30–NF 25*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

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

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

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

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

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STANDARDS DEVELOPMENT

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

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

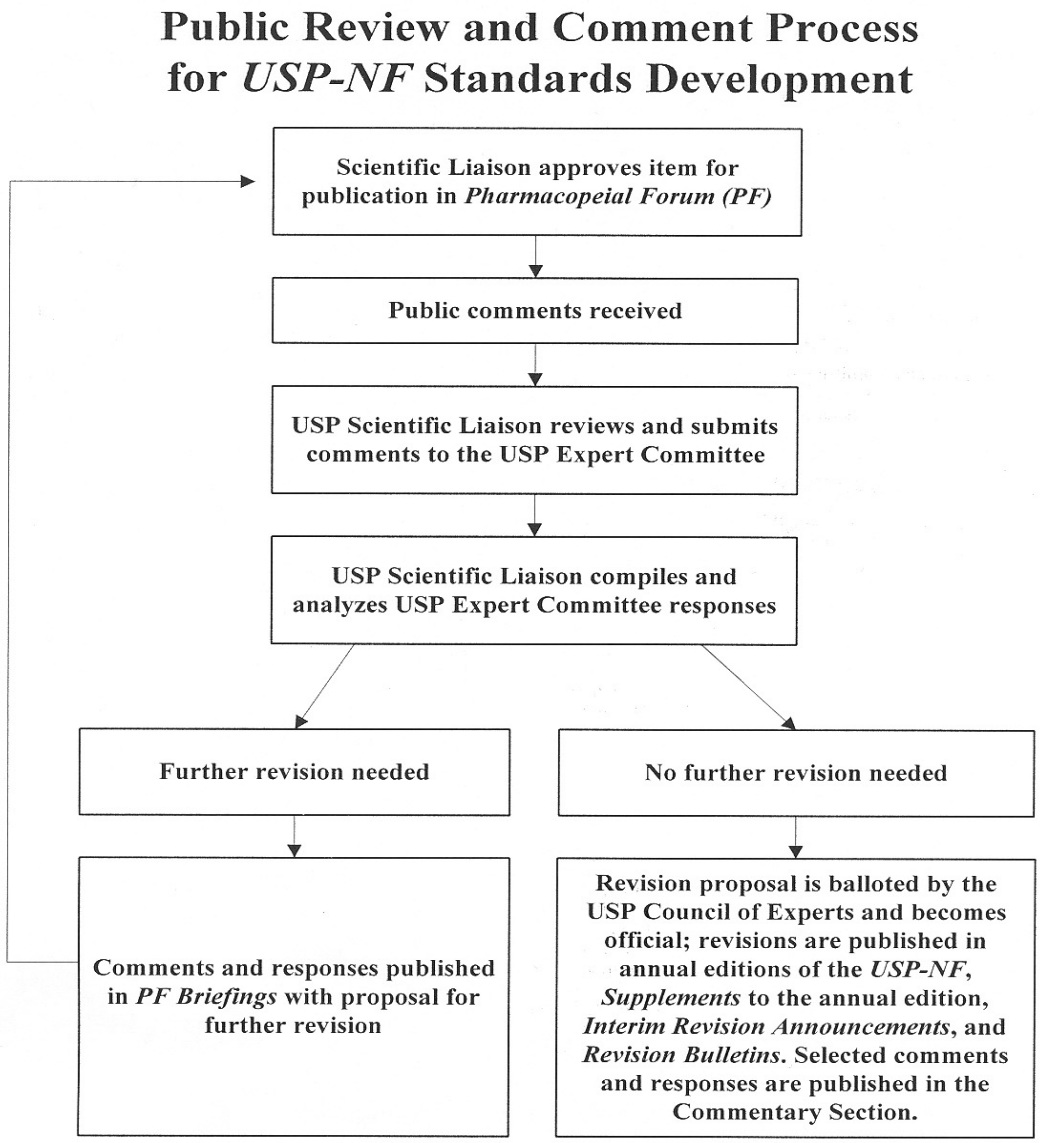
PF includes the following:

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

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

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

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



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@usp.org).

HOW TO USE *PF*

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

The content of the different sections of *PF* is briefly described below. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a *Request for Revision* is available in the *Guideline for Submitting Requests for Revision to the USP–NF* on the USP website (www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP–NF*

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

Other Sections

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

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

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

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

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

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Cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

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

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

EXPERT COMMITTEE DESIGNATIONS*

2005–2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell, Gene, and Tissue Therapies
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding
RMI	Radiopharmaceuticals and Medical Imaging Agents
RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics
VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005–2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

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POLICIES AND ANNOUNCEMENTS

This section includes information about general scientific and policy issues that may have an impact on *USP–NF* standards and processes and announcements about issues being considered by USP. This section also includes publication and comment schedules.

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- Run historical searches to track the progression of changes and chart comparisons. *PF Online* provides access to back issues, beginning with 2002.
- Bookmark monographs for easy access in the future.
- Bookmark frequently accessed information such as comment deadlines and liaison contact information.
- Find out if a new Reference Standard has been released by creating a search and run each time a new *PF Online* edition becomes available.

For subscription information and additional details about *PF Online,* please visit http://www.usp.org/products/PF/ or contact USP Customer Service at 1-800-227-8772 or +1-301-881-0666.

NOTICE OF CORRECTION TO *HELIUM, NITROUS OXIDE, NITROGEN,* AND *NITROGEN 97 PERCENT* MONOGRAPHS. Because the revisions to these monographs, which were published in the *First Supplement* to *USP 28–NF 23* have been postponed indefinitely, *USP 29–NF 24* by default should have shown the *Identification* and *Assay* tests as they originally appeared in the *USP 28–NF 23* on pages 939, 1388, 3041, and 3041, respectively. Instead, these sections of the monographs were printed in error without the original text. See the USP website www.usp.org/USPNF/notices/ for the original text.

Should you have any questions, please contact Kahkashan Zaidi, Ph.D., Senior Scientist, General Policies and Requirements Division (301-816-8269 or kxz@usp.org).

GENERAL CHAPTERS ⟨1⟩ AND ⟨905⟩ POSTPONEMENTS—CLARIFICATION. Two postponements that appeared in the *Fifth IRA* and *Sixth IRA,* respectively for ⟨1⟩ *Injections* and ⟨905⟩ *Uniformity of Dosage Units* do not appear as postponed in the *USP 29–NF 24*. This is due to USP's publication schedule, which slates the *Fifth IRA* and *Sixth IRA* for the *First Supplement* to *USP 29–NF 24,* rather than to the book. The *First Supplement* is scheduled to be published on February 15, 2006, and become official on April 1, 2006. The complete publication schedule appears in this section of *PF*.

For General Chapter ⟨1⟩ *Injections,* USP has postponed the text for *Printing on Ferrules and Cap Overseals* that was to become official on October 1, 2005, as stated in *USP 28–NF 23*. The reason for the postponement is that the Parenteral Products—Industrial, Nomenclature, and Safe Medication Use Expert Committees have approved a revision of this section that also appears in *Pharmacopeial Forum* 31(5), with an implementation date of February 1, 2009.

For General Chapter ⟨905⟩ *Uniformity of Dosage Units,* USP has postponed the official date from April 1, 2006 to January 1, 2007, to provide additional time for the Pharmacopeial Discussion Group to evaluate comments received concerning this revision.

Further information about these postponements is available on USP's website (www.usp.org). If you have any questions, please contact Beryl Voigt, Director, Executive Secretariat (301-816-8155 or bev@usp.org).

USP ISSUES NOTICE OF RETRACTION FOR RESIDUAL SOLVENTS. Please note the following retraction notice that has been included on page 14 of the *USP 29–NF 24*.

"*Residual Solvents* ⟨467⟩: *meet the requirements." is hereby withdrawn from all monographs in the USP and the NF. This retraction is made to allow the USP Council of Experts further time to evaluate the most appropriate manner to implement the Residual Solvents test. The General Notices statement concerning the application of Residual Solvents to all monographs is unaffected by this retraction.*

This notice also serves as an additional request for comments on this issue from all users of the USP. Please forward your comments to:

Todd Cecil, Ph.D.
Vice President
Department of Standards Development
USP
12601 Twinbrook Parkway
Rockville, MD 20852

Comments must be received by June 1, 2006 to ensure consideration.

EXPERT COMMITTEE SUMMARIES AVAILABLE ON THE USP WEBSITE. Summaries of the first meetings of the cycle for the 2005–2010 Standards Expert Committees are now posted and available at http://www.usp.org/USPNF/meetingSummaries/.

USP SEEKS SUBMISSION OF PROPOSALS FOR STABILITY-INDICATING ASSAY PROCEDURES FOR STEROIDS. The assay procedures for steroids in many *USP–NF* monographs are not stability indicating. In an effort to update the monographs, the Monograph Development—Pulmonary and Steroids Expert Committee is seeking submission of proposals for stability-indicating assay procedures for steroids, preferably HPLC- or GC-based, for inclusion in the following *USP–NF* monographs to replace the current procedures that are not stability indicating. The submissions should include data and other information recommended in the *USP Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/pdf/EN/USPNF/revisionGuide.pdf. Each submission should include analytical validation data, data demonstrating that the procedure is stability indicating, and results of analysis from three commercial batches. Please submit proposals for steroid assay procedures for the following *USP–NF* monographs to Daniel Bempong, Ph.D., or contact him for the details at 301-816-8143 or dkb@usp.org.

Drug Substance:

Clocortolone Pivalate
Danazol
Desoxycorticosterone Acetate
Estriol
Fludrocortisone Acetate
Flumethasone Pivalate
Hydrocortisone Sodium Phosphate
Hydrocortisone Sodium Succinate
Hydroxyprogesterone Caproate
Levonorgestrel
Meprednisone
Mestranol
Methylprednisolone Sodium Succinate
Nandrolone Phenpropionate
Norethindrone
Norethindrone Acetate
Norethynodrel
Norgestrel
Oxandrolone
Oxymetholone
Paramethasone Acetate
Prednisolone Hemisuccinate
Prednisolone Sodium Phosphate
Testosterone
Testosterone Enanthate
Testosterone Propionate

Dosage Form:

Betamethasone Oral Solution
Clocortolone Pivalate Cream
Desoxycorticosterone Acetate Injection
Desoxycorticosterone Acetate Pellets
Dexamethasone Gel
Dexamethasone Sodium Inhalation Aerosol
Dexamethasone Tablets
Dexamethasone Topical Aerosol
Estradiol Injectable Suspension
Estradiol Tablets
Estrone Injection
Flumethasone Pivalate Cream
Hydrocortisone Acetate Injectable Suspension
Hydrocortisone Acetate Ophthalmic Ointment
Hydrocortisone Acetate Ophthalmic Suspension
Hydrocortisone Injectable Suspension
Hydrocortisone Sodium Phosphate Injection
Hydroxyprogesterone Caproate Injection
Methylprednisolone Acetate Cream
Methyltestosterone Capsules
Methyltestosterone Tablets
Nandrolone Phenpropionate Injection
Norethindrone Acetate Tablets
Norethindrone Acetate and Ethinyl Estradiol Tablets (assay for both steroids)
Norethindrone Tablets
Norgestrel Tablets
Oxymetholone Tablets
Paramethasone Acetate Tablets
Penicillin G Procaine, Dihydrostreptomycin Sulfate, and Prednisolone Injectable Suspension (assay for Prednisolone)
Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment (assay for Prednisolone Acetate)
Prednisolone Sodium Phosphate Injection
Prednisolone Sodium Phosphate Ophthalmic Solution
Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment (assay for Prednisolone Sodium Phosphate)
Prednisolone Sodium Succinate for Injection
Prednisolone Cream
Progesterone Intrauterine Contraceptive System
Testosterone Enanthate Injection
Testosterone Injectable Suspension
Testosterone Propionate

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, other scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2006 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

2006 Calendar of Pharmacopeial Education Courses

Date	Name of Course	Location	Price
18-Jan-06	Effectively Using the *USP–NF*	California State University—Fullerton, CA	$595
24-25 Jan-06	Fundamentals of Dissolution—Lecture & Lab	North Brunswick, NJ	$1,500
14-Feb-06	Effectively Using the *USP–NF*	Basel, Switzerland	$595
15-Feb-06	Analytical Method Validation	Basel, Switzerland	$595
23-Feb-06	Effectively Using the *USP–NF*	North Carolina State University—Raleigh, NC	$595
29-Mar-06	Basic Statistics and their Practical Applications to the *USP–NF*	New Jersey, hosted by NJPQCA	$595
19-Apr-06	Effectively Using the *USP–NF*—Session I	USP Headquarters, Rockville, MD	$895
20-Apr-06	Effectively Using the *USP–NF*—Session II	USP Headquarters, Rockville, MD	$895 ($1,695 both days)

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

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

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

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

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

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

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

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

NEW *PHARMACOPEIAL FORUM* PUBLIC REVIEW AND COMMENT PERIOD DEADLINES. The full year's listing of comment period deadlines and the targeted official publications appear below. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts*, USP is implementing the 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing. Note that *PF* 31(6) and *PF* 32(1) have a combined comment deadline (April 17, 2006) due to the omission of the comment deadline dates in *PF* 31(6). Individual comment deadlines begin with *PF* 32(2) [Mar.–Apr. 2006].

* ***Section 9.04(b) of the Rules and Procedures of the 2005–2010 Council of Experts***
A period of at least ninety (90) days from the date of publication will be allowed for public review and comment. The time allowed for public comments shall be noted in the publication in the PF. For good cause shown, the Chairperson may alter the time specified.

The listing of comment period deadlines and the targeted official publications appear below.

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Publication Date	Official Date
PF 31(6)	April 17, 2006	*USP 30–NF 25*	November 2006	January 2007
PF 32(1)	April 17, 2006			
PF 32(2)	June 15, 2006	*USP 30–NF 25 1st Supplement*	February 2007	April 2007
PF 32(3)	August 15, 2006			
PF 32(4)	October 16, 2006	*USP 30–NF 25 2nd Supplement*	June 2007	August 2007
PF 32(5)	December 15, 2006			
PF 32(6)	February 15, 2007	*USP 31–NF 26*	November 2007	January 2008
PF 33(1)	April 16, 2007			
PF 33(2)	June 15, 2007	*USP 31–NF 26 1st Supplement*	February 2008	April 2008

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, official revisions are published in *PF* in the *Interim Revision Announcement;* these revisions are also incorporated in the upcoming *Supplement.* The official publication in which an *IRA* is incorporated will depend upon publication deadlines. The 5th *IRA* and the 6th *IRA* will not appear until *Supplement 1*. See table below. The electronic version of *USP–NF* is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement.* The new table below outlines the publications and their release and official dates, and the book or supplement which supersedes them.

Publication Schedules

Publication	Release Date	Official Date	Superseded by
USP 29–NF 24	Nov. 1, 2005	Jan. 1, 2006	*1st Supplement*
1st Supplement	Feb. 1, 2006	Apr. 1, 2006	*2nd Supplement*
1st *IRA* [*PF* 32(1)]	Jan. 1, 2006	Feb. 1, 2006	*2nd Supplement*
2nd *IRA* [*PF* 32(2)]	Mar. 1, 2006	Apr. 1, 2006	*2nd Supplement*
3rd *IRA* [*PF* 32(3)]	May 1, 2006*	June 1, 2006*	*USP 30–NF 25*
2nd Supplement	June 1, 2006*	Aug. 1, 2006*	*USP 30–NF 25*
4th *IRA* [*PF* 32(4)]	July 1, 2006*	Aug. 1, 2006*	*USP 30–NF 25*
5th *IRA* [*PF* 32(5)]	Sept. 1, 2006*	Oct. 1, 2006*	*1st Supplement USP 30–NF25*
6th *IRA* [*PF* 32(6)]	Nov. 1, 2006*	Dec. 1, 2006*	*1st Supplement USP 30–NF25*
USP 30–NF 25	Nov. 1, 2006*	Jan. 1, 2007*	

*Tentative

CALL FOR HIGH PRIORITY MONOGRAPHS FOR DRUG SUBSTANCES AND PRODUCTS AND EXCIPIENTS. USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monographs are marked received upon receipt of a monograph proposal. Received monographs are removed from this list upon publication in *Pharmacopeial Forum.* (This list has been updated as of December 15, 2005). This list is also available on the USP website at http://www.usp.org/USPNF/submitMonograph/newMon.html. For further information, contact Karen Russo, Ph.D., kar@usp.org. Monograph sponsors should consult the *USP Guideline for Submitting Requests for Revision to the USP–NF* at http://www.usp.org/pdf/EN/USPNF/revisionGuide.pdf.

Noncomplex Actives (Drug Substances)

Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Amlodipine Besylate ***(Received)***	Anagrelide Hydrochloride ***(Received)***	Arsenic Trioxide
Azelaic Acid	Balsalazide Disodium	Bentoquatam
Bepridil Hydrochloride	Bivalirudin	Cabergoline
Calcipotriene	Calcium Trisodium Pentetate	Calfactant
Candesartan Cilexetil	Carmustine	Carvedilol
Cefdinir	Cefditoren Pivoxil	Ceftibuten
Cetirizine Hydrochloride ***(Received)***	Cetrorelix	Cevimeline
Chloroxine	Colfosceril	Cytarabine Liposome
Dalfopristin	Dantrolene Sodium ***(Received)***	Dapirazole Hydrochloride
Desirudin	Dexrazoxane	Difloxacin Hydrochloride
Docosanol	Entacapone	Epoprostenol
Erythromycin Phosphate	Erythromycin Thiocyanate	Esomeprazole Magnesium
Esmolol	Estazolam	Estramustine Phosphate Sodium
Estradiol Benzoate	Ethanolamine Oleate	Etomidate
Etoposide Phosphate	Exemestane	Felbamate
Fluoromethane F 18	Foscarnet Sodium	Fosfomycin Tromethamine
Gadobenate Dimeglumine	Galantamine Hydrobromide	Gadopentetic Acid
Gallium Nitrate	Ganirelix	Glyceryl Aminobenzoate
Granisetron	Halobetasol Propionate	Haloperidol Decanoate ***(Received)***
Hydrocodone Polistirex	Ibandronate Sodium	Imipramine Pamoate
Imiquimod	Irinotecan	Isosulfan Blue
Itraconazole	Lamotrigine ***(Received)***	Latanoprost
Lawsone	Levetriacepam	Levobetaxolol
Levofloxacin ***(Received)***	Levomethadyl Acetate	Lomustine
Lopinavir	Metipranolol Hydrochloride	Midazolam Hydrochloride
Miglitol	Mifepristone	Misoprostol ***(Received)***
Mivacurium	Moexipril	Nalbuphine Hydrochloride
Nalmefene Hydrochloride	Nateglinide	Nedocromil
Nicardipine Hydrochloride	Nilutamide	Nisoldipine
Olopatadine	Olsalazine Sodium	Orbifloxacin
Orlistat ***(Received)***	Oxcarbazepine ***(Received)***	Pantoprazole Sodium
Pemoline	Pentamidine Isethionate	Piperonyl Butoxide
Pirbuterol Acetate	Poractant Alpha	Proguanil
Quetiapine Fumarate	Rose Bengal	Salmeterol Xinafoate
Sertraline Hydrochloride	Sodium Phenylbutyrate	Simethicone Powder
Sterile Methotrexate Sodium	Streptozocin	Sulfacytine
Tacrolimus	Terbinafine Hydrochloride	Terconazole
Tiludronate Disodium	Tiopronin	Tranexamic Acid
Trimipramine Maleate	Trovafloxacin Mesylate	Voriconazole
Zinc Tridosium Pentetate		

Noncomplex Actives (Drug Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol for Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Supository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Amlodipine and Benazepril Hydrochloride Capsules	Aminopterin Sodium Tablets
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Metered-Dose Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Brompheniramine Maleate, Dextromethorphan Hydrobromide and Pseudoephedrine HCl Oral Solution
Bivalirudin Injection	Budesonide Metered-Dose Inhalation Aerosol	Budesonide Inhalation Aerosol
Bupivacaine and Lidocaine Hydrochlorides Injection	Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules
Butalbital and Acetaminophen Tablets	Calcipotriene Topical Solution Cabergoline Tablets	Calcipotriene Cream
Calcipotriene Ointment	Calcitriol Capsules	Calcitriol Oral Solution
Calcium Acetate Capsules	Calfactant Intratracheal Suspension	Calcium Trisodium Pentetate Injection
Carbidopa and Levodopa Extended-Release Tablets	Carbidopa and Levodopa Tablets for Oral Suspension	Carbidopa, Levidopa, and Entacapone Tablets
Carmustine Implant	Carmustine for Injection	Carvedilol Tablets
Cefditoren Pivoxil Tablets	Cefdinir Tablets	Ceftibuten Capsules
Ceftibuten for Oral Suspension	Cetirizine Hydrochloride Oral Solution	Ceftiofur Hydrochloride Oral Suspension
Cetrorelix Injection	Cetirizine Hydrochloride Tablets	Cevimeline Hydrochloride Capsules
Choline and Magnesium Salicylates Oral Solution	Chloroxine Cream	Chlorpromazine Hydrochloride Extended-Release Capsules
Ciclopirox Shampoo	Choline and Magnesium Salicylates Tablets	Choline Salicylate Oral Solution
Ciclopirox Topical Gel	Ciclopirox Topical Solution	Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension
Cilostazol Tablets ***(Received)***	Cimetidine Oral Solution	Citalopram Hydrobromide Oral Solution
Ciprofloxacin Otic Solution	Cladribine Injection	Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation
Clonazepam Orally-Disintegrating Tablets	Clemastine Fumarate Syrup	Clobetasol Propionate Gel
Clotrimazole and Betamethasone Dipropionate Lotion	Clorazepate Dipotassium Capsules	Clorazepate Dipotassium Extended-Release Tablets
Colfosceril and Tyloxapol Suspension	Colestipol Hydrochloride Tablets	Conjugated Estrogens and Medroxyprogesterone Acetate Tablets
Compound Undecylenic Acid Cream	Compound Undecylenic Acid Topical Powder	Cyclosporine Modified Oral Solution
Cromolyn Sodium Metered-Dose Nasal Solution	Cyclosporine Modified Capsules	Cysteamine Bitartrate Capsules
Cyclosporine Ointment	Cyclosporine Topical Solution	Cytarabine Liposome Injection
Dantrolene Sodium Capsules ***(Received)***	Dalfopristin and Quinupristin Injection	Dapiprazole for Ophthalmic Solution
Dantrolene Sodium for Injection ***(Received)***	Dantrolene Sodium Oral Suspension	Desirudin for Injection

Noncomplex Actives (Drug Products) *(Continued)*

Desonide ***(Received)***	Desonide Cream	Dexrazoxane for Injection
Dextroamphetamine Sulfate Extended-Release Capsules	Dextromethorphan Polistirex Extended-Release Oral Suspension	Diazepam Injectable
Diclofenac Sodium Ophthalmic Solution	Didanosine Chewable Tablets ***(Received)***	Diethylpropion Hydrochloride Extended-Release Tablets
Difenoxin and Atropine Tablets	Difloxacin Hydrochloride Tablets	Dihydroergotamine Mesylate Metered Spray
Diltiazem Malate Extended-Release Tablets	Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets
Divalproex Sodium Delayed-Release Capsules	Dorzolamide and Timolol Ophthalmic Solution	Dorzolamide Ophthalmic Solution
Doxacurium Chloride Injection	Doxepin Hydrochloride Cream	Doxycycline Oral Gel
Econazole Nitrate Cream	Edrophonium Chloride and Atropine Sulfate Injection	Enalaprilat Injection
Enalapril Maleate and Diltiazem Malate Extended-Release Tablets	Enalapril Maleate and Felodipine Extended-Release Tablets	Entacapone Tablets
Ephedrine Sulfate and Guaifenesin Tablets	Epoprostenol for Injection	Epoprostenol Injection
Esmolol Hydrochloride Injection	Esomeprazole Magnesium Capsules	Estazolam Tablets
Estramustine Phosphate Sodium Capsules	Ethanolamine Oleate Injection	Etomidate Injection
Etidronate Disodium Injection Concentrate	Exemestane Tablets	Famotidine Injection ***(Received)***
Famotidine Orally Disintegrating Tablets	Felbamate Oral Suspension	Felbamate Tablets
Fentanyl Lozenges	Fentanyl Transdermal System	Ferrous Fumarate and Docusate Sodium Extended-Release Capsules
Flavoxate Hydrochloride	Flavoxate Hydrochloride Tablets	Fluconazole Injection
Flunisolide Nasal Spray	Fluconazole Tablets	Flunisolide Inhalation Aerosol
Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution	Fluticasone Propionate Inhalation Powder
Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***	Fluticasone Propionate Ointment ***(Received)***
Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection	Fosfomycin for Oral Solution
Gabapentin Oral Solution	Gabapentin Tablets	Gadobenate Dimeglumine Injection
Gallium Nitrate Injection	Galantamine Hydrobromide Tablets	Ganirelix Acetate Injection
Ganciclovir Capsules	Gentamicin Sulfate Oral Solution	Gatifloxacin Injection
Gatifloxacin Tablets	Glipizide Extended-Release Tablets	Gentamicin Sulfate Soluble Powder
Glimepiride Tablets	Granisetron Tablets	Granisetron Injection
Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets	Guaifenesin and Salts of Dextromethorphan and Pseudoephedrine Oral Solution	Guanidine Hydrochloride
Guanidine Hydrochloride Tablets	Halobetasol Propionate Ointment	Halobetasol Propionate Cream
Haloperidol Decanoate Injection	Haloperidol Lactate Injection	Haloperidol Lactate Oral Concentrate
Hydrochlorothiazide Oral Solution Concentrate	Hydrocodone Bitartrate and Acetaminophen Oral Solution	Hydralazine Hydrochloride and Hydrochlorothiazide Capsules
Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrochlorothiazide Capsules	Hydrocodone Bitartrate and Guaifenesin Oral Solution
Hydrocodone Bitartrate and Aspirin Tablets	Hydrocortisone Butyrate Lotion	Hydrocodone Bitartrate and Homatropine Methylbromide Tablets
Hydrocortisone Acetate Rectal Foam Aerosol	Hydroquinone Lotion	Hydrocortisone Acetate Dental Paste
Hydroflumethiazide and Reserpine Tablets	Hydromorphone Hydrochloride Oral Solution	Ibuprofen Capsules
Ibandronate Sodium Tablets	Idarubicin Hydrochloride Injection	Imipramine Pamoate Capsules
Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol	Ipratropium Bromide Inhalation Solution
Irinotecan Hydrochloride Injection	Isosulfan Blue Injection	Isradipine Extended-Release Tablets
Itraconazole Injection	Itraconazole Oral Solution	Ketoconazole Cream
Ketoconazole Shampoo	Ketoprofen Capsules	Ketoprofen Extended-Release Capsules
Ketotifen Fumarate	Ketotifen Fumarate Ophthalmic Solution	Ketoprofen Tablets
Lactic Acid Lotion	Lamivudine Tablets	Latanoprost Ophthalmic Solution
Levetriacepam Tablets	Levobetaxolol Ophthalmic Suspension	Levocabastine Ophthalmic Suspension
Leucovorin Calcium for Injection	Levomethadyl Acetate Hydrochloride Oral Concentrate	Levofloxacin Solution
Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder	Liothyronine Injection	Lisinopril and Hydrochlorothiazide Tablets

Noncomplex Actives (Drug Products) *(Continued)*

Lomustine Capsules	Lopinavir Capsules	Lopinavir Solution
Lopinavir and Ritonavir Solution	Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***	Loratadine Orally-Disintegrating Tablets
Losartan Potassium Tablets	Mesalamine Suppositories	Methacholine Chloride for Inhalation Solution
Mesoridazine Besylate Concentrate	Mefloquine Hydrochloride Tablets	Methoxsalen Softgels
Methadone Hydrochloride Oral Concentrate	Melphalan for Injection	Metaraminol Bitartrate Injection
Methyclothiazide and Deserpidine Tablets	Methocarbamol and Aspirin Tablets	Metipranolol Ophthalmic Solution
Metronidazole Cream	Metronidazole Lotion	Metronidazole Extended-Release Tablets
Methylphenidate Hydochloride Chewable Tablets	Metronidazole Capsules	Midazolam Hydrochloride Injection
Metronidazole Hydrochloride for Injection	Miconazole Nitrate Topical Aerosol	Mifepristone Tablets
Miglitol Tablets	Milrinone Injection	Misoprostol Dispersion ***(Received)***
Misoprostol Tablets ***(Received)***	Mivacurium in Dextrose Injection	Mivacurium Injection
Moexipril Hydrochloride and Hydrochlorothiazide Tablets	Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution
Morphine Sulfate for Injection Concentrate	Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate
Morphine Sulfate Tablets	Mycophenolate Mofetil Tablets	Mycophenolate Mofetil Oral Solution
Mycophenolate Mofetil Capsules	Nalbuphine Hydrochloride Injection	Naproxen Extended-Release Tablets
Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution	Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution	Nalmefene Hydrochloride Injection
Nateglinide Tablets	Nedocromil Sodium Inhalation Aerosol	Neomycin Sulfate Oral Powder
Nevirapine Oral Suspension ***(Received)***	Nevirapine Tablets ***(Received)***	Nicardipine Hydrochloride Capsules
Nilutamide Tablets	Nimodipine Capsules	Nisoldipine Extended-Release Tablets
Nitroglycerin Solution In Acrylic Adhesive	Nizatidine Tablets	Ofloxacin Injection
Ofloxacin In Dextrose Injection	Ofloxacin Tablet ***(Received)***	Olopatadine Ophthalmic Solution
Olsalazine Sodium Capsules	Ondansetron Oral Solution	Ondansetron Tablets
Orbifloxacin Tablets	Orlistat Capsules ***(Received)***	Orphenadrine Citrate, Aspirin, and Caffeine Tablets
Orphenadrine Citrate Extended Release Tablets	Oxcarbazepine Suspension	Oxcarbazepine Tablets
Oxiconazole Cream	Pancuronium Bromide Injection ***(Received)***	Pantoprazole Sodium Tablets
Pantoprazole Sodium for Injection	Paroxetine Hydrochloride Extended-Release Tablets	Paroxetine Oral Suspension
Pemirolast Potassium Ophthalmic Solution	Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution
Pentaerythritol Tetranitrate Extended-Release Capsules	Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation
Pentamidine Isethionate for Injection	Pentazocine Hydrochloride and Acetaminophen Tablets	Permethrin Cream ***(Received)***
Phendimetrazine Tartrate Extended-Release Capsules	Phenobarbital Capsules	Phentermine Resin Complex
Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules	Phenylephrine Hydrochloride, Chlor pheniramine Maleate, and Acetaminophen Extended-Release Tablets	Phentermine Resin Complex Capsules
Phosphate Oral Solution	Pilocarpine Hydrochloride Ophthalmic Gel	Pilocarpine Hydrochloride Ophthalmic Ointment
Pilocarpine Hydrochloride Tablets	Piperonyl Butoxide and Pyrethrins Aerosol Foam	Pirbuterol Acetate Inhalation Aerosol
Povacrylate Solution	Poractant Alpha Supension	Porfimer Sodium for Injection
Povacrylate-Iodine Topical Solution	Povidone-Iodine Gauze	Povidone-Iodine Swabsticks
Povidone-Iodine Topical Aerosol Foam	Povidone-Iodine Vaginal Suppositories	Pramipexole Dihydrochloride Tablets
Prazosin Hydrochloride and Polythiazide Capsules	Prednisolone Sodium Phosphate Oral Solution	Prochlorperazine Maleate Extended-Release Capsules

Noncomplex Actives (Drug Products) *(Continued)*

Progesterone Capsules	Promethazine Hydrochloride and Codeine Phosphate Oral Solution	Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup
Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup	Promethazine and Phenylephrine Hydrochlorides Syrup	Propafenone Hydrochloride Tablets
Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets	Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution
Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution
Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pyrilamine Maleate Injection	Quinidine Sulfate Injection
		Ramipril Capsules
Ranitidine Capsules	Rauwolfia Serpentina and Endroflumethiazide Tablets	Reserpine and Polythiazide Tablets
Rimantadine Hydrochloride Oral Solution	Risperidone Oral Solution	Risperidone Orally Disintegrating Tablets
Risperidone Tablets	Rivastigmine Tartrate Capsules	Rivastigmine Tartrate Oral Solution
Rocuronium Bromide Injection	Ropinirole Hydrochloride Tablets	Rose Bengal Ophthalmic Solution
Rosiglitazone Maleate Tablets	Salicylic Acid and Sulfur Cleansing Lotion	Salicylic Acid and Sulfur Lotion
Salicylic Acid and Sulfur Shampoo	Salicylic Acid Cream	Salicylic Acid Ointment
Salmeterol Inhalation Aerosol	Salmeterol Xinafoate Inhalation Powder	Scopolamine Transdermal System
Selegiline Hydrochloride Capsules	Serpacwa Topical Cream	Sertraline Hydrochloride Oral Solution
Sibutramine Hydrochloride Capsules	Sodium Bicarbonate and Sodium Citrate for Oral Solution	Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension
Sodium Chlorophyllin Copper Complex Tablets	Sodium Iodide Injection	Sodium Phenylbutyrate Oral Powder
Sodium Phenylbutyrate Tablets	Sodium Phosphates for Oral Suspension	Sodium Phosphates Tablets
Sodium Salicylate and Sulfur Shampoo	Sterile Talc Aerosol	Streptozocin for Injection
Sucralfate Oral Suspension	Sulconazole Nitrate Cream	Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution
Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension	Sulfacytine Tablets	Sulfanilamide Vaginal Cream
Sulfasalazine Oral Suspension	Sumatriptan Tablets	Sulisobenzone Lotion
Sumatriptan Injection	Tacrolimus Capsules	Tacrolimus Ointment
Tacrolimus Injection	Tamsulosin Hydrochloride Capsules	Technetium Tc 99M Teboroxime Injection
Tenofovir Disoproxil Fumarate Tablets	Terbinafine Hydrochloride Cream	Terbinafine Tablets
Terbinafine Topical Solution	Terconazole Vaginal Cream	Terconazole Vaginal Suppositories
Testosterone Transdermal System	Tetracycline Hydrochloride Periodontal Fiber	Theophylline Extended-Release Tablets
Tioconazole Vaginal Ointment	Tiopronin Tablets	Tolnaftate Topical Aerosol Solution
Topiramate Capsules	Topiramate Tablets	Torsemide Injection
Torsemide Tablets	Trandolapril and Verapamil Hydrochloride Extended-Release Tablets	Trandolapril Tablets
Tranexamic Acid Injection	Tranylcypromine Sulfate	Tranylcypromine Sulfate Tablets
Tretinoin Capsules	Tretinoin Microsphere Gel	Triamcinolone Acetonide Metered-Dose Nasal Suspension
Trifluridine Ophthalmic Solution	Trimetrexate for Injection	Trimipramine Maleate Capsules
Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup	Trolamine Salicylate Cream	Trolamine Salicylate Gel
Trolamine Salicylate Topical Emulsion	Trovafloxacin Injection	Trovafloxacin Mesylate for Injection
Undecylenic Acid Topical Foam Aerosol	Unoprostone Isopropyl Ophthalmic Solution	Urea Cream
Vecuronium Bromide for Injection	Venlafaxine Extended-Release Capsules	Venlafaxine Tablets
Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules	Voriconazole Injection
Voriconazole Oral Suspension	Voriconazole Tablets	Yttrium Y-90 Chloride Solution
Yttrium Y-90 Glass Microspheres	Yttrium Y-90 Microspheres Injection	Ziprasidone Hydrochloride Capsules
Zidovudine and Lamivudine Tablets	Zinc Acetate Capsules	Zoledronic Acid for Injection
Zinc Tridosium Pentetate Injection		

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	*N*-Acetyl-L- Methionine
Aconitic Acid (Achilleic Acid)	Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal
Aliphatic Polyesters	Aluminum Ammonium Sulfate	Aluminum Hydroxide
Aluminum Lactate	Aluminum Oxide	Aluminum Ammonium Sulfate
Aluminum Potassium Sulfate	Aluminum Silicate	Aluminum Sodium Sulfate
Aluminum Stearate	Allantoin-Sodium Pyrrolidone Carboxylate	Ammonium Bicarbonate
Ammonium Calcium Alginate	Ammonium Phosphate	L-Ascorbyl Stearate
L-Asparagine	Batylalcohol Monostearate	Beeswax, Synthetic
Benzododecinium Bromide	Benzyl Chloride	Benzyl Nicotinate
Brominated Vegetable Oil	Butadiene-Styrene Rubber	Beta Naphthol
Butylene Glycol	Butylphthalyl Butylglycolate	Butylated Hydromethylphenol
Calcium Alginate	Calcium Alginate and Ammonium Alginate	Calcium Acid Pyrophosphate
Calcium Chloride Solution	Calcium Glycerophosphate ***(Received)***	Calcium Bromide
Calcium Phospahte Dibasic, Monohydrate	Calcium Phosphate Monobasic	Calcium Phosphate Dibasic, Anhydrous
Calcium Pyrophosphate	Calcium Sorbate	Calcium Propionate
Calcium Sulfate Dihydrate	Calcium Sulfate, Anhydrous	Calcium Stearoyl Lactylate
Calteridol Calcium	Canola Oil	Caldiamide Sodium
Caprylic/Capric Diglyceril Succinate	Carbon	Capric Acid
Carboxymethylamylopectin Sodium	Carboxymethylcellulose Potassium	Carboxymethyl Starch
Cetostearyl Isononanoate	Cholic Acid	Cinnamaldehyde
Chlorodifluoroethane	Cocamide Diethanolamine	Cocamide Oxide
Coconut Oil Hydrogenated ***(Received)***	Cocoyl Caprylocaprate	Coconut Oil
Crystal Gum	Cutina	Copper Sulfate
L-Cysteine Monohydrochloride	Dammar Gum	Cystine
Decanoic Acid	Decyl Oleate	Dehydroacetic Acid
Desoxycholic Acid	Dextrin Palmitate	Dextrins Modified
Diacetyl Tartaric Acid Esters Of Mono- and Diglycerides	Dicetyl Phosphate	Dichlorofluoromethane
Diethylene Glycol Monopalmitostearate	Diethyl Sebacate	Difluoroethane
Diglycol Stearate	Diisobutyl Adipate	Diisopropyl Adipate
Diisopropylbenzothiazyl-2-Sulfenamide	Dilauryl Thiodipropionate	Dimethyl Dicarbonate
Dimyristoyl Lecithin	Dimyristoyl Phosphatidylglycerol	Dioctyl Sodium Sulfosuccinate
Dipropylene Glycol	Disodium Edisylate	Disodium Guanylate
Disodium Inosinate	Disodium Monooleamide Sulfasuccinate	Docusate Sodium/Sodium Benzoate
Erythorbic Acid	Erythrosine	Ethoxylated Mono- and Diglycerides
Ethoxyquin	Ethyl Hexanediol	Ethyl Linoleate
Ethyl Maltol	Ethylene Dichloride	Ethylene Glycol Monopalmitostearate
Ethylurea	Ferric Ammonium Citrate	Ferric Citrate
Ferric Oxide, Brown	Ferric Phosphate	Ferric Pyrophosphate
Ferrous Citrate	Ferrous Glycinate	Ferrous Lactate
Fluorochlorohydrocarbons	Formic Acid	Furcelleran
Gamma-Cyclodextrin	Gentistic Acid	Geraniol
L-Glutamic Acid	Glutamic Acid Hydrochloride	Gluten
Glycerol Ester of Gum Rosin (Ester Gum)	Glyceryl Laurate	Glyceryl Palmitate
Glyceryl Ricinoleate	Glyceryl Tristearate	Glycine Hydrochloride
Glycofurol	Glycol Stearate	Heptafluoropropane
Heptylparaben	Hexadecyl Isostearate	Hexane
Hexanetriol(-1,2,6-)	Hydrocarbon Gel	Hydrogenated Starch Hydrolysate
Hydroxyethylmethylcellulose	Hydroxylated Lecithin	Hydroxypropyl Beta Cyclodextrin
Indigotine	Inositol	Iron Carbonyl
Iron Subcarbonate	Isobutylated-Isoprene Copolymer	Isooctylacrylate
Isopropyl Isostearate	Isopropyl Stearate	Isostearic Acid
Isostearyl Alcohol	Lactobionic Acid	Lactose Ferrin, Bovine
Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol	Lactylic Esters of Fatty Acids	Lanolin Anhydrous
Lanolin Alcohols, Acetylated	Lanolin (Wool Fat), Hydrogenated	Lanolin Hydrous
Lauramine Oxide	Lauric Acid	Lauric Diethanolamide

Excipients *(Continued)*

Lauric Myristic Diethanolamide	Lavender Oil	Lecithin, Hydroxylated
L-Leucine	Linoleic Acid	Macrogol Lauryl Ether
Macrogol Oleate	Macrogol Sorbitan Tristearate	Macrogol Stearyl Ether
Macrogolglycerol Cocoates	Macrogolglycerol Triisostearate	Magnesium Aluminum Silicate Hydrate
Magnesium Aspartate	Magnesium Aspartame Dihydrate	Magnesium Phosphate, Diabasic, Trihydrate
Magnesium Phosphate Tribasic	Magnesium Tartrate	Maltitol Syrup
Maltol Isobutyrate	Malt Syrup	Manganese Chloride
Manganese Citrate	Manganese Glycerophosphate	Manganese Hypophosphite
D-Mannose	Medical Antifoam Emulsion C	Medronate Disodium
Medronic Acid	Methyl Chloride	Methylchloroisothiazolinone
Methyl Hydroxyethyl Cellulose	Methylisothiazolinone	*N*-Methylpyrrolidone ***(Received)***
Microcrystalline Cellulose, Silicified ***(Received)***	Mineral Spirits	Monoisostearyl Glyceryl Ester
Monopotassium Glutamate Monohydrate	Monosodium Citrate	Mullein Leaf
Myristyl Gamma-Picolinium Chloride	Myristyl Lactate	*N,N*-Bis(2-Hydroxyethyl) Stearamide
Naphtha	Non-Pareil Seeds	Nutmeg Oil
Octanoic Acid	Oxystearin	Palm Kernel Oil
Palm Oil	Pentasodium Triphosphate	Pentetate Calcium Trisodium
Pentetate Pentasodium	Phenprobamate	Phenylmercuric Acetate
Phenylmercuric Nitrate	Pine Oil	Polacrilin
Polyacrylate Dispersion 30 Percent ***(Received)***	Polydextrose	Polydextrose Solution
Polyglycerol Esters of Fatty Acids	Polyglycerol Polyricinoleic Acid	Polyoxyethylene Castor Oil (USP has 35)
Polyoxyl Stearate (USP has 40)	Polypropylene Oleate	Polyvinyl Acetate ***(Received)***
Polyvinylacetal	Polyvinylacetal Diethylanoacetate	Polyvinylpolypyrrolidone
Polypropylene Stearyl Ether	Polyvinylpyrrolidone Ethylcellulose	Polysorbate 65
Potassium Acid Tartrate	Potassium Bromate	Potassium Carbonate Solution
Potassium Dichloroisocyanurate	Potassium Gibberellate	Potassium Glycerophospate
Potasssium Iodate	Potassium Nitrite	Potassium Phosphate
Potassium Phosphate Tribasic	Potassium Polymetaphosphate	Potassium Pyrophosphate
Potassium Stearate	Potassium Sulfate	Potassium Sulfite
Potassium Tripolyphosphate	Propylene Glycol Diacetate	Propylene Glycol Mono- and Diesters
Propyl Propionate	Purified Polyoxyl 35 Castor Oil ***(Received)***	Rapeseed Oil, Hydrogenated
Rapeseed Oil, Superglycerinated	Rice Bran Wax	Rosin
Silicone	Sodium Acid Pyrophosphate	Sodium Aluminosilicate
Sodium Aluminum Phosphate Acidic	Sodium Aluminum Phosphate Basic	Sodium Aspartate
Sodium Bisulfate	Sodium Bisulfite	Sodium Carbonate Hydrate
Sodium Carboxymethyl Betaglucan	Sodium Caseinate	Sodium Chlorate
Sodium Citrate, Dibasic	Sodium Citrate, Monobasic	Sodium Dehydroacetate
Sodium Diacetate	Sodium Erythorbate	Sodium Ferric Pyrophosphate
Sodium Ferrocyanide	Sodium Hypophosphite	Sodium Laureth Sulfate
Sodium Lauroyl Sarcosinate	Sodium Lauryl Sulfoacetate	Sodium Magnesium Aluminosilicate
Sodium Magnesium Silicate	Sodium Malate	Sodium Metaphosphate, Insoluble
Sodium Metasilicate	Sodium Methylate	Sodium Polyphosphates Glassy
Sodium Potassium Tripolyphosphate	Sodium Pyrophosphate	Sodium Pyrrolidone Carboxylate
Sodium Sesquicarbonate	Sodium Sesquinoleate	Sodium Stearoyl Lactylate
Sodium Thiomalate	Sodium Trimetaphosphate	Sodium Trioleate
Sodium Tripolyphosphate	Soy Polysaccharides	Stannous Chloride
Stannous Tartrate	Starch, Pregelatinized Corn	Starch, Pregelatinized Tapioca
Stearalkonium Chloride	Stearyl Citrate	Stearyl Monoglyceridyl Citrate
Succinylated Monoglycerides	Sucrose Acetate Isobutyrate	Sucrose Fatty Acid Esters
Sucrose Stearate	Sucrose Syrup	Sugar Fruit Fine
Sulfobutyl Ether Beta Cyclodextran	Tallow	Tallow Glycerides
Tallow Oil	Tetrafluoroethane	Thioglycerol
Thyme Oil	Tribehenin	Tricetеareth-4 Phosphate

Excipients *(Continued)*

Trichloroethylene	Trimyristin	Trisidium Citrate
Trolamine Lauryl Sulfate	Vegetable Oil	Wheat Flour
Wheat Gluten	Wheat Germ Oil	Whey

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

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

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

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ■new text■, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ■■, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement*, and ■2S (*USP29*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 29*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in the next available *Supplement*, and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

SECOND INTERIM REVISION ANNOUNCEMENT to *USP 29* and to *NF 24*

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

John W. Mauger, *Chair*
USP Board of Trustees

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

Roger L. Williams, M.D. *Chief Standards Officer, Acting*

Official April 1, 2006 **Released March 1, 2006**

All inquiries and comments regarding *USP 29* text and *NF 24* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were not available when the associated monograph was made official, have since become available. The respective official date of each *USP 29* or *NF 24* standard, test, or assay requiring the use of the following USP Reference Standards is indicated in parentheses after the name of the Reference Standard.

USP Berberine Chloride (May 1, 2006)
USP Budesonide RS (September 1, 2006)
USP Clopidogrel Bisulfate RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound A RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound B RS (March 1, 2006)
USP Clopidogrel Bisulfate Related Compound C RS (March 1, 2006)
USP Fluticasone Propionate Resolution Mixture RS (September 1, 2006)
USP Fluticasone Propionate System Suitability Mixture RS (September 1, 2006)
USP Hydrastine RS (May 1, 2006)
USP Insulin Lispro RS (March 1, 2006)
USP Mefloquine Hydrochloride RS (May 1, 2006)
USP Mefloquine Related Compound A RS (May 1, 2006)
USP Norphenylephrine Hydrochloride RS (May 1, 2006)
USP Ondansetron RS (May 1, 2006)
USP Polyoxyl 20 Cetostearyl Ether RS (March 1, 2006)
USP Polyoxyl 20 Stearyl Ether RS (March 1, 2006)
USP Ropivacaine Related Compound A RS (September 1, 2006)
USP Ropivacaine Related Compound B RS (September 1, 2006)
USP Somatropin RS (May 1, 2006)
USP Tiagabine Related Compound A RS (May 1, 2006)
USP Racemic Tiagabine Hydrochloride Mixture RS (May 1, 2006)
USP Tiagabine Hydrochloride RS (May 1, 2006)
USP Tinidazole Related Compound B RS (September 1, 2006)

Unavailable First-Time Official USP Reference Standards

The official dates of any *USP 29* or *NF 24* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards. This listing was updated as of January 5, 2006.

USP Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Aprotinin RS
USP Aprotinin System Suitability RS
USP Cetrimonium Bromide RS
USP Citalopram Hydrobromide RS
USP Cladribine RS
USP Cladribine Related Compound A RS
USP Copolymer Polypropylene RS
USP Decoquinate RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Escin RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluticasone Propionate RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Fluvastatin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Lamivudine Resolution Mixture B RS
USP Alpha Lipoic Acid RS
USP Maritime Pine Extract RS
USP Mecamylamine Related Compound A RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Naratriptan Resolution Mixture RS
USP Near Infrared Calibrator
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Paricalcitol Solution RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Polyisobutylene RS
USP Polyoxyl 10 Oleyl Ether RS
USP Potassium Perchlorate RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Ropivacaine Hydrochloride RS
USP Powdered St John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Sulisobenzone RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Powdered Valerian RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS

NOTICE OF POSTPONEMENT

Mannitol Injection Monograph

In accordance with Section 9.06c of the Rules and Procedures of the Council of Experts, the Nomenclature Expert Committee has postponed the official date of the new *Labeling* requirement for the *Mannitol Injection* monograph from January 1, 2006 to August 1, 2007. This requirement currently appears in *USP 29–NF 24* on page 1311.

The text of the postponed *Labeling* requirement states: ''The label also states that it should be warmed before use to dissolve any crystals that may have formed.''

The postponement is to provide additional time for manufacturers to meet the new *Labeling* standard. The text of the new *Labeling* standard is not being changed, only its implementation date.

Should you have any questions, please contact W. Larry Paul, Ph.D., Scientific Fellow and Scientific Liaison to the Nomenclature Expert Committee (301-816-8331 or wlp@usp.org).

Mannitol Injection

Change to read:

Labeling—The label states the total osmolar concentration in mOsmol per L. Where the contents are less than 100 mL, or where the label states that the Injection is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in mOsmol per mL. ▲The label also states that it should be warmed before use to dissolve any crystals that may have formed.▲*USP29*

•(Official August 1, 2007)•2

Interim Revision Announcement

NOTICE OF POSTPONEMENT

Identification, Loss on drying, and *Limit of potassium* tests under *Sodium Chloride* (*First Supplement* to *USP 29–NF 24,* page 3582)

USP has **postponed indefinitely** the official date of the revisions to the *Identification, Loss on drying,* and *Limit of potassium* tests under the *Sodium Chloride* monograph, which is published on page 3582 of the *First Supplement* to *USP 29–NF 24.* This postponement applies to the official date of the changes, April 1, 2006. The monograph remains official as it appears on page 1975 of *USP 29.* This postponement is intended to give the industry more time to comment on the proposed changes.

If you have any questions or concerns, please contact Kevin Moore, Ph.D., Scientist, DSD, and scientific liaison to the Pharmacopeial Discussion Group (301-816-8369 or ktm@usp.org).

Sodium Chloride

Change to read:

Identification—

•**A:** Dissolve in 2 mL of water a quantity of the substance to be examined equivalent to about 2 mg of chloride (Cl^-). Acidify with diluted nitric acid, and add 0.4 mL of a silver nitrate solution containing about 42.5 g per L. Shake, and allow to stand. A curdled, white precipitate is formed. Centrifuge, and wash the precipitate with three quantities, each 1 mL, of water. Carry out this operation rapidly in subdued light, disregarding the fact that the supernatant may not become perfectly clear. Suspend the precipitate in 2 mL of water, and add 1.5 mL of ammonium hydroxide. The precipitate dissolves easily with the possible exception of a few large particles that dissolve slowly.

B: Introduce into a test tube a quantity of the substance to be examined equivalent to about 15 mg of chloride (Cl^-). Add 0.2 g of potassium dichromate and 1 mL of sulfuric acid. Place a filter-paper strip impregnated with 0.1 mL of *Diphenylcarbazide solution,* prepared below, over the opening of the test tube. The paper turns violet-red. The impregnated paper must not come into contact with the potassium dichromate.

Diphenylcarbazide solution—Dissolve 0.2 g of diphenylcarbazide in 10 mL of glacial acetic acid, and dilute with alcohol to 100 mL. Prepare immediately before use.

C: Dissolve 0.1 g of the substance to be examined in 2 mL of water. Add 2 mL of a 150 g per L solution of potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of *Potassium pyroantimonate solution,* prepared below, and heat to boiling. Allow to cool in ice water, and if necessary rub the inside of the test tube with a glass rod. A dense white precipitate is formed.

Potassium pyroantimonate solution—Dissolve 2 g of potassium pyroantimonate in 95 mL of hot water. Cool quickly and add a solution containing 2.5 g of potassium hydroxide in 50 mL of water and 1 mL of sodium hydroxide solution containing 8.5 g of sodium hydroxide in 100 mL of water. Allow to stand for 24 hours, filter, and dilute with water to 150 mL.

D: Dissolve a quantity of the substance to be examined equivalent to about 2 mg of sodium (Na^+) in 0.5 mL of water. Add 1.5 mL of *Methoxyphenylacetic reagent,* prepared below, and cool in ice water for 30 minutes. A voluminous, white, crystalline precipitate is formed. Place in water at 20°, and stir for 5 minutes. The precipitate does not disappear. Add 1 mL of ammonia TS. The precipitate dissolves completely. Add 1 mL of ammonium carbonate solution (158 g per L). No precipitate is formed.

Methoxyphenylacetic reagent—Dissolve 2.7 g of methoxyphenylacetic acid in 6 mL of 10% tetramethylammonium hydroxide solution in methanol, and add 20 mL of alcohol. Store in a polyethylene container.

(Postponed indefinitely)•2

Change to read:

Loss on drying ⟨731⟩**—**Dry the test material at 105° for 2 hours: it loses not more than 0.5% of its weight, determined on •about 1.000 g of sample.

(Postponed indefinitely)•2

Change to read:

Limit of potassium (where it is labeled as intended for use in the manufacture of injectable dosage forms, peritoneal dialysis solutions, hemodialysis solutions, or hemofiltration solutions)—

Test solution—Transfer 1.00 g of Sodium Chloride to a 100-mL volumetric flask, add water and swirl to dissolve, dilute with water to volume, and mix.

Standard solution—[NOTE—The *Standard solution* and the *Test solution* may be modified, if necessary, to obtain solutions of suitable concentrations adaptable to the linear or working range of the instrument.] Dissolve 1.144 g of potassium chloride, previously dried at 105° for 3 hours, in water, dilute with water to 1000 mL, and mix. This solution contains the equivalent of 600 µg of potassium per mL. Dilute as required to obtain not fewer than three solutions at concentrations that span the expected value in the *Test solution*.

Procedure—Using atomic •emission•2 spectrophotometry (see *Spectrophotometry and Light-Scattering* ⟨851⟩), measure, at least three times, the emission intensity of the *Test solution* and the *Standard solution* using an air–acetylene flame and a wavelength of 766.5 nm. Prepare a calibration curve from the mean of the readings obtained with the *Standard solution,* and determine the concentration of potassium in the *Test solution.* The limit is 0.05%.

•(Postponed indefinitely)•2

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NOTICE OF POSTPONEMENT

⟨621⟩ *Chromatography*

General Chapter ⟨621⟩ *System Suitability (USP 29–NF 24,* page 2647)

USP has **postponed indefinitely** the implementation of the requirement of the text pertaining to detection sensitivity under *System Suitability* that is published on page 2647 of *USP 29–NF 24* and slated to become official on June 1, 2006. On the basis of comments received, the General Chapters Expert Committee has decided that additional time is necessary to review the impact of this proposal, specifically on older methods that were not developed to meet this requirement. The postponement will give the Expert Committee time to define a better strategy to implement this requirement. Should you have any questions, please contact Horacio Pappa, Ph.D., Senior Scientist, General Policies and Requirements Division, and Scientific Liaison to the General Chapters Expert Committee (301-816-8319 or hp@usp.org).

⟨621⟩ CHROMATOGRAPHY

Change to read:

SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the ▲detection sensitivity,▲*USP29* ●(Postponed indefinitely)●2 resolution, and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.

▲The detection sensitivity is a measure used to ensure the suitability of a given chromatographic procedure for the complete detection of the impurities in the *Chromatographic purity* or *Related compounds* tests by injecting a volume of a quantitation limit solution equal to that of the *Test solution*. Unless otherwise specified in the individual monograph, the quantitation limit solution may be prepared by dissolving the drug substance Reference Standard in the same solvent as that used for the *Test solution* at a 0.05% concentration level relative to the amount of drug substance in the *Test solution* for drug substances, and a 0.1% level relative to the amount of drug substance in the *Test solution* for drug products. The signal-to-noise ratio for the drug substance peak obtained with the quantitation limit solution should be not less than 10.▲*USP29* ●(Postponed indefinitely)●2

The resolution, *R*, [NOTE—All terms and symbols are defined in the *Glossary of Symbols*] is a function of column efficiency, *N,* and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, S_R, if the requirement is 2.0% or less; data from six replicate injections are used if the relative standard deviation requirement is more than 2.0%.

The tailing factor, *T,* a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see *Figure 2*). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.

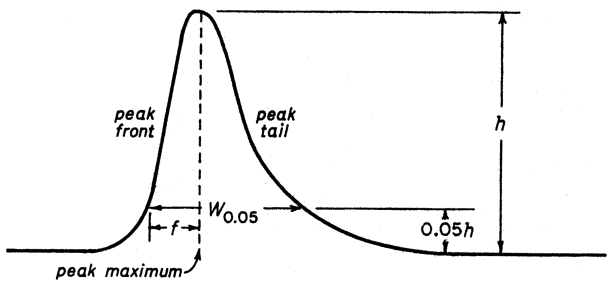

Figure 2. Asymmetrical chromatographic peak

These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see *Procedures* under *Tests and Assays* in the *General Notices*). Adjustments of operating conditions to meet system suitability requirements may be necessary.

Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.

To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals. The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails requirements are unacceptable.

MONOGRAPHS (USP)

Glucagon

Change to read:

Assay—[NOTE—All buffers have a final pH of 7.4, unless otherwise indicated. •The concentration range of the *Standard preparations* and the *Assay preparations* may be modified to fall within the linear range of the *Assay.* The calculations should be adjusted accordingly. Alternatively, full curve analysis using validated nonlinear statistical methods can be used, provided that parallelism is demonstrated when comparing the responses of the *Standard preparations* and the *Assay preparations*.]•2

HEPATOCYTE PREPARATION—

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

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

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

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

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

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

Suitability—The concentrations of cells may vary due to the collagenase activity and the viability of the hepatocytes. To check cell viability and to determine viable cell concentration, dilute duplicate 100-µL aliquots of cell suspension with 400 µL of *Wash buffer* and 500 µL of isotonic 0.4% trypan blue. The aliquots are counted in a hemocytometer. The cells are suspended in *Incubation buffer* to obtain a viable cell concentration of not less than 3×10^6 per mL. Count several distinct fields. [NOTE—Viable cells are those cells that exclude the trypan blue.]

NEGATIVE CONTROL SOLUTION—Prepare a solution containing 0.5% BSA in sterile water.

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

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

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

D-GLUCOSE DETERMINATION—

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

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

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

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

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

To conform to the linear range of the instrument being used, it may be necessary to adjust by dilution each of the preparations. Use a glucose analyzer that has demonstrated appropriate specificity, accuracy, precision, and linear response over the range of concentrations being determined. [NOTE—A suitable analyzer may

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use an immobilized, oxidase-enzyme membrane or jacket-generating hydrogen peroxide, which is then detected at the electrode.] Perform the glucose analysis in the following sequence: *Negative control solution 1, Standard preparations, Assay preparations,* and *Negative control solution 2.* Determine the percentage of glucose against the *Negative control solution* for each preparation.

CALCULATIONS—

Linearity test—Use an analysis of variance (ANOVA) with one sample assayed against a standard, and using two replicates each, construct a table (see *Table 1*). Compare the value of the ratio $MSNL/MSRES_1$ to a critical value obtained from a table for an F distribution with $m-2$ and $3m-3$ degrees of freedom, where m is the number of dose levels for each preparation. If the ratio $MSNL/MSRES_1$ does not indicate the presence of significant nonlinearity (ratio value is lower than the critical value), then proceed to the test for parallelism. If the ratio exceeds the critical value (significance level of •0.025),•2 the nonlinearity is statistically significant and the test is repeated, discarding the results from either the highest or lowest dose of both the *Standard preparations* and the *Assay preparations* (four dose levels). If the ratio $MSNL/MSRES_1$ does not indicate the presence of significant nonlinearity, then proceed to the test for parallelism.

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

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

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

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

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

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

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

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

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

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

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

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

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

and calculate

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

and

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

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

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

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

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

Table 1. ANOVA for the Rat Hepatocyte Assay for Glucagon

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

$$SSRES_2 = SSRES_3 - SSNP$$

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

$$SSRES_1 = SSRES_2 - SSNL$$

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

Diluted Isosorbide Mononitrate

Change to read:

USP Reference standards ⟨11⟩—*USP Isosorbide RS.* •[NOTE—The following Reference Standards are dry mixtures of an active component with suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component based on the content stated on the label.]•₂ *USP Diluted Isosorbide Dinitrate RS. USP* •*Diluted*•₂ *Isosorbide Mononitrate RS. USP Isosorbide Mononitrate Related Compound A RS.*

Change to read:

Identification—

A: •Shake a quantity of it, equivalent to about 25 mg of isosorbide mononitrate, with 10 mL of acetone for 5 minutes. Filter, evaporate to dryness at a temperature below 40°, and dry the residue in a vacuum over phosphorus pentoxide for 16 hours: the IR absorption spectrum of a potassium bromide dispersion prepared from the residue so obtained exhibits maxima only at the same wavelengths as that of a similar preparation from the residue obtained from USP Diluted Isosorbide Mononitrate RS.•₂

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

Delete the following:

•**pH** ⟨791⟩**:** between 4.8 and 6.5. To prepare the test solution, dissolve 5.6 g of Diluted Isosorbide Mononitrate in 50 mL of boiling water, sonicate for 5 minutes, and allow to cool to room temperature.•₂

Delete the following:

•**Water,** *Method Ic* ⟨921⟩**:** between 0.4% and 0.8%. Proceed as directed for hygroscopic materials. To 1.0 g of sample, accurately weighed, add 5 mL of methanol, shake for 30 minutes, and centrifuge at about 2500 rpm for 5 minutes. Use 1.0 mL of the resulting supernatant.•₂

Delete the following:

•**Residue on ignition** ⟨281⟩**:** not more than 0.1%.

Caution—Material is explosive upon heating; digest the sample thoroughly before ignition.•₂

Change to read:

Related compounds—

TEST 1—

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

Standard solution 1—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.0125 mg of isosorbide per mL.

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Standard solution 2—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.025 mg of isosorbide per mL.

Standard solution 3—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.05 mg of isosorbide per mL.

Test solution—Transfer a portion of Diluted Isosorbide Mononitrate, equivalent to about 200 mg of isosorbide mononitrate, accurately weighed, to a suitable container, add 20.0 mL of absolute alcohol, sonicate for 10 minutes, and then centrifuge. Use the supernatant.

Application volume: 20 µL.

Developing solvent system: a mixture of absolute alcohol and toluene (8 : 2).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. After developing, dry the plate with warm air for about 10 minutes, dip the plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at 105° for 5 minutes. Any spot in the chromatogram obtained from the *Test solution* and corresponding to the R_F value of the spots obtained from the *Standard solutions* is not more intense than the spot in the chromatogram obtained from *Standard solution 3:* not more than 0.5% of any individual impurity is found. If the spot in the chromatogram obtained from the *Test solution* is nearly as intense as the spot obtained from *Standard solution 3,* further dilute the *Test solution* (1 : 1) with absolute alcohol, repeat the test, and compare the intensity of the isosorbide spot in the diluted *Test solution* with the intensity of the spots obtained from the *Standard solutions,* correcting the percent level for the additional dilution of the *Test solution.*

TEST 2—

Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Isosorbide mononitrate related compound A standard solution—Prepare as directed for *Isosorbide mononitrate related compound A standard preparation* in the *Assay.*

Isosorbide dinitrate standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, sonicate and warm if necessary, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.125 mg of isosorbide dinitrate per mL.

Standard solution—Transfer a quantity of USP •Diluted$_{•2}$ Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, quantitatively add a volume of *Isosorbide mononitrate related compound A standard solution* and a volume of *Isosorbide dinitrate standard stock solution,* and dilute with water to volume to obtain a solution having a known concentration of about 2.0 mg of •isosorbide mononitrate$_{•2}$ per mL, 0.005 mg of isosorbide mononitrate related compound A per mL, and 0.005 mg of isosorbide dinitrate per mL. Filter a portion of the solution, discarding the first few mL of the filtrate.

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

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of isosorbide mononitrate related compound A and isosorbide dinitrate relative to the amount of isosorbide mononitrate in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$•100(CV/W)(r_U/r_S)_{•2}$$

in which C is the concentration, in mg per mL, of •isosorbide mononitrate related compound A or isosorbide dinitrate, as appropriate,$_{•2}$ in the *Standard solution; W* is the •amount, in mg, of isosorbide mononitrate in the portion$_{•2}$ of Diluted Isosorbide Mononitrate used to prepare the *Test solution;* •based on the label claim; V is the volume, in mL, of the *Test solution;*$_{•2}$ and r_U and r_S are the peak areas of the corresponding components obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.25% of isosorbide mononitrate related compound A is found; and not more than 0.25% of isosorbide dinitrate is found. Calculate the percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak area for each other impurity obtained from the *Test solution;* and r_s is the sum of the areas of all the peaks: not more than 0.5% of total impurities is found, including isosorbide mononitrate related compound A and isosorbide dinitrate; and not more than 0.5% of total impurities is found, the results for *Test 1* and *Test 2* being considered.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (95 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer an accurately weighed quantity of USP •Diluted$_{•2}$ Isosorbide Mononitrate RS to a suitable volumetric flask, dissolve in water, add a volume of methanol equivalent to 4% of the flask volume, and dilute with water to volume to obtain a solution having a known concentration of about 2.0 mg •of isosorbide mononitrate$_{•2}$ per mL.

Isosorbide mononitrate related compound A standard preparation—Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 1.0 mg per mL. Quantitatively dilute a portion of this solution with water to obtain a solution having a known concentration of about 0.05 mg per mL.

Resolution solution—Transfer 10.0 mL of *Isosorbide mononitrate related compound A standard preparation,* 1.0 mL of *Standard preparation,* and 4.0 mL of methanol to a 100-mL volumetric flask, and dilute with water to volume. Filter a portion of the solution, discarding the first few mL of the filtrate.

Assay preparation—Transfer •an accurately weighed amount of Diluted Isosorbide Mononitrate, equivalent to 100 mg of isosorbide mononitrate,$_{•2}$ to a 50-mL volumetric flask, dissolve in about 25 mL of water, add 2 mL of methanol, dilute with water to volume, and mix. Filter a portion of the solution, discarding the first few mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4-mm × 12.5-cm column that contains packing L1. The flow rate is about 1.5 mL per minute, increasing to 3.0 mL per minute at about 8.5 minutes to ensure that the isosorbide mononitrate peak has completely eluted. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for isosorbide mononitrate related compound A, 1.0 for isosorbide mononitrate, and 4.1 for isosorbide dinitrate; and the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the isosorbide mononitrate peaks. Calculate the quantity, in mg, of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$•CV(r_U/r_S)_{•2}$$

in which C is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;* •V is the volume, in mL, of the *Assay preparation;*$_{•2}$ and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

MONOGRAPHS (NF)

Sorbitol Sorbitan Solution

(Title for this monograph—to become official August 1, 2010)
•***(Prior to August 1, 2010, the current practice of labeling the article of commerce with the name Anhydrized Liquid Sorbitol may be continued. Use of the name Sorbitol Sorbitan Solution will be permitted as of August 1, 2005, but the use of this name will not be mandatory until August 1, 2010. The 60-month extension will provide the time needed by the manufacturers and users to make necessary changes.)***•2

GENERAL CHAPTERS

General Tests and Assays

Chemical Tests and Assays

OTHER TESTS AND ASSAYS

⟨467⟩ ORGANIC VOLATILE IMPURITIES

(Current title—not to change until January 1, 2007)
(Chapter title change—to become official January 1, 2007)
See ⟨467⟩ Residual Solvents

Change to read:

••2

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. This General Chapter does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Because residual solvents do not provide therapeutic benefit, they should be removed, to the extent possible, to meet ingredient and product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Solvents that are known to cause unacceptable toxicities (Class 1, *Table 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Solvents associated with less severe toxicity (Class 2, *Table 2*) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, *Table 3*) should be used where practical. The complete list of solvents included in this General Chapter is given in *Appendix 1*. These tables and the list are not exhaustive. Where other solvents have been used, based on approval by the competent regulatory authority, such solvents may be added to the tables and list.

Testing of drug substances, excipients, and drug products for residual solvents should be performed when production or purification processes are known to result in the presence of such residual solvents. It is only necessary to test for residual solvents that are used or produced in the manufacture or purification processes.

Although manufacturers may choose to test the drug product, a cumulative procedure may be used to calculate the residual solvent levels in the product from the levels in its ingredients. If the calculation results in a level equal to or below that recommended in this General Chapter, no testing of the drug product for residual solvents needs to be considered. If, however, the calculated levels are above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent levels to within acceptable amounts. A drug product should also be tested if a residual solvent is used during its manufacture.

See *Appendix 2* for additional background information related to residual solvents.

Change to read:

LIMITS OF RESIDUAL SOLVENTS

Ethylene Oxide

[NOTE—The test for ethylene oxide is conducted only where specified in the individual monograph.] The standard solution parameters and the procedure for determination are described in the individual monograph. Unless otherwise specified in the individual monograph, the limit is 10 μg per g.

Class 1

Class 1 residual solvents *(Table 1)* should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if •their use in order to produce a medicinal product is unavoidable,•2 their levels should be restricted as shown in *Table 1,* unless otherwise stated in the individual monograph. The solvent 1,1,1-trichloroethane is included in *Table 1* because it is an environmental hazard. The stated limit of 1500 ppm is based on safety data.

When Class 1 residual solvents are used •or produced in the manufacture or purification of a drug substance, excipient, or drug product, these solvents should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible.•2 Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for •evaluation.•2

Table 1. Class 1 Residual Solvents

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

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Class 2

Class 2 residual solvents *(Table 2)* should be limited in drug substances, excipients, and drug products because of the inherent toxicities of the residual solvents. PDEs are given to the nearest 0.1 mg per day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of the determination procedure. Precision should be determined as part of the procedure validation.

If Class 2 residual solvents are present at greater than their *Option 1* limits, they should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for •evaluation.•2

[NOTE—The following Class 2 residual solvents are not readily detected by the headspace injection conditions described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter: formamide, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, *N*-methylpyrrolidone, and sulfolane. Other appropriate validated procedures are to be employed for the •quantification•2 of these residual solvents. Such procedures shall be submitted to the USP for •review and possible•2 inclusion in the relevant individual monograph.]

Table 2. Class 2 Residual Solvents

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
•Trichloroethylene•2	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene

Class 3

Class 3 residual solvents *(Table 3)* may be regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

Unless otherwise stated in the individual monograph, Class 3 residual solvents are limited to not more than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*). If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day, that residual solvent should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter, •with appropriate modifications to the standard solutions,•2 are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for •evaluation. USP Reference Standards, where available, should be used in these procedures.•2

Table 3. Class 3 Residual Solvents
(limited by GMP or other quality-based requirements in drug substances, excipients, and drug products)

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone
tert-Butylmethyl ether	Methylisobutylketone
Cumene	2-Methyl-l-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Other Residual Solvents

The residual solvents listed in *Table 4* may also be of interest to manufacturers of drug substances, excipients, or drug products. However, no adequate toxicological data on which to base a PDE was found. ••2

Table 4. Other Residual Solvents
(for which no adequate toxicological data was found)

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Solvent hexane
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

Change to read:

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

[NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.]

Class 1 and Class 2 Residual Solvents

WATER-SOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

•*Class 2 Standard Stock Solutions*—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A.* Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B.*

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.•2

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution,* apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution, Class 1 System Suitability Solution,* and *Class 2* •*Mixture A*•2 *Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2* •*Mixture A*•2 *Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in the table below) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution,* •*Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,*•2 and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or •either of the two *Class 2 Mixture Standard Solutions,*•2 proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Table 5. Headspace Operating Parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock •*Solutions,*•2 *Class 2* •*Mixture A*•2 *Standard Solution,* •*Class 2 Mixture B Standard Solution,*•2 *Test Stock Solution, Test Solution,* and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

•*Class 2 System Suitability Solution*—Transfer 1.0 mL of USP Residual Solvent Class 2—Acetonitrile RS and 1.0 mL of USP Residual Solvent Class 2—Trichloroethylene RS to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.•2

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 0.25-µm layer of phase G16, or a 0.53-mm × 30-m wide-bore column coated with a 0.25-µm layer of phase G16. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second and a split ratio of 1 : 5. The column temperature is maintained at 50° for 20 minutes, then raised at a rate of 6° per minute to 165°, and maintained at 165° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2* •*System Suitability*•2 *Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of benzene in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; •and•2 the resolution, *R,* between acetonitrile and trichloroethylene in the *Class 2* •*System Suitability*•2 *Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution,* the *Class 2* •*Mixture A*•2 *Standard Solution,* •the *Class 2 Mixture B Standard Solution,*•2 and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or •either of•2 the •two•2 *Class 2* •*Mixture*•2 *Standard* •*Solutions,*•2 proceed to *Procedure C* to quantify the •peak(s);•2 otherwise the article meets the requirements of this test.

Procedure C—

•*Class 1 Standard Stock Solution,*•2 *Class 1 Standard Solution,* •*Class 2 Standard Stock Solution A,*•2 *Class 2* •*Mixture A*•2 *Standard Solution, Test Stock Solution, Test Solution,* and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Standard Solution—•[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*]•2 Transfer an accurately measured volume of •each individual•2 USP Reference Standard •corresponding to•2 each •residual solvent•2 peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of •1/20•2 of the value stated in *Table 1* or *2* (under *Concentration Limit*). Transfer •1.0 mL•2 of this solution to an appropriate headspace vial, add •5.0 mL•2 of water, apply the stopper, cap, and mix.

•*Spiked Test Solution*—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of the *Standard Solution,* apply the stopper, cap, and mix.•2

Chromatographic System (see *Chromatography* ⟨621⟩)—[NOTE—If the results of the chromatography from *Procedure A* are found to be inferior to those found with *Procedure B,* the *Chromatographic System* from *Procedure B* may be substituted.] The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2* •*Mixture A*•2 *Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the

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Class 1 System Suitability Solution is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2* •*Mixture A*$_{•2}$ *Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution,* •the$_{•2}$ *Test Solution,* •and the *Spiked Test Solution*$_{•2}$ into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$•5(C/W)[r_U/(r_{ST} - r_U)]_{•2}$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and $•r_{ST•2}$ are the peak responses of each residual solvent obtained from the *Test Solution* and the •*Spiked Test*$_{•2}$ *Solution,* respectively.

WATER-INSOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution •*A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,*$_{•2}$and *Chromatographic System*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

•*Class 2 Standard Stock Solution C*—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture C RS to a 100-mL volumetric flask, dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix.

Class 2 Mixture C Standard Solution—[NOTE—This solution is used for the identification and quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer 1.0 mL of *Class 2 Standard Stock Solution C* to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.$_{•2}$

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

Test Solution 1—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Test Solution 2—•[NOTE—This solution is used for the identification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.]$_{•2}$ Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix. Transfer 5.0 mL of this solution to an appropriate headspace vial, add 1.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution,* •*Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution,*$_{•2}$ *Test Solution 1,* and *Test Solution 2* •(if applicable)$_{•2}$ into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in *Test Solution 1* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or •any of the three *Class 2 Mixture Standard Solutions,*$_{•2}$ proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2* •*Mixture C*$_{•2}$ *Standard Solution,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, •*Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution,* and *Class 2 Mixture B Standard Solution*—$_{•2}$Prepare as directed for *Procedure A* under *Water-Soluble Articles.*

•*Class 2 Standard Stock Solution C, Class 2 Mixture C Standard Solution,*$_{•2}$ *Test Stock Solution, Test Solution 1,* and *Test Solution 2*—Proceed as directed for *Procedure A.*

•*Class 2 System Suitability Solution* and$_{•2}$ *Chromatographic System*—Proceed as directed for *Procedure B* under *Water-Soluble Articles.*

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution,* •*Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution,*$_{•2}$ *Test Solution 1,* and/or *Test Solution 2* •(if applicable)$_{•2}$ into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in *Test Solution 1* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or •any of$_{•2}$ the •three *Class 2 Mixture Standard Solutions,*$_{•2}$ proceed to *Procedure C* to quantify the •peak(s);$_{•2}$ otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2* •*Mixture C*$_{•2}$ *Standard Solution,* proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test.

Procedure C—

•*Class 1 Standard Stock Solution,*$_{•2}$ *Class 1 Standard Solution, Class 1 System Suitability Solution,* •*Class 2 Standard Stock Solution A,*$_{•2}$ and *Class 2* •*Mixture A*$_{•2}$ *Standard Solution*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

•*Standard Solution 1*—[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with dimethylformamide to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Standard Solution 2—[NOTE—This solution is used for the quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS and/or an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS to a suitable container; and dilute quantitatively, and stepwise if necessary, with 1,3-dimethyl-2-imidazolidinone to obtain a solution having a final concentration of 1/20 of the value stated in *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.$_{•2}$

Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

•*Spiked Test Solution 1*—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 1,* apply the stopper, cap, and mix.

Spiked Test Solution 2—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Solution 2* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 2,* apply the stopper, cap, and mix.$_{•2}$

•$_{•2}$ *Chromatographic System*—Proceed as directed for *Procedure C* under *Water-Soluble Articles.*

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution, Test Solution 1* and/or *Test Solution 2,* •and *Spiked Test Solution 1* and/or *Spiked Test Solution 2*•2 into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$•5(C/W)[r_U/(r_{ST} - r_U)]•2$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and $•r_{ST}•2$ are the peak responses of each residual solvent obtained from *Test Solution 1* or *Test Solution 2* and •*Spiked Test Solution 1* or *Spiked Test Solution 2,*•2 respectively.

Class 3 Residual Solvents

If only Class 3 solvents are present, the level of residual solvents is to be determined as directed under *Loss on Drying* ⟨731⟩. If the loss on drying value is greater than 0.5%, a water determination should be performed on the test sample as directed under *Water Determination* ⟨921⟩. Determine the water by *Method Ia*, unless otherwise specified in the individual monograph. If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*), that residual solvent should be identified and quantified, and the procedures as described above, •with appropriate modifications to the standard solutions,•2 are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for •evaluation. USP Reference Standards, where available, should be used in these procedures.•2 A flow diagram for the application of residual solvent limit tests is shown in *Figure 1*.

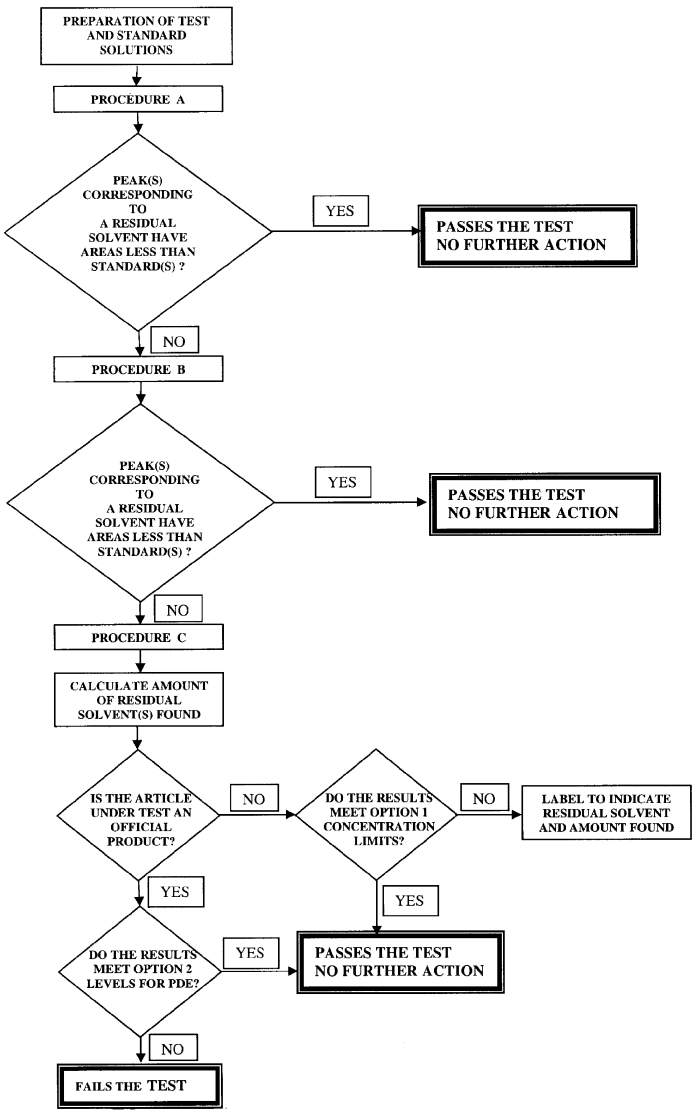
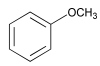
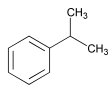


Figure 1. Diagram relating to the identification of residual solvents and the application of limit tests.

Change to read:

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	*n*-Butyl alcohol Butan-1-ol	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methylpropane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methylethyl)benzene		Class 3
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C{=}CCl_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$ClHC{=}CHCl$	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,*N*-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,*N*-Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	*p*-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethylene glycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1′-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		$HCOOH$	Class 3
Heptane	*n*-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	*n*-Hexane	$CH_3(CH_2)_4CH_3$	Class 2

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APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER *(Continued)*

Solvent	Other Names	Structure	Class
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutylketone	2-Hexanone Hexan-2-one	$CH_3(CH_2)_3COCH_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylene chloride	Dichloromethane	CH_2Cl_2	Class 2
Methylethylketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methyl isobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	*n*-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydronaphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH_3CCl_3	Class 1

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APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER *(Continued)*

Solvent	Other Names	Structure	Class
•Trichloroethylene•[2]	1,1,2-Trichloroethene	$HClC{=}CCl_2$	Class 2
Xylene*	Dimethybenzene Xylol		Class 2

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

Change to read:

•⟨467⟩ RESIDUAL SOLVENTS

(Chapter under this new title—to become official January 1, 2007)

(Current chapter title is ⟨467⟩ Organic Volatile Impurities)

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. This General Chapter does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Because residual solvents do not provide therapeutic benefit, they should be removed, to the extent possible, to meet ingredient and product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Solvents that are known to cause unacceptable toxicities (Class 1, *Table 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Solvents associated with less severe toxicity (Class 2, *Table 2*) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, *Table 3*) should be used where practical. The complete list of solvents included in this General Chapter is given in *Appendix 1*. These tables and the list are not exhaustive. Where other solvents have been used, based on approval by the competent regulatory authority, such solvents may be added to the tables and list.

Testing of drug substances, excipients, and drug products for residual solvents should be performed when production or purification processes are known to result in the presence of such residual solvents. It is only necessary to test for residual solvents that are used or produced in the manufacture or purification processes.

Although manufacturers may choose to test the drug product, a cumulative procedure may be used to calculate the residual solvent levels in the product from the levels in its ingredients. If the calculation results in a level equal to or below that recommended in this General Chapter, no testing of the drug product for residual solvents needs to be considered. If, however, the calculated levels are above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent levels to within acceptable amounts. A drug product should also be tested if a residual solvent is used during its manufacture.

See *Appendix 2* for additional background information related to residual solvents.

CLASSIFICATION OF RESIDUAL SOLVENTS BY RISK ASSESSMENT

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and the term "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The term "permitted daily exposure" (PDE) is defined as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs of the same substance.

Residual solvents specified in this General Chapter are listed in *Appendix 1* by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1	Residual Solvents: Solvents to be Avoided Known human carcinogens Strongly suspected human carcinogens Environmental hazards
Class 2	Residual Solvents: Solvents to be Limited Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.
Class 3	Residual Solvents: Solvents with Low Toxic Potential Solvents with low toxic potential to humans; no health-based exposure limit is needed. [NOTE—Class 3 residual solvents may have PDEs of up to 50 mg or more per day.]*

* For residual solvents with PDEs of more than 50 mg per day, see the discussion in the section *Class 3* under *Limits of Residual Solvents*.

PROCEDURES FOR ESTABLISHING EXPOSURE LIMITS

The procedure used to establish permitted daily exposures for residual solvents is presented in *Appendix 3*.

OPTIONS FOR DETERMINING LEVELS OF CLASS 2 RESIDUAL SOLVENTS

Two options are available to determine levels of Class 2 residual solvents.

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Option 1

The concentration limits in ppm stated in *Table 2* are used. They were calculated using equation (1) below by assuming a product weight of 10 g administered daily.

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}} \quad (1)$$

Here, PDE is given in terms of mg per day, and dose is given in g per day.

These limits are considered acceptable for all drug substances, excipients, and drug products. Therefore, this option may be applied if the daily dose is not known or fixed. If all drug substances and excipients in a formulation meet the limits given in *Option 1,* these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day are to be considered under *Option 2.*

Option 2

It is not necessary for each component of the drug product to comply with the limits given in *Option 1.* The PDE in terms of mg per day as stated in *Table 2* can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in a drug product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process. The limits should also reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the application of *Option 1* and *Option 2* to acetonitrile concentration in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus, the *Option 1* limit is 410 ppm. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Drug product	5.0	728	3.64

Excipient l meets the *Option 1* limit, but the drug substance, excipient 2, and drug product do not meet the *Option 1* limit. Nevertheless, the drug product meets the *Option 2* limit of 4.1 mg per day and thus conforms to the acceptance criteria in this General Chapter.

Consider another example using acetonitrile as the residual solvent. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	2000	1.80
Excipient 2	3.8	800	3.04
Drug product	5.0	1016	5.08

In this example, the drug product meets neither the *Option 1* nor the *Option 2* limit. The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced to the allowed limit during formulation, the product fails the requirements of the test.

LIMITS OF RESIDUAL SOLVENTS

Ethylene Oxide

[NOTE—The test for ethylene oxide is conducted only where specified in the individual monograph.] The standard solution parameters and the procedure for determination are described in the individual monograph. Unless otherwise specified in the individual monograph, the limit is 10 µg per g.

Class 1

Class 1 residual solvents *(Table 1)* should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if their use in order to produce a medicinal product is unavoidable, their levels should be restricted as shown in *Table 1,* unless otherwise stated in the individual monograph. The solvent 1,1,1-trichloroethane is included in *Table 1* because it is an environmental hazard. The stated limit of 1500 ppm is based on safety data.

When Class 1 residual solvents are used or produced in the manufacture or purification of a drug substance, excipient, or drug product, these solvents should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation.

Table 1. Class 1 Residual Solvents

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Class 2

Class 2 residual solvents *(Table 2)* should be limited in drug substances, excipients, and drug products because of the inherent toxicities of the residual solvents. PDEs are given to the nearest 0.1 mg per day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of the determination procedure. Precision should be determined as part of the procedure validation.

If Class 2 residual solvents are present at greater than their *Option 1* limits, they should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation.

[NOTE—The following Class 2 residual solvents are not readily detected by the headspace injection conditions described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter: formamide, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, *N*-methylpyrrolidone, and sulfolane. Other ap-

propriate validated procedures are to be employed for the quantification of these residual solvents. Such procedures shall be submitted to the USP for review and possible inclusion in the relevant individual monograph.

Table 2. Class 2 Residual Solvents

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
Trichloroethylene	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene

Class 3

Class 3 residual solvents *(Table 3)* may be regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

Unless otherwise stated in the individual monograph, Class 3 residual solvents are limited to not more than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*). If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day, that residual solvent should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation. USP Reference Standards, where available, should be used in these procedures.

Table 3. Class 3 Residual Solvents
(limited by GMP or other quality-based requirements in drug substances, excipients, and drug products)

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone
tert-Butylmethyl ether	Methylisobutylketone
Cumene	2-Methyl-l-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Other Residual Solvents

The residual solvents listed in *Table 4* may also be of interest to manufacturers of drug substances, excipients, or drug products. However, no adequate toxicological data on which to base a PDE was found.

Table 4. Other Residual Solvents
(for which no adequate toxicological data was found)

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Solvent hexane
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

[NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.]

Class 1 and Class 2 Residual Solvents

WATER-SOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A.* Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B.*

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution,* apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution, Class 1 System Suitability Solution,* and *Class 2 Mixture A Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in the table below) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Table 5. Headspace Operating Parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock Solutions, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Class 2 System Suitability Solution—Transfer 1.0 mL of USP Residual Solvent Class 2—Acetonitrile RS and 1.0 mL of USP Residual Solvent Class 2—Trichloroethylene RS to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 0.25-µm layer of phase G16, or a 0.53-mm × 30-m wide-bore column coated with a 0.25-µm layer of phase G16. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second and a split ratio of 1 : 5. The column temperature is maintained at 50° for 20 minutes, then raised at a rate of 6° per minute to 165°, and maintained at 165° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2 System Suitability Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of benzene in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and trichloroethylene in the *Class 2 System Suitability Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution,* the *Class 2 Mixture A Standard Solution,* the *Class 2 Mixture B Standard Solution,* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions,* proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock Solution A, Class 2 Mixture A Standard Solution, Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Standard Solution—[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of the *Standard Solution,* apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—[NOTE—If the results of the chromatography from *Procedure A* are found to be inferior to those found with *Procedure B,* the *Chromatographic System* from *Procedure B* may be substituted.] The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2 Mixture A Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution,* the *Test Solution,* and the *Spiked Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{ST} - r_U)]$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_{ST} are the peak responses of each residual solvent obtained from the *Test Solution* and the *Spiked Test Solution,* respectively.

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WATER-INSOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, and *Chromatographic System*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

Class 2 Standard Stock Solution C—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture C RS to a 100-mL volumetric flask, dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix.

Class 2 Mixture C Standard Solution—[NOTE—This solution is used for the identification and quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer 1.0 mL of *Class 2 Standard Stock Solution C* to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

Test Solution 1—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Test Solution 2—[NOTE—This solution is used for the identification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix. Transfer 5.0 mL of this solution to an appropriate headspace vial, add 1.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution, Test Solution 1,* and *Test Solution 2* (if applicable) into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in *Test Solution 1* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or any of the three *Class 2 Mixture Standard Solutions,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Mixture C Standard Solution,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution, and *Class 2 Mixture B Standard Solution*—Prepare as directed for *Procedure A* under *Water-Soluble Articles.*

Class 2 Standard Stock Solution C, Class 2 Mixture C Standard Solution, Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

Class 2 System Suitability Solution and *Chromatographic System*—Proceed as directed for *Procedure B* under *Water-Soluble Articles.*

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution, Test Solution 1,* and/or *Test Solution 2* (if applicable) into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in *Test Solution 1* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or any of the three *Class 2 Mixture Standard Solutions,* proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Mixture Standard Solution, C* proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, and *Class 2 Mixture A Standard Solution*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

Standard Solution 1—[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with dimethylformamide to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Standard Solution 2—[NOTE—This solution is used for the quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS and/or an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS to a suitable container; and dilute quantitatively, and stepwise if necessary, with 1,3-dimethyl-2-imidazolidinone to obtain a solution having a final concentration of 1/20 of the value stated in *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

Spiked Test Solution 1—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 1,* apply the stopper, cap, and mix.

Spiked Test Solution 2—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Solution 2* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 2,* apply the stopper, cap, and mix.

Chromatographic System—Proceed as directed for *Procedure C* under *Water-Soluble Articles.*

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution, Test Solution 1* and/or *Test Solution 2,* and *Spiked Test Solution 1* and/or *Spiked Test Solution 2* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{ST} - r_U)]$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_{ST} are the peak responses of each residual solvent obtained from *Test Solution 1* or *Test Solution 2* and *Spiked Test Solution 1* or *Spiked Test Solution 2,* respectively.

Class 3 Residual Solvents

If only Class 3 solvents are present, the level of residual solvents is to be determined as directed under *Loss on Drying* ⟨731⟩. If the loss on drying value is greater than 0.5%, a water determination should be performed on the test sample as directed under *Water Determination* ⟨921⟩. Determine the water by *Method Ia*, unless otherwise specified in the individual monograph. If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*), that residual solvent should be identified and quantified, and the procedures as described above, with ap-

propriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for evaluation. USP Reference Standards, where available, should be used in these procedures. A flow diagram for the application of residual solvent limit tests is shown in *Figure 1*.

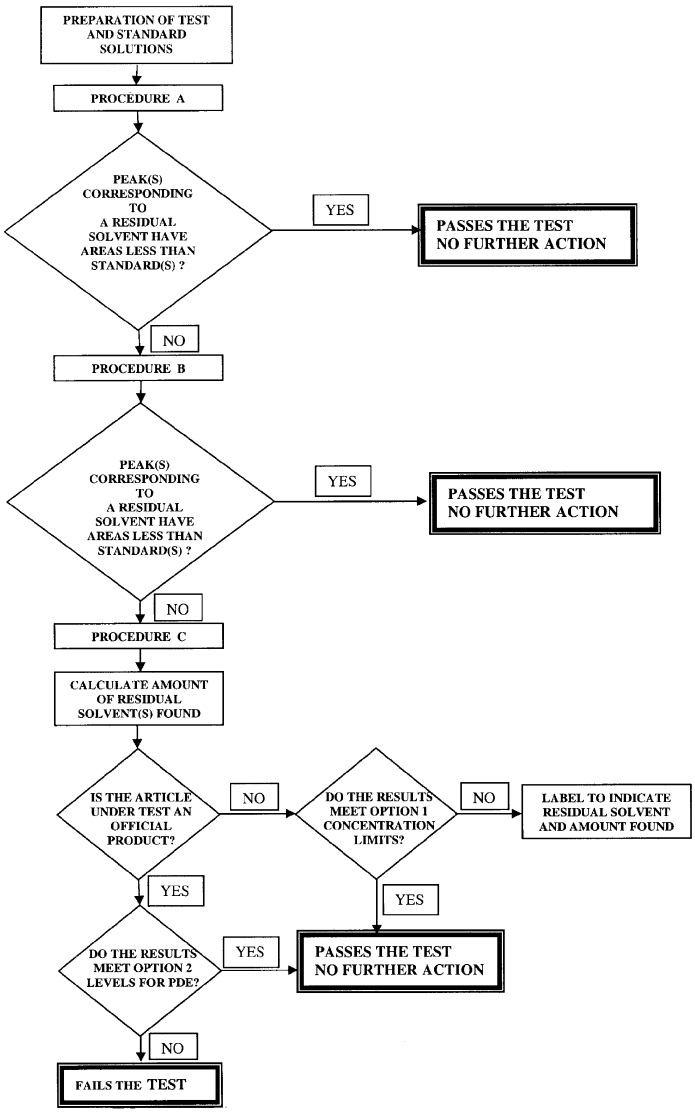


Figure 1. Diagram relating to the identification of residual solvents and the application of limit tests.

GLOSSARY

Genotoxic carcinogens: Carcinogens that produce cancer by affecting genes or chromosomes.

Lowest-observed-effect level (LOEL): The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Modifying factor: A factor determined by professional judgment of a toxicologist and applied to bioassay data so that the data can be safely related to humans.

Neurotoxicity: The ability of a substance to cause adverse effects on the nervous system.

No-observed-effect level (NOEL): The highest dose of a substance at which there are no biologically significant increases in frequency or severity of any effects in exposed humans or animals.

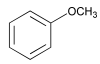
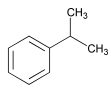
Permitted daily exposure (PDE): The maximum acceptable intake per day of a residual solvent in pharmaceutical products.

Reversible toxicity: The occurrence of harmful effects that are caused by a substance and that disappear after exposure to the substance ends.

Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence of carcinogenesis but for which there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

Teratogenicity: The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	*n*-Butyl alcohol Butan-1-ol	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methylpropane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methylethyl)benzene		Class 3
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C{=}CCl_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$ClHC{=}CHCl$	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,*N*-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,*N*-Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	*p*-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethylene glycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1′-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		$HCOOH$	Class 3
Heptane	*n*-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	*n*-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3

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APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER *(Continued)*

Solvent	Other Names	Structure	Class
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutylketone	2-Hexanone Hexan-2-one	$CH_3(CH_2)_3COCH_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylene chloride	Dichloromethane	CH_2Cl_2	Class 2
Methylethylketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methyl isobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	*n*-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydronaphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH_3CCl_3	Class 1
Trichloroethylene	1,1,2-Trichloroethene	$HClC{=}CCl_2$	Class 2
Xylene*	Dimethybenzene Xylol		Class 2

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

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APPENDIX 2. ADDITIONAL BACKGROUND

A2.1. Environmental Regulation of Organic Volatile Solvents

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in Environmental Health Criteria (EHC) monographs and in the Integrated Risk Information System (IRIS). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (EPA), and the United States Food and Drug Administration (FDA) include the determination of acceptable exposure levels. The goal is maintenance of environmental integrity and protection of human health against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The procedures involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter term study data can be used with modification of the approach, such as use of larger safety factors. The approach described therein relates primarily to long-term or lifetime exposure of the general population in the ambient environment (i.e., ambient air, food, drinking water, and other media).

A2.2. Residual Solvents in Pharmaceuticals

Exposure limits in this General Chapter are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, the following specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits.

1. Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.
2. The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.
3. Residual solvents are unavoidable components in pharmaceutical production and will often be a part of medicinal products.
4. Residual solvents should not exceed recommended levels except in exceptional circumstances.
5. Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described, for example, by the Organization for Economic Cooperation and Development (OECD), EPA, and the FDA Red Book.

APPENDIX 3. PROCEDURES FOR ESTABLISHING EXPOSURE LIMITS

The Gaylor-Kodell method of risk assessment (Gaylor, D. W. and Kodell, R. L. Linear Interpolation Algorithm for Low Dose Assessment of Toxic Substance. *Journal of Environmental Pathology and Toxicology,* 4 : 305, 1980) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 residual solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the no-observed-effect level (NOEL). Detection and quantification of these residual solvents should be performed by state-of-the-art analytical techniques.

Acceptable exposure levels in this General Chapter for Class 2 residual solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (page 5748 of *PF* 15(6) [Nov.–Dec. 1989]), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (*Environmental Health Criteria 170,* WHO, 1994). These procedures are similar to those used by the U.S. EPA (IRIS) and the U.S. FDA *(Red Book)* and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values presented in *Table 2* of this document.

PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL), in the most relevant animal study as follows:

$$\text{PDE} = \frac{\text{NOEL} \times \text{Weight Adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}} \quad (1)$$

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in Environmental Health Criteria (*Environmental Health Criteria 170,* WHO, Geneva, 1994) and "modifying factors" or "safety factors" in *Pharmacopeial Forum.* The assumption of 100 percent systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species
- F1 = 2 for extrapolation from dogs to humans
- F1 = 2.5 for extrapolation from rabbits to humans
- F1 = 3 for extrapolation from monkeys to humans
- F1 = 5 for extrapolation from rats to humans
- F1 = 10 for extrapolation from other animals to humans
- F1 = 12 for extrapolation from mice to humans

F1 takes into account the comparative surface area to body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67}, \quad (2)$$

in which M = body weight, and the constant k has been taken to be 10. The body weights used in the equation are those shown below in *Table A3.-1*.

F2 = A factor of 10 to account for variability between individuals. A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this General Chapter.

F3 = A variable factor to account for toxicity studies of short-term exposure.
- F3 = 1 for studies that last at least one half-lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys).
- F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.
- F3 = 2 for a 6-month study in rodents, or a 3.5-year study in nonrodents.
- F3 = 5 for a 3-month study in rodents, or a 2-year study in nonrodents.
- F3 = 10 for studies of a shorter duration.

In all cases, the higher factor has been used for study durations between the time points (e.g., a factor of 2 for a 9-month rodent study).

F4 = A factor that may be applied in cases of severe toxicity, e.g., nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity. In studies of reproductive toxicity, the following factors are used:
- F4 = 1 for fetal toxicity associated with maternal toxicity
- F4 = 5 for fetal toxicity without maternal toxicity
- F4 = 5 for a teratogenic effect with maternal toxicity
- F4 = 10 for a teratogenic effect without maternal toxicity

F5 = A variable factor that may be applied if the no-effect level was not established.

When only a LOEL is available, a factor of up to 10 can be used depending on the severity of the toxicity. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kilograms (kg). This relatively low weight provides an additional safety

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factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in *Pharmeuropa,* Vol. 9, No. 1, Supplement, April 1997, page S24. The NOEL is calculated to be 50.7 mg kg^{-1} day^{-1}. The PDE for acetonitrile in this study is calculated as follows:

$$\text{PDE} = \frac{50.7\ \text{mg kg}^{-1}\ \text{day}^{-1} \times\ 50\ \text{kg}}{12\times10\times5\times1\times1} = 4.22\ \text{mg day}^{-1}$$

In this example,

F1 = 12 to account for the extrapolation from mice to humans
F2 = 10 to account for differences between individual humans
F3 = 5 because the duration of the study was only 13 weeks
F4 = 1 because no severe toxicity was encountered
F5 = 1 because the no-effect level was determined

A3.-1. - Values Used in the Calculations in This Document

Rat body weight	425 g
Pregnant rat body weight	330 g
Mouse body weight	28 g
Pregnant mouse body weight	30g
Guinea-pig body weight	500 g
Rhesus monkey body weight	2.5 kg
Rabbit body weight (pregnant or not)	4 kg
Beagle dog body weight	11.5 kg
Rat respiratory volume	290 L/day
Mouse respiratory volume	43 L/day
Rabbit respiratory volume	1440 L/day
Guinea-pig respiratory volume	430 L day
Human respiratory volume	28,800 L/day
Dog respiratory volume	9000 L/day
Monkey respiratory volume	1150 L/day
Mouse water consumption	5 mL/day
Rat water consumption	30 mL/day
Rat food consumption	30 g/day

The equation for an ideal gas, $PV = nRT$, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/m^3. Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) summarized in *Pharmeuropa,* Vol. 9, No. 1, Supplement, April 1997, page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300\times10^{-6}\ \text{atm}\times153\ 840\ \text{mg mol}^{-1}}{0.082\ \text{L at mK}^{-1}\ \text{mol}^{-1}\times298\ \text{K}} = \frac{46.15\ \text{mg}}{24.45\ \text{L}} = 1.89\ \text{mg/L}$$

The relationship 1000 L = 1 m^3 is used to convert to mg/ m^3.●2

Physical Tests and Determinations

⟨711⟩ DISSOLUTION

Change to read:

This general chapter is harmonized with the corresponding texts of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia.*●●2 These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.

Portions of the present general chapter text that are national USP text, and therefore not part of the harmonized text, are marked with symbols (◆◆) to specify this fact.

This test is provided to determine compliance with the dissolution requirements ◆where stated in the individual monograph◆ for dosage forms administered orally. In this general chapter, a dosage unit is defined as 1 tablet or 1 capsule or the amount specified. ◆Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and where a dissolution or disintegration test that does not specifically state that it is to be applied to delayed-release articles is included in the individual monograph, the procedure and interpretation given for *Delayed-Release Dosage Forms* is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the *Dissolution* specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual monograph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

USP Reference Standards ⟨11⟩—*USP Chlorpheniramine Maleate Extended-Release Tablets RS (Drug Release Calibrator, Single Unit). USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating). USP Salicylic Acid Tablets RS. (Dissolution Calibrator, Nondisintegrating).*◆

Change to read:

PROCEDURE

Apparatus 1 and Apparatus 2

IMMEDIATE-RELEASE DOSAGE FORMS

Place the stated volume of the *Dissolution Medium* (±1%) in the vessel of the specified apparatus ◆given in the individual monograph◆, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage unit in the apparatus, taking care to exclude air bubbles from the surface of the dosage unit, and immediately operate the apparatus at the specified rate ◆given in the individual monograph◆. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Where multiple sampling times are specified, replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement

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of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis ◆as directed in the individual monograph◆ using a suitable assay method.[3] Repeat the test with additional dosage form units.

If automated equipment is used for sampling or the apparatus is otherwise modified, verification that the modified apparatus will produce results equivalent to those obtained with the standard apparatus described in this general chapter is necessary.

Dissolution Medium—A suitable dissolution medium is used. Use the solvent specified ◆in the individual monograph◆. The volume specified refers to measurements made between 20° and 25°. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the specified pH ◆given in the individual monograph◆. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. If dissolved gases influence the dissolution results, dissolved gases should be removed prior to testing.[4]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. Specimens are to be withdrawn only at the stated times within a tolerance of ±2%.

●◆**Procedure for a Pooled Sample for Immediate-Release Dosage Forms**—Use this procedure where *Procedure for a Pooled Sample* is specified in the individual monograph. Proceed as directed in *Procedure* for *Apparatus 1 and Apparatus 2* in *Immediate-Release Dosage Forms.* Combine equal volumes of the filtered solutions of the six or twelve individual specimens withdrawn, and use the pooled sample as the test specimen. Determine the average amount of the active ingredient dissolved in the pooled sample.◆●[2]

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms.*

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms.*

Time—The test-time points, generally three, are expressed in hours.

DELAYED-RELEASE DOSAGE FORMS

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

Use *Method A* or *Method B* and the apparatus specified ◆in the individual monograph◆. All test times stated are to be observed within a tolerance of ±2%, unless otherwise specified.

Method A—

Procedure ◆(unless otherwise directed in the individual monograph)◆—

ACID STAGE—Place 750 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the specified rate ◆given in the monograph◆.

After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph.◆

BUFFER STAGE—[NOTE—Complete the operations of adding the buffer and adjusting the pH within 5 minutes.]

With the apparatus operating at the rate specified ◆in the monograph◆, add to the fluid in the vessel 250 mL of 0.20 M tribasic sodium phosphate that has been equilibrated to 37 ± 0.5°. Adjust, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph◆. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for the minimum amount dissolved is met at an earlier time.◆

Method B—

Procedure ◆(unless otherwise directed in the individual monograph)◆—

ACID STAGE—Place 1000 mL of 0.1 N hydrochloric acid in the vessel, and assemble the apparatus. Allow the medium to equilibrate to a temperature of 37 ± 0.5°. Place 1 dosage unit in the apparatus, cover the vessel, and operate the apparatus at the rate specified ◆in the monograph◆. After 2 hours of operation in 0.1 N hydrochloric acid, withdraw an aliquot of the fluid, and proceed immediately as directed under *Buffer Stage*.

Perform an analysis of the aliquot using a suitable assay method. ◆The procedure is specified in the individual monograph.◆

BUFFER STAGE—[NOTE—For this stage of the procedure, use buffer that previously has been equilibrated to a temperature of 37 ± 0.5°.] Drain the acid from the vessel, and add to the vessel 1000 mL of pH 6.8 phosphate buffer, prepared by mixing 0.1 N hydrochloric acid with 0.20 M tribasic sodium phosphate (3 : 1) and adjusting, if necessary, with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. [NOTE—This may also be accomplished by removing from the apparatus the vessel containing the acid and replacing it with another vessel containing the buffer and transferring the dosage unit to the vessel containing the buffer.]

Continue to operate the apparatus for 45 minutes, or for the specified time ◆given in the individual monograph◆. At the end of the time period, withdraw an aliquot of the fluid, and perform the analysis using a suitable assay method. ◆The procedure is specified in the individual monograph. The test may be concluded in a shorter time period than that specified for the *Buffer Stage* if the requirement for minimum amount dissolved is met at an earlier time.◆

Apparatus 3 (Reciprocating Cylinder)

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA

IMMEDIATE-RELEASE DOSAGE FORMS

Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage-form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage unit, and immediately operate the apparatus as specified ◆in the individual monograph◆. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the *Dissolution Medium* and the bottom of each vessel. Perform the analysis as directed ◆in the individual monograph◆. If necessary, repeat the test with additional dosage-form units.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

[3] Test specimens are filtered immediately upon sampling unless filtration is demonstrated to be unnecessary. Use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

[4] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 3*.

Dissolution Medium—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Extended-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

DELAYED-RELEASE DOSAGE FORMS

Proceed as described for *Delayed-Release Dosage Forms, Method B* under *Apparatus 1 and Apparatus 2* using one row of vessels for the acid stage media and the following row of vessels for the buffer stage media and using the volume of medium specified (usually 300 mL).

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Apparatus 4 (Flow-Through Cell)

IMMEDIATE-RELEASE DOSAGE FORMS

Place the glass beads into the cell specified ◆in the monograph◆. Place 1 dosage unit on top of the beads or, if specified ◆in the monograph◆, on a wire carrier. Assemble the filter head, and fix the parts together by means of a suitable clamping device. Introduce by the pump the *Dissolution Medium* warmed to 37 ± 0.5° through the bottom of the cell to obtain the flow rate specified ◆in the individual monograph◆ and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed ◆in the individual monograph◆. Repeat the test with additional dosage-form units.

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

EXTENDED-RELEASE DOSAGE FORMS

Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

Dissolution Medium—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4*.

Time—Proceed as directed for *Immediate-Release Dosage Forms* under *Apparatus 4.*

DELAYED-RELEASE DOSAGE FORMS

Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2,* using the specified media.

Time—Proceed as directed for *Delayed-Release Dosage Forms* under *Apparatus 1 and Apparatus 2*.

Change to read:

INTERPRETATION

Immediate-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 1*. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient ◆specified in the individual monograph◆, expressed as a percentage of the labeled content of the dosage unit; the 5%, 15%, and 25% values in *Acceptance Table 1* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 1

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q – 15%.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

●◆**Immediate-Release Dosage Forms Pooled Sample**—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying *Acceptance Table for a Pooled Sample.* Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample

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

◆●[2]

Extended-Release Dosage Forms

Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the dosage units tested conform to *Acceptance Table 2*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified

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fractional dosing interval. Where more than one range is specified ◆in the individual monograph◆, the acceptance criteria apply individually to each range.

Acceptance Table 2

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

Delayed-Release Dosage Forms

NOT ACCEPTED BY THE JAPANESE PHARMACOPOEIA.

Acid Stage—Unless otherwise specified ◆in the individual monograph◆, the requirements of this portion of the test are met if the quantities, based on the percentage of the labeled content, of active ingredient dissolved from the units tested conform to *Acceptance Table 3*. Continue testing through all levels unless the results of both acid and buffer stages conform at an earlier level.

Acceptance Table 3

Level	Number Tested	Criteria
A_1	6	No individual value exceeds 10% dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.
A_3	12	Average of the 24 units ($A_1 + A_2 + A_3$) is not more than 10% dissolved, and no individual unit is greater than 25% dissolved.

Buffer Stage—Unless otherwise specified ◆in the individual monograph◆, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 4*. Continue testing through the three levels unless the results of both stages conform at an earlier level. The value of Q in *Acceptance Table 4* is 75% dissolved unless otherwise specified ◆in the individual monograph◆. The quantity, Q,◆specified in the individual monograph◆ is the total amount of active ingredient dissolved in both the *Acid* and *Buffer Stages*, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in *Acceptance Table 4* are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table 4

Level	Number Tested	Criteria
B_1	6	Each unit is not less than Q + 5%.
B_2	6	Average of 12 units ($B_1 + B_2$) is equal to or greater than Q, and no unit is less than Q – 15%.
B_3	12	Average of 24 units ($B_1 + B_2 + B_3$) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

GENERAL CHAPTERS

General Information

⟨1216⟩ TABLET FRIABILITY

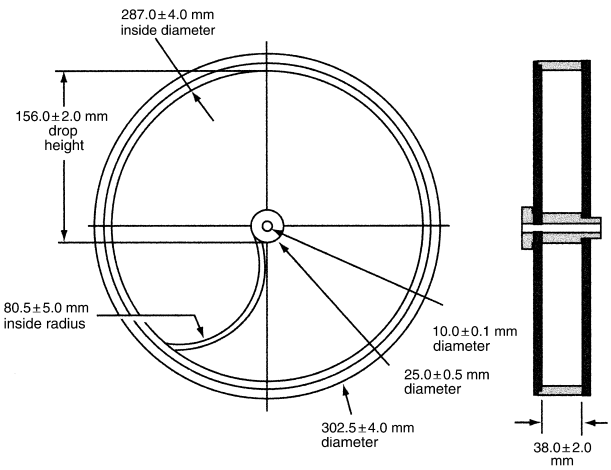
Change to read:

•This general information chapter has been harmonized with the corresponding texts of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. The harmonized texts of these three pharmacopeias are therefore interchangeable, and the methods of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* may be used for demonstration of compliance instead of the present *United States Pharmacopeia* general information chapter method. These pharmacopeias have undertaken not to make any unilateral change to this harmonized chapter.•2

This chapter provides guidelines for the friability determination of compressed, uncoated tablets. The test procedure presented in this chapter is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet •breaking force.•2

Use a drum,* with an internal diameter between 283 and 291 mm and a depth between 36 and 40 mm, of transparent synthetic polymer with polished internal surfaces, and ••2 subject to •minimum•2 static build-up (see figure for a typical apparatus). One side of the drum is removable. The tablets are tumbled at each turn of the drum by a curved projection with an inside radius between 75.5 and 85.5 mm that extends from the middle of the drum to the outer wall. •The outer diameter of the central ring is between 24.5 and 25.5 mm.•2 The drum is attached to the horizontal axis of a device that rotates at 25 ± 1 rpm. Thus, at each turn the tablets roll or slide and fall onto the drum wall or onto each other.

* The apparatus meeting these specifications is available from laboratory supply houses such as VanKel Technology Group, 13000 Weston Parkway, Cary, NC 27513, or from Erweka Instruments, Inc., 56 Quirk Road, Milford, CT 06460.



Tablet Friability Apparatus

For tablets with a unit •weight•2 equal to or less than 650 mg, take a sample of whole tablets corresponding •as near as possible•2 to 6.5 g. For tablets with a unit •weight•2 of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh.

Generally, the test is run once. If obviously cracked, cleaved, or broken tablets are present in the tablet sample after tumbling, the sample fails the test. If the results are •difficult to interpret•2 or if the weight loss is greater than the targeted value, the test should be repeated twice and the mean of the three tests determined. A maximum mean weight loss from the three samples of not more than 1.0% is considered acceptable for most products.

If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10° with the •horizontal•2 and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned. In the case of hygroscopic tablets, an appropriate humidity-controlled environment is required for testing.

Drums with dual scooping projections, or an apparatus with more than one drum, for the running of multiple samples at one time, are also permitted.

•(Official August 1, 2006)•2

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ERRATA

Following is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP 29–NF 24*. If necessary, this list will be updated with every issue of *PF*. This information will also be available as a cumulative table in the next available *Supplement* and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
294	*Bisoprolol Fumarate and Hydrochlorothiazide Tablets*	*Assay*	Line 2 under *Diluent:* Change "a mixture of water and acetonitrile." to: a mixture of water and acetonitrile (1:1).
1045	*Helium*	*USP Reference standards*	There is no USP Reference Standard for this monograph. Therefore, text in this section that appears in *USP 29–NF 24* and is marked "Postponed indefinitely" should be disregarded.
		Assay	The *Assay* was postponed indefinitely in the *USP 29–NF 24* official text, leaving the *Assay* in *USP 28–NF 23* as official text. In addition to the *USP 29–NF 24* text, the following official *USP 28–NF 23* text should also be included: Introduce a specimen of Helium into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of nitrogen and oxygen from Helium, although the nitrogen and oxygen may not be separated from each other. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by an air-helium certified standard (see under *Reagents* in the section *Reagents, Indicators, and Solutions*), and indicates not more than 1.0% of air when compared to the peak response of the air-helium certified standard, and not less than 99.0%, by volume, of He.

ERRATA *(Continued)*

Page	Title	Section	Description
1547	*Nitrous Oxide*	*USP Reference standards*	There is no USP Reference Standard for this monograph. Therefore, text in this section that appears in *USP 29–NF 24* and is marked "Postponed indefinitely" should be disregarded.
		Identification	The *Identification* test was postponed indefinitely in the *USP 29–NF 24* official text, leaving the *Identification* test in *USP 28–NF 23* as official text. In addition to the *USP 29–NF 24* text the following official *USP 28–NF 23* text should also be included: **A:** With the container temperatures the same and maintained between 15° and 25°, concomitantly read the pressure of the Nitrous Oxide container and of a container of nitrous oxide certified standard (see under *Reagents* in the section *Reagents, Indicators, and Solutions*). [NOTE—Do not use the nitrous oxide certified standard if it has been depleted to less than half of its full capacity.] The pressure of the Nitrous Oxide container is within 50 psi of that of the nitrous oxide certified standard. **B:** Pass 100 ± 5 mL released from the vapor phase of the contents of the Nitrous Oxide container through a carbon dioxide detector tube at the rate specified for the tube: no color change is observed *(distinction from carbon dioxide)*. **C:** Collect about 100 mL of the gas under test in a 100-mL tube fitted at the top with a stopcock. Open the stopcock, and quickly add a freshly prepared solution of 500 mg of pyrogallol in 2 mL of water and a freshly prepared solution of 12 g of potassium hydroxide in 8 mL of water. Immediately close the stopcock, and mix: the gas is not absorbed, and the solution does not become brown *(distinction from oxygen)*.
		Assay	The *Assay* was postponed indefinitely in the *USP 29–NF 24* official text, leaving the *Assay* in *USP 28–NF 23* as official text. In addition to the *USP 29–NF 24* text the following official *USP 28–NF 23* text should also be included: Introduce a specimen of Nitrous Oxide taken from the liquid phase, as directed in the test for *Nitrogen dioxide,* into a gas chromatograph by means of a gas-sampling valve. Select the operating conditions of the gas chromatograph such that the peak response resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 6 m in length and 4 mm in inside diameter and is packed with porous polymer beads, which permits complete separation of N_2 and O_2 from N_2O, although the N_2 and O_2 may not be separated from each other. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by an air-helium certified standard (see under *Reagents* in the section *Reagents, Indicators, and Solutions*), and is equivalent to not more than 1.0% of air when compared to the peak response of the air-helium certified standard, indicating not less than 99.0%, by volume, of N_2O.
2567	⟨381⟩ *Elastomeric Closures for Injections*	*Physicochemical Test Procedures*	Line 5 under *Procedure:* Change "121 ± 0.5°" to: 121 ± 2°
3273	*Ammonium Sulfate*	*Microbial limits*	Lines 1 through 3: Change "The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 1000 cfu per g." to: The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 10 cfu per g.

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ERRATA *(Continued)*

Page	Title	Section	Description
3380	*Nitrogen*	*USP Reference standards*	There is no USP Reference Standard for this monograph. Therefore, text in this section that appears in *USP 29–NF 24* and is marked ''Postponed indefinitely'' in the *USP 29–NF 24* should be disregarded.
		Identification	The *Identification* test was postponed indefinitely in the *USP 29–NF 24* official text, leaving the *Identification* test in *USP 28–NF 23* as official text. In addition to the *USP 29–NF 24* text the following official *USP 28–NF 23* text should also be included: The flame of a burning wood splinter is extinguished when inserted into a test tube filled with Nitrogen. [NOTE—Exercise caution.]
		Assay	The *Assay* was postponed indefinitely in the *USP 29–NF 24* official text, leaving the *Assay* test in *USP 28–NF 23* as official text. In addition to the *USP 29–NF 24* text the following official *USP 28–NF 23* text should also be included: Introduce a specimen of Nitrogen into a gas chromatograph by means of a gas sampling valve. Select the operating conditions of the gas chromatograph such that the standard peak signal resulting from the following procedure corresponds to not less than 70% of the full-scale reading. Preferably, use an apparatus corresponding to the general type in which the column is 3 m in length and 4 mm in inside diameter and is packed with a molecular sieve prepared from a synthetic alkali-metal aluminosilicate capable of absorbing molecules having diameters of up to 0.5 nm, which permit complete separation of oxygen from nitrogen. Use industrial grade helium (99.99%) as the carrier gas, with a thermal-conductivity detector, and control the column temperature: the peak response produced by the assay specimen exhibits a retention time corresponding to that produced by an oxygen-helium certified standard (see under *Reagents* in the section *Reagents, Indicators, and Solutions*), and is equivalent to not more than 1.0% of oxygen when compared to the peak response of the oxygen-helium certified standard, indicating not less than 99.0%, by volume, of N_2.
3381	*Nitrogen 97 Percent*	*USP Reference standards*	There is no USP Reference Standard for this monograph. Therefore, text in this section that appears in *USP 29–NF 24* and is marked ''Postponed indefinitely'' should be disregarded.
		Identification	The *Identification* test was postponed indefinitely in the *USP 29–NF 24* official text, leaving the *Identification* test in *USP 28–NF 23* as official text. In addition to the *USP 29–NF 24* text the following official *USP 28–NF 23* text should also be included: The flame of a burning wood splinter is extinguished when inserted into a test tube filled with Nitrogen 97 Percent. [NOTE—Exercise caution.]
		Assay	The *Assay* was postponed indefinitely in the *USP 29–NF 24* official text, leaving the *Assay* in *USP 28–NF 23* as official text. In addition to the *USP 29–NF 24* text the following official *USP 28–NF 23* text should also be included: Proceed with Nitrogen 97 Percent as directed in the *Assay* for *Nitrogen*. The peak response produced by the assay specimen exhibits a retention time corresponding to that produced by an oxygen-helium certified standard (see under *Reagents* in the section *Reagents, Indicators, and Solutions*) and is equivalent to not more than 3.0% of oxygen when compared to the peak response of the oxygen-helium certified standard, indicating not less than 97.0%, by volume, of N_2.

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IN-PROCESS REVISION

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

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

BRIEFING

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

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

•new text•

if slated for an *Interim Revision Announcement to USP 29–NF 24* (*IRA*);

▲new text▲*USP30*

if slated for *USP 30–NF 25*; and

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, ■2S (*USP 29*) indicates that the proposed revision is slated for the *Second Supplement to USP 29*, and ▲*USP30* and ▲*NF25* indicate that the revisions are proposed for *USP 30* and *NF 25*, respectively.

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

In-Process Revision

In-Process Revision

MONOGRAPHS (USP)

BRIEFING

Allopurinol, *USP 29* page 75. On the basis of comments received, it is proposed to cancel the revision proposal previously published on page 1386 of *PF* 28(5) [Sept.–Oct. 2002], and to make the following changes:

1. Replace the current thin-layer chromatographic procedure in the test for *Chromatographic purity* with a new single chromatographic procedure for the test for *Related compounds*. The proposed procedure is based on analyses performed with the 5-µm Zorbax Eclipse XDB C18 brand of L1 column. The typical retention time for allopurinol is about 4.6 minutes.
2. Resubmit the previously proposed stability-indicating liquid chromatographic procedure for the *Assay* with minor changes. It is based on analyses performed with the 5-µm Hypersil-ODS brand of L1 column. The typical retention time for allopurinol is about 6.1 minutes.
3. Change the acceptance criteria in the Definition from "not less than 98.0 percent and not more than 101.0 percent" to "not less than 98.0 percent and not more than 102.0 percent," which are typical for chromatographic procedures.
4. Indicate storage at room temperature under the *Packaging and storage* section.

(MD-GRE: E. Gonikberg) RTS—41003-1

Change to read:

» Allopurinol contains not less than 98.0 percent and not more than ~~101.0~~

■102.0■1S (*USP30*)
percent of $C_5H_4N_4O$, calculated on the dried basis.

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at room temperature.■1S (*USP30*)

Change to read:

USP Reference standards ⟨11⟩**—***USP Allopurinol RS. USP Allopurinol Related Compound A RS.*

■*USP Allopurinol Related Compound B RS. USP Allopurinol Related Compound C RS. USP Allopurinol Related Compound D RS. USP Allopurinol Related Compound E RS. USP Allopurinol Related Compound F RS.*■1S (*USP30*)

Delete the following:

■~~**Chromatographic purity**~~

~~*Adsorbent:* 0.1-mm layer of chromatographic cellulose containing a fluorescent indicator.~~

~~*Test solution*—Dissolve 250 mg of Allopurinol in a mixture of 6 N ammonium hydroxide and 1 N sodium hydroxide (9 : 1) to make 10.0 mL, and mix.~~

~~*Standard solution*—Dissolve a suitable quantity of USP Allopurinol Related Compound A RS in 6 N ammonium hydroxide to obtain a solution having a known concentration of 50 µg per mL.~~

~~*Application volume:* 10 µL.~~

~~*Developing solvent system*—Shake 200 mL of butyl alcohol and 200 mL of 6 N ammonium hydroxide, discard the lower layer, and add 20 mL of butyl alcohol to the top layer.~~

~~*Procedure*—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Develop the chromatogram until the solvent front is 1 cm from the top of the plate, air-dry, and examine under UV light. Any spot in the chromatogram obtained from the *Test solution*, except for the principal spot, is not more intense than the spot in the chromatogram obtained from the *Standard solution*: not more than 0.2% of any individual impurity is found.~~■1S (*USP30*)

Add the following:

■**Related compounds—**[NOTE—Store and inject the *Standard solution* and the *Test solution* at 8°, using a cooled autosampler.]

Solution A—Dissolve 1.25 g of monobasic potassium phosphate in 1000 mL of water, filter, and degas.

Solution B—Use methanol.

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

Diluent—Prepare a mixture of *Solution A* and *Solution B* (90 : 10).

Standard stock solution—Accurately weigh about 5 mg of each of USP Allopurinol RS, USP Allopurinol Related Compound A RS, USP Allopurinol Related Compound B RS, USP Allopurinol Related Compound C RS, USP Allopurinol Related Compound D RS, USP Allopurinol Related Compound E RS, and USP Allopurinol Related Compound F RS, and transfer to a 100-mL volumetric flask. Add 2.0 mL of 0.1 N sodium hydroxide to dissolve, promptly sonicate with swirling for not more than 1 minute, add 80 mL of *Diluent,* and sonicate for an additional 5 minutes. Dilute with *Diluent* to volume. [NOTE—This solution is stable for 48 hours when stored at 8°.]

Standard solution—Quantitatively dilute an accurately measured volume of the *Standard stock solution* with *Diluent* to obtain a solution having known concentrations of about 0.5 µg of allopurinol and about 0.5 µg of each of allopurinol related compounds A, B C, D, E, and F per mL.

Test solution—Transfer about 25 mg of Allopurinol, accurately weighed, to a 100-mL volumetric flask, add 5.0 mL of 0.1 N sodium hydroxide to dissolve, promptly sonicate with swirling for not more than 1 minute, add 80 mL of *Diluent,* and sonicate for an additional 5 minutes. Dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 30°. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–30	90→70	10→30	linear gradient
30–35	70	30	isocratic
35–36	70→90	30→10	linear gradient
36–46	90	10	re-equilibration

Chromatograph the *Standard solution,* identify the peaks (see *Table 1*), and record the peak responses as directed for *Procedure:* the resolution, *R,* between allopurinol related compounds C and B is not less than 0.8; and the tailing factor for the allopurinol peak is not more than 1.5.

Procedure—Separately inject equal volumes (about 40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify the allopurinol peak and the peaks due to impurities listed in *Table 1.*

Table 1

Name	Relative Retention Time	Limit (%)
Allopurinol related compound A[1]	0.62	0.2
Allopurinol related compound C[3]	0.79	0.2
Allopurinol related compound B[2]	0.81	0.2
Allopurinol	1.0	—
Allopurinol related compound D[4]	4.4	0.2
Allopurinol related compound E[5]	4.8	0.2
Allopurinol related compound F[6]	6.5	0.2

[1] 3-Amino-1*H*-pyrazole-4-carboxamide
[2] 5-(Formylamino)-1*H*-pyrazole-4-carboxamide
[3] 5-(4*H*-1,2,4-Triazol-4-yl)-1*H*-pyrazole-4-carboxamide
[4] Ethyl-5-amino-1*H*-pyrazole-4-carboxylate
[5] Ethyl-5-(formylamino)-1*H*-pyrazole-4-carboxylate
[6] Ethyl-(E/Z)-3-(2-carbethoxy-2-cyanoethenyl)amino-1*H*-pyrazole-4-carboxylate

Calculate the percentage of each impurity in the portion of Allopurinol taken by the formula:

$$10(C/W)(r_i/r_S)$$

in which C is the concentration, in µg per mL, of each individual impurity in the *Standard solution; W* is the weight, in mg, of Allopurinol taken to prepare the *Test solution;* and r_i and r_S are the peak responses for each individual impurity obtained from the *Test solution* and the *Standard solution*, respectively. [NOTE—For unspecified impurities, r_S is the peak response for the allopurinol peak obtained from the *Standard solution.*] In addition to not exceeding the limits for each impurity in *Table 1*, not more than 0.1% of any individual unspecified impurity is found; and not more than 1.0% of total impurities is found.■1S *(USP30)*

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Change to read:

Assay—~~Dissolve about 100 mg of Allopurinol, accurately weighed, in 30 mL of dimethylformamide, warming if necessary. Titrate with 0.1 N tetrabutylammonium hydroxide VS, determining the endpoint potentiometrically, using a calomel-glass electrode system and taking the necessary precautions to prevent the absorption of atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N tetrabutylammonium hydroxide is equivalent to 13.61 mg of $C_5H_4N_4O$.~~

■[NOTE—Store and inject the *System suitability solution,* the *Standard preparation,* and the *Assay preparation* at 8°, using a cooled autosampler.]

Mobile phase—Dissolve 1.25 g of monobasic potassium phosphate in 1000 mL of water, filter, and degas.

System suitability solution—Transfer accurately weighed quantities of USP Allopurinol RS, USP Allopurinol Related Compound B RS, and USP Allopurinol Related Compound C RS, each to a suitable volumetric flask, dissolve in a small volume of 0.1 N sodium hydroxide, and immediately and quantitatively dilute with *Mobile phase* to obtain solutions having known concentrations of about 0.05 mg per mL. Transfer 1.0 mL of each of these three solutions to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Allopurinol RS in a small volume of 0.1 N sodium hydroxide, and immediately and quantitatively dilute with *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL. Quantitatively dilute an accurately measured volume of this solution with *Mobile phase* to obtain a solution having a known concentration of about 0.08 mg of allopurinol per mL.

Assay preparation—Transfer about 50 mg of Allopurinol, accurately weighed, to a 100-mL volumetric flask, dissolve in 5.0 mL of 0.1 N sodium hydroxide, immediately dilute with *Mobile phase* to volume, and mix. Quantitatively dilute an accurately measured volume of this solution with *Mobile phase* to obtain a solution having a known concentration of about 0.08 mg of allopurinol per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.8 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between allopurinol related compound B and allopurinol related compound C is not less than 1.1, and that between allopurinol related compound C and allopurinol is not less than 6.0. [NOTE—For the purpose of identification, the relative retention times are about 0.7 for allopurinol related compound B, 0.8 for allopurinol related compound C, and 1.0 for allopurinol.] Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_5H_4N_4O$ in the portion of Allopurinol taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_U and C_S are the concentrations, in mg per mL, of allopurinol in the *Assay preparation* and the *Standard preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■IS (*USP30*)

In-Process Revision

BRIEFING

Amoxicillin Tablets, *USP 29* page 160. It is proposed to include separate requirements for each strength of chewable tablets in the *Dissolution* test. In the absence of any significant adverse comments, it is proposed to implement this revision via the *Fourth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of August 1, 2006.

(BPC: M. Marques) RTS—43832-1; 43833-1

Change to read:

Dissolution ⟨711⟩—

Medium: water; 900 mL.
Apparatus 2: 75 rpm.
Time: 30 minutes.

Determine the amount of $C_{16}H_{19}N_3O_5S$ dissolved by employing the following method.

pH 5.0 Buffer—Dissolve 27.2 g of monobasic potassium phosphate in 3 L of water, adjust with a 45% (w/w) solution of potassium hydroxide to a pH of 5.0 ± 0.1, dilute with water to obtain 4 L of solution, and mix.

Mobile phase—Prepare a mixture of *pH 5.0 Buffer* and acetonitrile (3900 : 100), and pass through a filter having a 0.5-µm or finer porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Amoxicillin RS in *pH 5.0 Buffer* to obtain a solution having a known concentration of about 0.05 mg per mL. Use this solution within 6 hours.

Test solution—Pass a portion of the solution under test through a filter having a 0.5-µm or finer porosity. Quantitatively dilute an accurately measured volume of the filtrate with water to obtain a solution having an estimated concentration of about 0.045 mg of amoxicillin per mL. Use this solution within 6 hours.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector, a 3.9-mm × 30-cm analytical column that contains packing L1, and a 2-mm × 2-cm guard column that contains packing L2. The analytical column is maintained at a constant temperature of about 40 ± 1°. The flow rate is about 0.7 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′,* is between 1.1 and 2.8; the column efficiency is not less than 1700 theoretical plates; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of amoxicillin ($C_{16}H_{19}N_3O_5S$) dissolved by the formula:

$$0.9DCP(r_U/r_S)$$

in which *D* is the dilution factor used in preparing the *Test solution; C* is the concentration, in mg per mL, of USP Amoxicillin RS in the *Standard solution; P* is the stated content, in µg of amoxicillin ($C_{16}H_{19}N_3O_5S$) per mg, of USP Amoxicillin RS; and r_U and r_S are the amoxicillin peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 30 minutes.

FOR PRODUCTS LABELED AS CHEWABLE TABLETS—Proceed as directed above.

•FOR CHEWABLE TABLETS LABELED TO CONTAIN 200 MG OR 400 MG:•4

Time: 20 minutes.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 20 minutes.

•FOR CHEWABLE TABLETS LABELED TO CONTAIN 125 MG OR 250 MG:

Time: 90 minutes.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 90 minutes.•4

FOR VETERINARY PRODUCTS—Proceed as directed above, except to use *Apparatus 2* at 100 rpm.

BRIEFING

Atracurium Besylate, *USP 29* page 216. It is proposed to include an identified impurity, laudanosine, along with appropriate acceptance criteria to the test for *Chromatographic purity.* Laudanosine elutes at an approximate relative retention time of about 0.3 and is quantified using a response factor of 1.9 relative to atracurium besylate. Additionally, in the test for *Chromatographic purity* and in the *Assay,* the relative retention time information, which is currently listed along with system suitability criteria, has been moved to a *Note,* which clearly indicates that it is intended for identification purposes only.

(MD-PP: R. Ravichandran) RTS—43921-1

Change to read:

Chromatographic purity—

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

Standard solution—Transfer 1.0 mL of the *Standard preparation,* prepared as directed in the *Assay,* to a 100-mL volumetric flask, dilute with *Solution A* to volume, and mix.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the responses of the *cis-cis* isomers from not fewer than two injections do not differ by more than 10%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses, except the three main isomeric peaks. Calculate the percentage of each impurity in the portion of Atracurium Besylate taken by the formula:

~~$10{,}000C/W)(r_i/r_s)$~~

$$\blacksquare 10{,}000(1/F)(C/W)(r_i/r_S)_{\blacksquare 1S\ (USP30)}$$

in which

■*F* is the relative response factor of the impurity peak, which is 1.9 for laudanosine and 1.0 for all other unidentified impurities;■1S *(USP30)*

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C is the concentration, in mg per mL, of the *cis-cis* isomer in the *Standard solution; W* is the weight, in mg, of Atracurium Besylate taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for the *cis-cis* isomer obtained from the *Standard solution:* ~~not more than 1.5% of any individual impurity is found,~~

■not more than 0.5% of laudanosine is found, not more than 1.0% of any other individual impurity is found,■1S (*USP30*) and not more than 3.5% of total impurities is found.

■[NOTE—For identification purposes, the relative retention time for laudanosine is about 0.3.]■1S (*USP30*)

Change to read:

Assay—

Buffer solution—Transfer about 10.2 g of monobasic potassium phosphate to a 1000-mL volumetric flask, and dissolve in about 950 mL of water. While stirring, adjust with phosphoric acid to a pH of 3.1, dilute with water to volume, and mix.

Solution A—Prepare a mixture of *Buffer solution,* acetonitrile, and methanol (75 : 20 : 5).

Solution B—Prepare a mixture of *Buffer solution,* methanol, and acetonitrile (50 : 30 : 20).

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

Standard preparation—Dissolve an accurately weighed quantity of USP Atracurium Besylate RS in *Solution A* to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Transfer about 100 mg of Atracurium Besylate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 25-cm column that contains base-deactivated packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	80	20	equilibration
0–5	80	20	isocratic
5–15	80→40	20→60	linear gradient
15–25	40	60	isocratic
25–30	40→0	60→100	linear gradient

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.8, 0.9, and 1.0 for the *trans-trans* isomer, the *cis-trans* isomer, and the *cis-cis* isomer, respectively;~~

■■1S (*USP30*) the resolution, *R,* between the *trans-trans* isomer and the *cis-trans* isomer and between the *cis-trans* isomer and the *cis-cis* isomer is not less than 1.1; and the relative standard deviation for replicate injections is not more than 2.0%.

■[NOTE—For identification purposes, the relative retention times are about 0.8, 0.9, and 1.0 for the *trans-trans* isomer, the *cis-trans* isomer, and the *cis-cis* isomer, respectively.]■1S (*USP30*)

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the three isomeric peaks. Calculate the quantity, in mg, of $C_{65}H_{82}N_2O_{18}S_2$ in the portion of Atracurium Besylate taken by the formula:

$$100C(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of USP Atracurium Besylate RS in the *Standard preparation;* and r_U and r_S are the sums of the peak responses for the *trans-trans* isomer, the *trans-cis* isomer, and the *cis-cis* isomer obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Azithromycin, *USP 29* page 227. It is proposed to revise the test for *Limit of related substances* to include an alternative procedure *(Test 2)* to accommodate a different synthesis route for the azithromycin drug substance. The reverse-phase HPLC procedure was validated using a Kromasil KR 100 brand of L1 column; azithromycin elutes at approximately 14 minutes on this system. It is proposed to add USP Azithromycin Identity RS and USP Azithromycin-*N*-oxide RS to support the proposed procedure in *Test 2* and to add a *Labeling* statement to reflect the proposed addition of another test.

(MD-ANT: B. Gilbert) RTS—42419-1; 42816-1; 42817-1

Change to read:

Labeling—Label it to indicate whether it is the monohydrate or the dihydrate. Where the quantity of azithromycin is indicated in the labeling of any preparation containing Azithromycin, this shall be understood to be in terms of anhydrous azithromycin ($C_{38}H_{72}N_2O_{12}$).

■The labeling states with which *Limit of related substances* test the article complies if a test other than *Test 1* is used.■1S (*USP30*)

Change to read:

USP Reference standards ⟨11⟩**—***USP Azithromycin RS. USP Azaerythromycin A RS.*

■*USP Azithromycin Identity RS. USP Azithromycin-N-oxide RS.* ■1S (*USP30*)
USP N-Demethylazithromycin RS. USP Desosaminylazithromycin RS.

Change to read:

Limit of related substances—

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

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TEST 1—■1S *(USP30)*
[NOTE—Use water that has a resistivity of not less than 18 Mohm-cm.]

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

pH 7.5 Potassium phosphate buffer—Transfer 2.7 g of monobasic potassium phosphate to a 1000-mL volumetric flask. Dilute with water to volume, and mix. Adjust with 10 N potassium hydroxide to a pH of 7.5 ± 0.1.

Dilution solution—Prepare a mixture of *pH 7.5 Potassium phosphate buffer* and acetonitrile (750 : 250).

Standard stock solution—Quantitatively dissolve accurately weighed quantities of USP Desosaminylazithromycin RS, USP *N*-Demethylazithromycin RS, and USP Azithromycin RS with acetonitrile to obtain a solution having known concentrations of about 45 µg per mL, 105 µg per mL, and 160 µg per mL, respectively.

Standard solution—Transfer 4.0 mL of the *Standard stock solution* to a 200-mL volumetric flask, dilute with *Dilution solution* to volume, and mix. This solution contains known concentrations of USP Desosaminylazithromycin RS, USP *N*-Demethylazithromycin RS, and USP Azithromycin RS of about 0.9 µg per mL, 2.1 µg per mL, and 3.2 µg per mL, respectively.

Test solution—Transfer about 33 mg of Azithromycin, accurately weighed, to a 100-mL volumetric flask, add 5 mL of acetonitrile, and sonicate for about 20 seconds to dissolve. Dilute with *Dilution solution* to volume, and mix. [NOTE—Use this solution within 6 hours.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with an amperometric electrochemical detector with dual glassy carbon electrodes operated in the oxidative screen mode with electrode 1 set at +0.70 ± 0.05 V and electrode 2 set at +0.85 ± 0.05 V , and the background current optimized to 95 ± 25 nanoamperes, a 4.6-mm × 5-cm guard column that contains 5-µm packing L29, and a 4.6-mm × 15-cm analytical column that contains 5-µm packing L29 or 3-µm packing L49 without the guard column. [NOTE—In general, maintain electrode 1 at 0.12 V less than electrode 2, and maintain the electrodes at a constant temperature of about 26°.] The flow rate is about 0.4 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1500 theoretical plates for the azithromycin peak; the tailing factor for each of these compounds is not more than 1.5; and the relative standard deviation for replicate injections is not more than 5% for each of these compounds. [NOTE—For the purpose of identification, the relative retention times are about 0.38 for desosaminylazithromycin, 0.54 for *N*-demethylazithromycin, and 1.0 for azithromycin]

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, using an elution period for the *Test solution* that is 3.3 times the elution time of the azithromycin peak in the chromatogram of the *Standard solution,* and measure the areas for all of the peaks. Calculate the percentages of desosaminylazithromycin and *N*-demethylazithromycin in the Azithromycin taken by the formula:

$$0.1(CP/W)(r_i/r_S)$$

in which C is the concentration, in µg per mL, of the appropriate USP Reference Standard in the *Standard solution; P* is the designated potency, in percentage, of the relevant USP Reference Standard; W is the weight, in mg, of Azithromycin taken to prepare the *Test solution;* and r_i and r_S are the peak area responses for the relevant analyte in the chromatograms obtained from the *Test solution* and the *Standard solution*, respectively. Calculate the percentages of other related substances in the Azithromycin taken by the formula:

$$0.01(CP/W)(r_i/r_S)$$

in which C is the concentration, in µg per mL, of USP Azithromycin RS in the *Standard solution; P* is the designated purity, in µg per mg, of USP Azithromycin RS; W is the weight, in mg, of Azithromycin taken to prepare the *Test solution;* r_i is the peak area response for an individual related substance peak in the chromatogram obtained from the *Test solution;* and r_S is the peak area response for the azithromycin peak in the chromatogram obtained from the *Standard solution*. Not more than 0.3% of desosaminylazithromycin, 0.7% of *N*-demethylazithromycin, and 1.0% of any other individual related substance is found; and the sum of all related substances is not more than 3.0%.

■TEST 2—

Phosphate buffer solution—Dissolve about 8.7 g of dibasic potassium phosphate in 1 L of water, adjust with 20% phosphoric acid to a pH of 8.2, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Phosphate buffer solution* (6 : 4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution 1—Dissolve an accurately weighed quantity of USP Azithromycin RS in *Mobile phase,* and quantitatively dilute to obtain a solution having a known concentration of about 35 µg per mL.

Standard solution 2—Prepare a solution in *Mobile phase* containing about 7 mg of USP Azithromycin Identity RS per mL.

Standard solution 3—Prepare a solution in *Mobile phase* containing about 14 µg of USP Azithromycin-*N*-oxide RS per mL.

Test solution—Transfer about 70.0 mg of Azithromycin, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

System suitability solution—Prepare a solution in *Mobile phase* containing about 0.07 mg of USP Azaerythromycin A RS and 7 mg of USP Azithromycin RS per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 0.9 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between azaerythromycin A and azithromycin is not less than 8.0;

and the tailing factor for the azithromycin peak is not more than 2.5. [NOTE—For the purpose of identification, the relative retention times are about 0.47 for azaerythromycin A and 1.00 for azithromycin.]

Procedure—Separately inject equal volumes (about 50 µL) of *Standard solution 1, Standard solution 2, Standard solution 3, Test solution,* and *Mobile phase* into the chromatograph, record the chromatograms, identify the peaks in the chromatogram of the *Test solution* by comparison with the chromatograms obtained from *Standard solution 2* and *Standard solution 3,* and measure the peak area responses. Disregard any peak due to the solvent front and any peak corresponding to those obtained from the *Mobile phase*. Calculate the percentage of each impurity in the portion of Azithromycin taken by the formula:

$$(CP/W)(1/F)(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Azithromycin RS in *Standard solution 1; P* is the designated purity, in µg per mg, of USP Azithromycin RS; W is the weight, in mg, of Azithromycin taken to prepare the *Test solution; F* is the relative response factor (see *Table 1*); r_i is the peak area response for each impurity obtained from the *Test solution;* and r_S is the peak area response for azithromycin obtained from *Standard solution 1*. The impurities meet the limits specified in *Table 1*.

Table 1

Compound	Relative Retention Time	Relative Response Factor	Limit (w/w, %)
Azithromycin-*N*-oxide	0.20	0.45	0.40
3′-(*N,N*-didemethyl)-3′-*N*-formyl-azithromycin	0.26	1.8	0.30
3′-*N*-demethyl-3′-*N*-formylazithromycin (rotamer 1)	0.34	4.1	0.15
3′-*N*-demethyl-3′-*N*-formylazithromycin (rotamer 2)	0.37	4.1	0.15
6-Demethylazithromycin (azaerythromycin A)	0.47	0.67	0.50
3′-De(dimethylamino)-3′-oxoazithromycin	0.80	1.9	0.25
2-Desethyl-2-propylazithromycin	1.52	1.0	0.50
3-Deoxyazithromycin (azithromycin B)	1.60	1.0	0.50
3′-*N*-demethyl-3′-*N*-[(4-methylphenyl)sulfonyl]azithromycin	2.14	7.0	0.50
Individual unknown impurity	—	1.0	0.20
Total impurities	—	—	2.0

■1S (*USP30*)

In-Process Revision

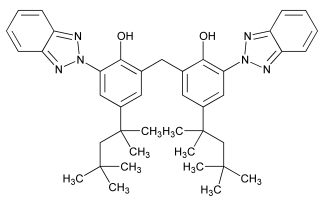
BRIEFING

Bisoctrizole. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on validated methods, is being proposed. The liquid chromatographic procedures in the tests for *Related compounds* and *Limit of bisoctrizole related compound A and the bisoctrizole isomer* and the *Assay* are based on analyses performed with a Nucleosil brand of L1 column. The typical retention time for bisoctrizole is about 24 minutes.

(MD-OOD: C. Anthony; NOM: L. Paul) RTS—41734-1

Add the following:

■Bisoctrizole



$C_{41}H_{50}N_6O_2$ 658.90

Phenol, 2,2′-methylenebis[6-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)]-.

2,2′-Methylenebis[6-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol] [*103597-45-1*].

» Bisoctrizole contains not less than 96.0 percent and not more than 102.0 percent of $C_{41}H_{50}N_6O_2$, calculated on the as-is basis.

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

USP Reference standards ⟨11⟩**—***USP Bisoctrizole RS. USP Bisoctrizole Related Compound A RS. USP Bisoctrizole Resolution Mixture RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

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

Limit of bisoctrizole related compound A and the bisoctrizole isomer—

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

Standard stock solution A—Dissolve an accurately weighed quantity of USP Bisoctrizole RS in tetrahydrofuran to obtain a solution having a known concentration of about 0.65 mg per mL.

Standard stock solution B—Dissolve an accurately weighed quantity of USP Bisoctrizole Related Compound A RS in tetrahydrofuran to obtain a solution having a known concentration of about 0.40 mg per mL.

Standard solution—Quantitatively transfer 5 mL of *Standard stock solution A* and 1.0 mL of *Standard stock solution B* to a 100-mL volumetric flask. Add 60 mL of tetrahydrofuran, and dilute with *Diluent* to volume.

Test solution—Proceed as directed for *Assay preparation.*

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure*: the resolution, *R,* between bisoctrizole and the bisoctrizole isomer is not less than 1.5. [NOTE—For identification purposes, the relative retention times are about 0.42 for bisoctrizole related compound A and about 1.1 for the bisoctrizole isomer.]

Procedure—Inject a volume (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of bisoctrizole related compound A taken by the formula:

$$10{,}000(C/W)(r_U/r_S)$$

In-Process Revision

in which C is the concentration, in mg per mL, of USP Bisoctrizole Related Compound A RS; W is the weight, in mg, of Bisoctrizole taken; r_U is the peak response for bisoctrizole related compound A in the *Test solution;* and r_S is the peak response for bisoctrizole related compound A in the *Standard solution:* not more than 0.5% of bisoctrizole related compound A is found. Calculate the percentage of the bisoctrizole isomer taken by the formula:

$$10{,}000(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Bisoctrizole RS; W is the weight, in mg, of Bisoctrizole taken; r_U is the peak response for the bisoctrizole isomer in the *Test solution;* and r_S is the peak response for bisoctrizole in the *Standard solution:* not more than 4.0% of the bisoctrizole isomer is found.

Related compounds—

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

Test solution—Proceed as directed for the *Assay preparation.*

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Bisoctrizole taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak response for each individual impurity, and r_s is the sum of the responses of all the peaks: not more than 0.1% of any individual impurity, excluding bisoctrizole related compound A and the bisoctrizole isomer, is found. Not more than 4.0% of total impurities, including bisoctrizole related compound A, and the bisoctrizole isomer, determined in the test for *Limit of bisoctrizole related compound A and the bisoctrizole isomer,* is found.

Limit of residual solvents—

Standard addition solution—Transfer 21 mg of methanol, 42 mg of 2-propanol, and 104 mg of xylene to a 100-mL volumetric flask, dilute with 1,2,4-trichlorobenzene to volume, and mix. Pipet 4.0 mL of this solution into a 25-mL volumetric flask, dilute with 1,2,4-trichlorobenzene to volume, and mix.

Standard solution 1—Transfer 3 mL of *Standard addition solution* to a 20-mL headspace vial.

Standard solution 2—In a 20-mL headspace vial, dissolve 1000 mg of bisoctrizole, accurately weighed, in 3 mL of *Standard addition solution.* [NOTE—The 3 mL of *Standard addition* solution contains about 100 µg of methanol, 200 µg of 2-propanol, and 500 µg of xylene.]

Test solution—In a 20-mL headspace vial, dissolve 1000 mg of Bisoctrizole, accurately weighed, in 3 mL of 1,2,4-trichlorobenzene.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector and a flame-ionization detector, and contains a 0.32-mm × 30-m column coated with a 5-µm film of liquid phase G27. The carrier gas is helium, flowing at a rate of 1.5 mL per minute. The split ratio is (2 : 1). Vials containing *Standard solution 1, Standard solution 2,* and the *Test solution* are equilibrated for 60 minutes at 95° in the headspace sampler. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 40° for 5 minutes, then the temperature is increased at a rate of 12° per minute to 250° and held at 250° for 5 minutes. The injection port temperature and the detector temperature are maintained at 250°. Chromatograph *Standard solution 1,* and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 10.0% for each of the three solvents.

Procedure—Separately inject equal volumes (about 1 mL) of the gaseous headspace of *Standard solution 2* and the *Test solution* into the chromatograph, record the chromatograms,

and measure the responses for the major peaks. Calculate the content of methanol, 2-propanol, and xylene, in ppm, in the portion of Bisoctrizole taken by the formula:

$$C[r_U/(r_S - r_U)]$$

in which C is the concentration, in µg, of solvent per mL of *Standard solution 1;* r_U is the peak response of the individual solvent in the *Test solution;* and r_S is the peak response of the individual solvent in *Standard solution 2:* not more than 1000 ppm of 2-propanol, 3000 ppm of methanol, and 1000 ppm of xylene is found. [NOTE—For identification purposes, the relative retention times are about 0.44 for 2-propanol and about 0.25 for methanol. The peak area of xylene is the sum of the peak areas for the individual *o*-, *m*-, and *p*-xylene isomers and ethylbenzene. For identification purposes, the relative retention times for the *o-, m-,* and *p*-xylene isomers and ethylbenzene are about 1.03, 1.0, 1.0, and 0.99, respectively.]

Assay—

Diluent—Prepare a mixture containing tetrahydrofuran and a 0.2% (w/v) aqueous solution of 1-pentane sulfonic acid sodium salt (60 : 40).

Solution A—Prepare a filtered and degassed solution containing 0.4 g of 1-pentane sulfonic acid sodium salt, 800 mL of methanol, 200 mL of water, and 0.5 mL of phosphoric acid.

Solution B—Prepare a filtered and degassed solution containing 0.4 g of 1-pentane sulfonic acid sodium salt, 1000 mL of methanol, and 0.5 mL of phosphoric acid.

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

System suitability solution—Dissolve an accurately weighed quantity of USP Bisoctrizole Resolution Mixture RS in tetrahydrofuran, and dilute quantitatively with *Diluent* to obtain a solution having a known concentration of about 0.8 mg per mL of bisoctrizole.

Standard preparation—Transfer about 80 mg of USP Bisoctrizole RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in 60 mL of tetrahydrofuran, dilute with *Diluent* to volume, and mix.

Assay preparation—Transfer about 80 mg of Bisoctrizole, accurately weighed, to a 100-mL volumetric flask. Dissolve in 60 mL of tetrahydrofuran, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 346-nm detector and a 3.0-mm × 25-cm column that contains packing L1. The flow rate is about 0.8 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–1	70	30	isocratic
1–11	70→3	30→97	linear gradient
11–27	3	97	isocratic
27–28	3→70	97→30	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for bisoctrizole and 1.1 for the bisoctrizole isomer; the resolution, *R,* between bisoctrizole and the bisoctrizole isomer is not less than 1.5; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure

the responses for the major peaks. Calculate the quantity, in mg, of $C_{41}H_{50}N_6O_2$ in the portion of Bisoctrizole taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Bisoctrizole RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Bupropion Hydrochloride Extended-Release Tablets, *USP 29* page 322. It is proposed to include the instructions on how to prepare the *Medium* in *Test 2* under *Drug release* and *Dissolution*. Also, in both sections, it is proposed to add a new test for the product with a dosing every 24 hours and to categorize the tests according to the dosing interval, 12 hours or 24 hours.

(BPC: M. Marques) RTS—43493-1

Change to read:

Drug release ⟨724⟩—

■FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—■1S (*USP30*)

TEST 1—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, and 8 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
1	between 25% and 45%
4	between 60% and 85%
8	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Medium: 0.1 N hydrochloric acid, pH 1.5

■(prepared by transferring about 50 mL of concentrated hydrochloric acid to 6000 mL of water, adding about 18 g of sodium hydroxide, mixing, and adjusting with either diluted sodium hydroxide or hydrochloric acid to a pH of 1.5 ± 0.05.);■1S (*USP30*)

900 mL,

■deaerated.■1S (*USP30*)

Apparatus 1: 50 rpm.

Times: 1, 2, 4, and 6 hours.

Determine the percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing the following method.

Buffer solution—Dissolve 3.45 g of monobasic sodium phosphate monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 2.80 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration similar to the one expected in the *Test solution.*

Test solution—Use portions of the solution under test, and pass through a 0.45-µm nylon filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 298-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
1	between 25% and 50%
2	between 40% and 65%
4	between 65% and 90%
6	not less than 80%

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

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* except to use the wavelength at about 250 nm.

Times: 1, 2, 4, and 6 hours.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
1	between 30% and 55%
2	between 50% and 75%
4	between 70% and 90%
6	not less than 80%

In-Process Revision

■FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

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

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 1: 75 rpm.

Time: 2, 4, 8, and 16 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 252 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
2	not more than 20%
4	between 20% and 45%
8	between 65% and 85%
16	not less than 80%

■1S (*USP30*)

Change to read:

Dissolution ⟨711⟩—

■FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—■1S (*USP30*)

TEST 1—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, and 8 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	between 25% and 45%
4	between 60% and 85%
8	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 0.1 N hydrochloric acid, pH 1.5

■(prepared by transferring about 50 mL of concentrated hydrochloric acid to 6000 mL of water, adding about 18 g of sodium hydroxide, mixing, and adjusting with either diluted sodium hydroxide or hydrochloric acid to a pH of 1.5 ± 0.05.);■1S (*USP30*)
900 mL,

■deaerated.■1S (*USP30*)

Apparatus 1: 50 rpm.

Times: 1, 2, 4, and 6 hours.

Determine the percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing the following method.

Buffer solution—Dissolve 3.45 g of sodium phosphate monobasic monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 2.80 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration similar to the one expected in the *Test solution.*

Test solution—Use portions of the solution under test, and pass through a 0.45-µm nylon filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 298-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 25% and 50%
2	between 40% and 65%
4	between 65% and 90%
6	not less than 80%

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

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* except using the wavelength at about 250 nm.

Times: 1, 2, 4, and 6 hours.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 30% and 55%
2	between 50% and 75%
4	between 70% and 90%
6	not less than 80%

■FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

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

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 1: 75 rpm.

Time: 2, 4, 8, and 16 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 252 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	not more than 20%
4	between 20% and 45%
8	between 65% and 85%
16	not less than 80%

■1S (*USP30*)

(Official April 1, 2006)

In-Process Revision

BRIEFING

Cefaclor Tablets, page 1858 of *PF* 29(6) [Nov.–Dec. 2003]. It is proposed to add a *Dissolution* test to this monograph.

(BPC: M. Marques) RTS—44015-1

Add the following:

■Cefaclor Tablets

» Cefaclor Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$).

Packaging and storage—Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Label chewable Tablets to include the word "chewable" in juxtaposition to the official name. The labeling indicates that chewable Tablets are to be chewed before being swallowed.

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

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of cefaclor dissolved by employing UV absorption at the wavelength of maximum absorbance at about 264 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Cefaclor RS in the same *Medium*. Calculate the amount of cefaclor dissolved by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times D \times LC}$$

in which A_U and A_S are the absorbances obtained from the solution under test and the Standard solution, respectively; C_S is the concentration, in mg per mL, of the Standard solution; 900 is the volume, in mL, of *Medium*; 100 is the conversion factor to percentage; D is the dilution factor of the solution under test; and LC is the tablet label claim in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of cefaclor is dissolved in 30 minutes.

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

Water, *Method I* ⟨921⟩**:** not more than 5.0%.

Related compounds—

Solvent, Blank solution, Solution A, Solution B, Mobile phase, Standard solution, System suitability solution, and *Chromatographic system*—Proceed as directed for *Related compounds* under *Cefaclor.*

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the composite, equivalent to about 50 mg of cefaclor, to a 10-mL volumetric flask. Dissolve in *Solvent,* using brief sonication, if necessary, to dissolve. Avoid heating. Dilute with *Solvent* to volume, mix, and filter. [NOTE—Use this *Test solution* within 3 hours if stored at room temperature, or within 20 hours when stored under refrigeration.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak area responses for all the peaks. Calculate the quantity, in mg, of each related compound in the portion of Tablets taken by the formula:

$$0.01CP(r_i/r_S)$$

in which the terms are as defined for *Related compounds* under *Cefaclor*. Not more than 1.0% of any individual cefaclor related compound is found; and the sum of all cefaclor related compounds found is not more than 3.0%, not including the contribution of any peak that gives a result of less than 0.1%.

Assay—

Mobile phase, Standard preparation, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Cefaclor.*

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg of cefaclor, to a 250-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Sonicate, if necessary, to dissolve the cefaclor. Filter to obtain a clear solution.

Procedure—Proceed as directed in the *Assay* under *Cefaclor*. Calculate the quantity, in mg, of cefaclor ($C_{15}H_{14}ClN_3O_4S$) in the portion of Tablets taken by the formula:

$$5W_S(P/1000)(r_U/r_S)$$

in which the terms are as defined therein.■1S (*USP30*)

BRIEFING

Cefadroxil for Oral Suspension, *USP 29* page 404 and page 1045 of *PF* 31(4) [July–Aug. 2005]. It is proposed to add a test for *Dissolution* to this monograph.

(BPC: M. Marques) RTS—42555-1

Add the following:

■**Dissolution** ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 25 rpm.

Time: 30 minutes.

Procedure—Accurately weigh 5.0 mL of the constituted Oral Suspension, and transfer to the dissolution vessel. Determine the amount of cefadroxil dissolved by employing UV absorption at the wavelength of maximum absorbance at about 263 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison

with a Standard solution having a known concentration of USP Cefadroxil RS in the same *Medium*. Calculate the amount of cefadroxil dissolved by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times W \times D \times LC}$$

in which A_U and A_S are the absorbances obtained from the solution under test and the Standard solution, respectively; C_S is the concentration, in mg per mL, of the Standard solution; 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; W is the weight, in mg, of the 5 mL of constituted Oral Suspension taken; D is the dilution factor of the solution under test; and LC is the label claim, in mg per 5 mL.

Tolerances—Not less than 75% (Q) of the labeled amount of cefadroxil is dissolved in 30 minutes.■1S (*USP30*)

Change to read:

Water, *Method I* ⟨921⟩**:** not more than 2.0%,

■except where it is labeled as containing 100 mg of cefadroxil per mL after constitution, the limit is not more than 3.0%.■2S (*USP29*)

BRIEFING

Cefepime Hydrochloride, *USP 29* page 409. On the basis of comments from industry indicating difficulties in meeting the system suitability requirements for the tests for *Limit of N-methylpyrrolidine* and *Related compounds,* it is proposed to make revisions that will improve the performance of these tests.

(MD-ANT: B. Gilbert) RTS—43166-1; 43168-1; 43169-1

Change to read:

Limit of *N*-methylpyrrolidine—

Mobile phase—Prepare a filtered and degassed mixture of 0.01 N nitric acid and acetonitrile (100 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

■*Column rinse solution*—Transfer 1.9 mL of nitric acid to a 1-L volumetric flask, add 10 mL of acetonitrile, and mix. Dilute with water to volume, and mix.■1S (*USP30*)

Standard solution—Transfer about 0.16 mL of *N*-methylpyrrolidine, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 4.0 mL of this solution to a 100-mL volumetric flask, dilute with 0.01 N nitric acid to volume, and mix. This solution contains about 0.05 mg of *N*-methylpyrrolidine per mL.

Test solution—Transfer about 100 mg of Cefepime Hydrochloride, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with 0.01 N nitric acid to volume, and mix. [NOTE—Use this solution within 30 minutes.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector and a 4.6-mm × 5-cm column that contains 5-µm packing L52

■and a 4.4-mm × 5-cm guard column, placed between the pump and the injector, that contains packing L17.■1S (*USP30*) The flow rate is about 1 mL per minute.

■The typical background conductance is about 3500 µS.■1S (*USP30*)

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time of *N*-methylpyrrolidine is not less than 8 minutes, and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for *N*-methylpyrrolidine. Calculate the percentage of *N*-methylpyrrolidine in the portion of Cefepime Hydrochloride taken by the formula:

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

in which C is the concentration, in mg per mL, of *N*-methylpyrrolidine in the *Standard solution; W* is the quantity, in mg, of Cefepime Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the *N*-methylpyrrolidine peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.3% is found.

■[NOTE—Cefepime from the *Test solution* elutes as a broad peak at about 55 minutes. To minimize equilibration time at the start of the next day, it is recommended that the detector be turned on the night before and that *Mobile phase* be pumped through the system overnight at a flow rate of 0.2 mL per minute. After every third sample injection, it is recommended that the chromatograph be flushed with *Column rinse solution* for 60 minutes at a flow rate of 1 mL per minute to remove cefepime from the column; and that the system then be switched back to *Mobile phase* at a flow rate of 1 mL per minute for reequilibration.]■1S (*USP30*)

Change to read:

Related compounds—

Potassium phosphate solution—Dissolve 0.68 g of monobasic potassium phosphate in 1000 mL of water.

In-Process Revision

Solution A—Prepare a mixture of *Potassium phosphate solution* and acetonitrile (9 : 1). ~~Adjust with a potassium hydroxide solution (2 in 100) to a pH of 5.0, filter, and degas.~~

■Adjust with potassium hydroxide or phosphoric acid to a pH of 5.0, filter, and degas.■1S (*USP30*)

Solution B—Prepare a mixture of *Potassium phosphate solution* and acetonitrile (1 : 1). ~~Adjust with a potassium hydroxide solution (2 in 100) to a pH of 5.0, filter, and degas.~~

■Adjust with potassium hydroxide or phosphoric acid to a pH of 5.0, filter, and degas.■1S (*USP30*)

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

System suitability solution—Prepare a solution of USP Cefepime Hydrochloride System Suitability RS in *Solution A* containing about 1.4 mg per mL.

Test solution—Transfer about 70 mg of Cefepime Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, sonicate, and mix. [NOTE—Inject this solution immediately, or store in a refrigerator and inject within 12 hours.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	100	0	isocratic
10–30	100→50	0→50	linear gradient
30–35	50	50	isocratic
35–36	50→100	50→0	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 2.7 for cefepime related compound A, 4.3 for cefepime related compound B, and 1.0 for cefepime; and~~

■■1S (*USP30*)
the resolution, *R,* between cefepime and cefepime related compound A is not less than 5, and that between cefepime related compound A and cefepime related compound B is not less than 10. Chromatograph the *Test solution,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′,* is more than 0.6; the column efficiency is not less than 4000 theoretical plates; and the tailing factor is not more than ~~1.1~~

■1.5. [NOTE—For the purpose of identification, the relative retention times are about 1.0 for cefepime, 2.7 for cefepime related compound A, and about 4.3 for cefepime related compound B.]■1S (*USP30*)

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Cefepime Hydrochloride taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity; and r_s is the sum of the responses for all the peaks: not more than 0.3% of cefepime related compound A is found; not more than 0.2% of cefepime related compound B is found; and not more than 0.1% of any other impurity is found.

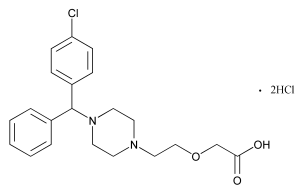
BRIEFING

Cetirizine Hydrochloride. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Hypersil Silica brand of L3 column. The typical retention time for cetirizine is about 10 minutes.

(MD-PS: D. Bempong) RTS—43595-1; 43753-1

Add the following:

■Cetirizine Hydrochloride



$C_{21}H_{25}ClN_2O_3 \cdot 2HCl$ 461.81

(±)-[2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid, dihydrochloride.

(±)-[2-[4-(*p*-Chloro-α-phenylbenzyl)-1-piperazinyl]ethoxy]acetic acid, dihydrochloride. [*83881-52-1*].

» Cetirizine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, protected from light and moisture. Store at room temperature.

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

Color of solution ⟨631⟩—

Reference solution—Mix 2.5 mL of *Matching Fluid G* and 97.5 mL of dilute hydrochloric acid (10 g per L).

Test solution—Transfer 500 mg of Cetirizine Hydrochloride to a 10-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

In-Process Revision

Procedure—Proceed as directed under *Color and Achromicity* ⟨631⟩: the *Test solution* is not more intensely colored than the *Reference solution*.

Clarity of solution—[NOTE—The *Test solution* is to be compared to *Reference suspension A* in diffused daylight 5 minutes after preparation of *Reference suspension A*.]

Hydrazine sulfate solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours before use.

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—Transfer 25.0 mL of *Hydrazine sulfate solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours. [NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.]

Opalescence standard—Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix. [NOTE—This suspension should not be used beyond 24 hours after preparation.]

Reference suspension A—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Prepare as directed under *Color of solution*.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A* and water to separate matching test tubes. Compare the *Test solution, Reference suspension A,* and water in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The diffusion of light must be such that *Reference suspension A* can readily be distinguished from water.] The clarity of the *Test solution* is not more than that of *Reference suspension A*.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of the test for *Chloride* ⟨191⟩.

pH ⟨791⟩**:** between 1.2 and 1.8, in an aqueous solution 1 in 20.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

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

Related compounds—

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

System suitability solution—Dissolve an accurately weighed quantity of USP Cetirizine Hydrochloride RS and USP Cetirizine Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having concentrations of about 4 µg per mL of USP Cetirizine Hydrochloride RS and about 4 µg per mL of USP Cetirizine Related Compound A RS.

Standard solution—Dissolve an accurately weighed quantity of USP Cetirizine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.5 µg per mL.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph the *System suitability solution* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cetirizine related compound A and cetirizine is not less than 2.0; and the tailing factor for the cetirizine peak is not more than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

In-Process Revision

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. [NOTE—Record the chromatogram of the *Test solution* for a period of time equivalent to 3 times the retention time of cetirizine.] Calculate the percentage of each related compound in the portion of Cetirizine Hydrochloride taken by the formula:

$$0.1C_S / C_U(1/F)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Cetirizine Hydrochloride RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Cetirizine Hydrochloride in the *Test solution;* F is the relative response factor as indicated in *Table 1;* r_i is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of of cetirizine obtained from the *Standard solution.* The limits of impurities are as specified in *Table 1*.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and 1 M sulfuric acid (93 : 6.6 : 0.4). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Cetirizine Hydrochloride RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Cetirizine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L3. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as

Table 1

Compound Name	Approximate Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
4-CBH[1]	0.3	1.4	0.1
Dimer[2]	0.5	1.8	0.1
2-Chlorocetirizine[3]	0.85	0.49	0.1
Cetirizine related compound A[4]	0.9	0.95	0.1
Cetirizine	1.0	—	—
Deschlorocetirizine[5]	1.4	0.45	0.1
CBHP[6]	1.45	1.6	0.1
Individual unknown	—	1.0	0.1
Total	—	—	0.3

[1] 4-Chlorobenzhydrol
[2] 1,4-Bis[(4-chlorophenyl)phenylmethyl]piperazine
[3] (RS)-2-[2-[4-[(2-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid
[4] (RS)-2-[2-[4-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid, ethyl ester (Cetirizine Ethyl Ester)
[5] (RS)-2-[2-[4-(Diphenylmethyl]piperazin-1-yl]ethoxy]acetic acid
[6] (RS)-1-[(4-Chlorophenyl)phenylmethyl]piperazine

directed for *Procedure:* the tailing factor for the cetirizine peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the cetirizine peaks. Calculate the quantity, in mg, of $C_{21}H_{25}ClN_2O_3 \cdot 2HCl$ in the portion of Cetirizine Hydrochloride taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Cetirizine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Cholestyramine Resin, *USP 29* page 503. It is proposed to update the information regarding suitable cellulose dialysis tubing in the footnote under the test for *Dialyzable quaternary amines,* and provide a clarification regarding its molecular weight.

(MD-GRE: E. Gonikberg) RTS—44050-1

In-Process Revision

Change to read:

Dialyzable quaternary amines—

pH 9.2 Buffer—Transfer 3.80 g of sodium borate decahydrate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Bromothymol blue solution—Transfer 150 mg of bromothymol blue and 405 mg of sodium carbonate to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solution—Take 1 mL of 60% benzyltrimethylammonium chloride solution, accurately pipeted, and dilute quantitatively, and stepwise, with water to obtain a stock solution having a concentration of 0.2 ± 0.01 mg per mL [NOTE—Prepare this solution fresh]. Cut a 20- to 25-cm piece of cellulose dialysis tubing* having a molecular weight cut-off ~~of 6,000 to 14,000~~

■that falls within the 6,000 to 14,000 range■1S (*USP30*) and a dry flat width of 5 to 9 cm, and place it in water to hydrate until pliable, appropriately sealing one end. Pipet 5 mL of the stock solution into the tubing, add 5 mL of water, appropriately seal the open end, place the tube in a suitable vessel containing 100 mL of water so that it is completely immersed in the water, and stir the fluid for 16 hours to effect dialysis.

Test solution—Cut a 20- to 25-cm piece of cellulose dialysis tubing* having a molecular weight cut-off ~~of 6,000 to 14,000~~

■that falls within the 6,000 to 14,000 range■1S (*USP30*) and a dry flat width of 5 to 9 cm, and place it in water to hydrate until pliable, appropriately sealing one end. Weigh 2 ± 0.01 g of Cholestyramine Resin, and carefully transfer the specimen into the tubing, taking care to ensure that none adheres to the upper walls of the tubing. Add 10 mL of water to the contents of the tube, appropriately seal the open end, and place the tube in a suitable vessel containing 100 mL of water so that it is completely immersed in the water. Stir the fluid for 16 hours to effect dialysis.

Procedure—Pipet the following into each of three separators: separator 1: 5 mL of *Standard solution,* 5 mL of *pH 9.2 Buffer,* 1 mL of *Bromothymol blue solution,* and 10 mL of chloroform; separator 2: 5 mL of *Test solution,* 5 mL of *pH 9.2 Buffer,* 1 mL of *Bromothymol blue solution,* and 10 mL of chloroform; separator 3: 5 mL of water, 5 mL of *pH 9.2 Buffer,* 1 mL of *Bromothymol blue solution,* and 10 mL of chloroform. Shake each separator, vigorously, for 1 minute, allow the phases to separate until the chloroform phase is clear, and collect the chloroform extracts in separate 25-mL volumetric flasks. Repeat the extraction process with a second 10-mL portion of chloroform, and combine with the previous extracts. Dilute each solution with chloroform to volume, if necessary, and mix. Concomitantly determine the absorbances of the *Test solution* and the *Standard solution* at the wavelength of maximum absorbance at about 420 nm, with a suitable spectrophotometer, using the solution from separator 3 as the blank: the absorbance of the *Test solution* does not exceed that of the *Standard solution* (0.05% as benzyltrimethylammonium chloride).

BRIEFING

Ciprofloxacin, *USP 29* page 516; **Ciprofloxacin Hydrochloride,** *USP 29* page 517. On the basis of supporting data and comments received, it is proposed to make several changes as follows:

1. Omit the reference to the *Standard preparation* in the *Chromatographic purity* test, because it is not used in this test.
2. In the *Assay,* change the *Resolution solution* to a more appropriate set of concentrations, approximately 0.5% w/w relative to Ciprofloxacin, for examining system suitability, because these concentrations more closely approximate the limit of analog in ciprofloxacin.
3. In the *Assay,* change the column dimensions for the *Chromatographic system* to reflect the column used for the procedure.

* ~~A suitable tubing is Visking No. C65, available from Union Carbide Corp., Films Packaging Div., 6733 West 65th St., Chicago, IL 60638, or Spectrapor 1, available from various laboratory supply houses, or equivalent.~~

■A suitable tubing is Spectra/Por 1, Item # 132 665, available from Spectrum Laboratories, Inc. (www.spectrapor.com), or equivalent.■1S (*USP30*)

4. In the *Procedure* in the *Assay,* make the tailing factor for the ciprofloxacin peak more restrictive. Additionally, include the relative retention times for the system suitability criteria as a *Note* for the purpose of identification rather than for the system suitability requirement. The liquid chromatographic procedure in the *Assay* is based on analyses performed with a 4.6-mm × 25-cm Prodigy ODS-3 (Phenomenax) brand of L1 column. Typical retention times are about 7.8 minutes for ciprofloxacin and about 5.5 minutes for ciprofloxacin ethylenediamine analog.

(MD-AA: B. Davani) RTS—44060-1

Change to read:

Chromatographic purity—

Mobile phase, ~~*Standard preparation,*~~

■■1S (*USP30*)
Resolution solution, Assay preparation, and *Chromatographic system*—Prepare as directed in the *Assay.*

Procedure—Proceed as directed for *Procedure* in the *Assay.* Calculate the percentage of each impurity peak in the chromatogram obtained from the *Assay preparation* taken by the formula:

$$100r_i / r_t$$

in which r_i is the response of each impurity peak; and r_t is the sum of the responses of all the peaks: not more than 0.2% of ciprofloxacin ethylenediamine analog or any other individual impurity peak is found; and the sum of all the impurity peaks is not more than 0.5%.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of 0.025 M phosphoric acid, previously adjusted with triethylamine to a pH of 3.0 ± 0.1, and acetonitrile (87 : 13). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 12.5 mg of USP Ciprofloxacin RS, accurately weighed, to a 25-mL volumetric flask. Add 0.1 mL of 7% phosphoric acid, dilute with *Mobile phase* to volume, and mix.

Resolution solution—~~Dissolve a quantity of USP Ciprofloxacin Ethylenediamine Analog RS in the *Standard preparation* to obtain a solution containing about 0.5 mg per mL.~~

■Prepare a 0.025 mg per mL solution of USP Ciprofloxacin Ethylenediamine Analog RS in *Mobile phase.* Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with *Standard preparation* to volume, and mix.■1S (*USP30*)

Assay preparation—Transfer about 25 mg of Ciprofloxacin, accurately weighed, to a 50-mL volumetric flask. Add 0.2 mL of 7% phosphoric acid, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a ~~4-mm × 25-cm~~

■4.6-mm × 25-cm■1S (*USP30*)
column that contains packing L1 and is maintained at a temperature of 30 ± 1°. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the responses as directed for *Procedure:* ~~the retention time for ciprofloxacin is between 6.4 and 10.8 minutes; the relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin; and~~

■■1S (*USP30*)
the resolution, *R,* between ciprofloxacin ethylenediamine analog and ciprofloxacin is not less than 6. Chromatograph the *Standard preparation,* and record the responses as directed for *Procedure:* the column efficiency, determined from the ciprofloxacin peak, is not less than 2500 theoretical plates; the tailing factor for the ciprofloxacin peak is not more than ~~4.0;~~

■2.5;■1S (*USP30*)
and the relative standard deviation for replicate injections is not more than 1.5%.

■[NOTE—For the purpose of identification, the relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin.]■1S (*USP30*)

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{17}H_{18}FN_3O_3$ in the portion of Ciprofloxacin taken by the formula:

$$50C(r_U / r_S)$$

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

BRIEFING

Ciprofloxacin and Dexamethasone Otic Suspension. Because there is no existing *USP* monograph for this dosage form, a new monograph based on submitted data is being proposed. The liquid chromatographic procedures in the tests for related compounds and in the assay for each are based on the Symmetry brand of L1 column. The typical retention time for ciprofloxacin formamide is from 3 to 4 minutes, and for ciprofloxacin and dexamethasone is from 8 to 10 minutes.

(MD-AA: B. Davani) RTS—43139-1

Add the following:

■Ciprofloxacin and Dexamethasone Otic Suspension

» Ciprofloxacin and Dexamethasone Otic Suspension is a sterile aqueous suspension containing ciprofloxacin hydrochloride and dexamethasone. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of

ciprofloxacin ($C_{17}H_{18}FN_3O_3$), and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dexamethasone ($C_{22}H_{29}FO_5$).

Packaging and storage—Preserve in tight containers, protected from light. Avoid freezing.

USP Reference standards ⟨11⟩—*USP Ciprofloxacin Ethylenediamine Analog RS. USP Ciprofloxacin Formamide RS. USP Ciprofloxacin Hydrochloride RS. USP Dexamethasone RS. USP Dexamethasone Acetate RS.*

Identification—

A: The chromatogram of the *Assay preparation,* obtained as directed in the *Assay for ciprofloxacin,* exhibits a major peak for ciprofloxacin, the retention time of which corresponds to that obtained in the chromatogram of the *Standard preparation,* obtained as directed in the *Assay for ciprofloxacin*.

B: The chromatogram of the *Assay preparation,* obtained as directed in the *Assay for dexamethasone,* exhibits a major peak for dexamethasone, the retention time of which corresponds to that obtained in the chromatogram of the *Standard preparation,* obtained as directed in the *Assay for dexamethasone*.

Sterility ⟨71⟩—It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*.

pH ⟨791⟩**:** between 3.8 and 4.8.

Particle size—

Carrier fluid—Heat Purified Water to a temperature of 40° to 50°, add 100 mg of dexamethasone per L while stirring, cool to room temperature while stirring, pass through a 0.2-μm filter, and store in a clean, covered container.

Test preparation—Dilute a volume of about 10 μL of Otic Suspension with *Carrier fluid* to 25 mL.

Procedure—(see *Light Obscuration Particle Count Test* under *Particulate Matter in Injections* ⟨788⟩). Analyze the *Test preparation* using an electronic, liquid-borne particle counting system that employs a light obscuration sensor with a suitable sample feeding device. Not less than 99.5% of the particles are $\leq$25 μm, not less than 99.95% are $\leq$50 μm, and not less than 99.995% are $\leq$100 μm.

Osmolality ⟨785⟩**:** between 270 and 330 mOsmol per kg.

Limit of ciprofloxacin formamide—

Buffer—Add 6.0 mL of phosphoric acid to 2.0 L of water. Adjust with 50% sodium hydroxide to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (73 : 27). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 25 mg of USP Ciprofloxacin Formamide RS, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume. Transfer 3.0 mL of this solution to a 50-mL volumetric flask and dilute with *Mobile phase* to volume to obtain a solution having a known concentration of about 0.015 mg per mL.

System suitability solution—Transfer about 2.5 mg of USP Dexamethasone RS and about 2.5 mg of USP Ciprofloxacin Formamide RS to a 100-mL volumetric flask. Dissolve in 15 mL of methanol, then dilute with *Mobile phase* to volume.

Test solution—Transfer an accurately weighed portion of freshly mixed Otic Suspension, equivalent to about 6 mg of ciprofloxacin, to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the column efficiency for ciprofloxacin formamide is not less than 2000 theoretical plates; the resolution, *R,* between ciprofloxacin formamide and dexamethasone is not less than 8; and the tailing factor for ciprofloxacin formamide is not more than 2.0. The relative standard deviation for replicate injections of the *Standard solution* is not more than 2.0%.

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Procedure— Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the peaks at the retention time of ciprofloxacin formamide. Calculate the percentage of ciprofloxacin formamide in the portion of the Otic Suspension taken by the formula:

$$10(C/VL)(r_U/r_S)100$$

in which C is the concentration, in mg per mL, of USP Ciprofloxacin Formamide RS in the *Standard solution; V* is the volume, in mL, of Otic Suspension taken; L is the labeled amount, in mg per mL, of ciprofloxacin; and r_U and r_S are the ciprofloxacin formamide peak responses obtained from the *Test solution* and the *Standard solution,* respectively. Ciprofloxacin formamide is not more than 0.5% of the labeled amount of ciprofloxacin.

Ciprofloxacin related compounds—

Procedure—From the chromatogram of the *Assay preparation,* obtained as directed in the *Assay for ciprofloxacin,* measure the responses for the ciprofloxacin ethylenediamine analog and the other minor peaks. Calculate the percentage of each related compound in the portion of Otic Suspension taken by the formula:

$$25(C/V)(r_U/r_S)100/FL$$

in which C is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Dilute standard preparation,* calculated on the anhydrous basis; V is the volume, in mL, of Otic Suspension taken; r_U and r_S are the related compound peak responses obtained from the *Assay preparation* and the ciprofloxacin peak response obtained from the *Dilute standard preparation,* respectively; F is the relative response factor (1.3 for ciprofloxacin ethylenediamine analog and 1.0 assumed for all other degradation products); and L is the labeled amount, in mg per mL, of ciprofloxacin. The ciprofloxacin ethylenediamine analog is not more than 0.4% of the labeled amount of ciprofloxacin. No other single related compound is greater than 0.2%, and the sum of all related compounds found is not more than 0.8%.

Dexamethasone related compounds—

Procedure—From the chromatogram of the *Assay preparation,* obtained as directed in the *Assay for dexamethasone,* measure the responses for the 21-dehydro-17-deoxy related compound, the 20-carboxy-17-desoxy related compound, and other minor peaks. Calculate the percentage of each related compound in the portion of the Otic Suspension taken by the formula:

$$10(C/VL)(r_U/r_S)100$$

in which C is the concentration, in mg per mL, of USP Dexamethasone RS in the *Dilute standard preparation; V* is the volume, in mL, of Otic Suspension taken; L is the labeled amount, in mg per mL, of dexamethasone; and r_U and r_S are the related compound peak responses obtained from the *Assay preparation* and the dexamethasone peak response obtained from the *Dilute standard preparation,* respectively. The 21-dehydro-17-deoxy related compound is not more than 0.6%, the 20-carboxy-17-desoxy related compound is not more than 2.6%, no other related compound is greater than 0.3%, and the sum of all related compounds found is not more than 3.0%. [NOTE—Identification of known related compounds is accomplished by measuring relative retention times versus dexamethasone. The relative retention times are about 1.4 to 1.6 for the 21-dehydro-17-deoxy related compound and about 2.8 to 3.2 for the 20-carboxy-17-desoxy related compound.]

Assay for ciprofloxacin—

Buffer—Add 6.0 mL of phosphoric acid and 8 g of diethylamine phosphate to 2.0 L of water. Adjust with 50% sodium hydroxide to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (89 : 11). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Accurately weigh about 37 mg of USP Ciprofloxacin Hydrochloride RS into a 25-mL volumetric flask, dissolve in and dilute with 0.1 N hydrochloric acid to volume. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume to obtain a solution having a known concentration of about 0.13 mg of ciprofloxacin per mL.

Dilute standard preparation—Transfer 2.0 mL of the *Standard preparation* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume to obtain a solution having a known concentration of about 0.0025 mg of ciprofloxacin per mL.

System suitability solution—Weigh about 1 mg of USP Ciprofloxacin Hydrochloride RS and 1 mg of USP Ciprofloxacin Ethylenediamine Analog RS into a 25-mL volumetric flask, and dilute with *Mobile phase* to volume. Transfer 2.0 mL of this solution to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Assay preparation—Transfer an accurately weighed portion of freshly mixed Otic Suspension, equivalent to about 3 mg of ciprofloxacin, to a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ciprofloxacin and the ciprofloxacin ethylenediamine analog is not less than 3.0; the column efficiency for ciprofloxacin is not less than 2500 theoretical plates; and the tailing factor for ciprofloxacin is not more than 2.0. The relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%; and the relative standard deviation for replicate injections of the *Dilute standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in each mL of the Otic Suspension taken by the formula:

$$(331.34/367.81)(25C/V)(r_U/r_S)$$

in which 331.34 and 367.81 are the molecular weights of ciprofloxacin and anhydrous ciprofloxacin hydrochloride, respectively; C is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Standard preparation,* calculated on the anhydrous basis; V is the volume, in mL, of Otic Suspension taken; and r_U and r_S are the ciprofloxacin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for dexamethasone—

Buffer and *Mobile phase*—Prepare as directed under *Limit of ciprofloxacin formamide.*

Standard preparation—Transfer about 50 mg of USP Dexamethasone RS, accurately weighed, to a 25-mL volumetric flask, dilute with acetonitrile to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. This solution contains about 0.2 mg of USP Dexamethasone RS per mL.

Dilute standard preparation—Transfer 2.0 mL of the *Standard preparation* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 0.004 mg of USP Dexamethasone RS per mL.

System suitability solution—Transfer about 2 mg of USP Dexamethasone RS and about 2 mg of USP Dexamethasone Acetate RS to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer an accurately weighed portion of freshly mixed Otic Suspension, equivalent to about 2 mg of dexamethasone, to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the column efficiency for dexamethasone is not less than 2000 theoretical plates; the resolution, *R,* between dexamethasone and dexamethasone acetate is not less than 12; the tailing factor for dexamethasone is not more than 2.0; the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%; and the relative standard deviation for replicate injections of the *Dilute standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of dexamethasone ($C_{22}H_{29}FO_5$) in each mL of the Otic Suspension taken by the formula:

$$10(C/V)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Dexamethasone RS in the *Standard preparation; V* is the volume, in mL, of Otic Suspension taken; and r_U and r_S are the dexamethasone peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Ciprofloxacin Hydrochloride, *USP 29* page 517—See briefing under *Ciprofloxacin.*

(MD-AA: B. Davani) RTS—44061-1

Change to read:

Chromatographic purity—

Mobile phase, ~~Standard preparation,~~

■■1S (*USP30*)
Resolution solution, Assay preparation, and *Chromatographic system*—Prepare as directed in the *Assay.*

Procedure—Proceed as directed for *Procedure* in the *Assay.* Calculate the percentage of each impurity peak in the chromatogram obtained from the *Assay preparation* taken by the formula:

$$100r_i/r_t$$

in which r_i is the response of each impurity peak; and r_t is the sum of the responses of all the peaks: not more than 0.2% of ciprofloxacin ethylenediamine analog or of any other individual impurity peak is found; and the sum of all the impurity peaks is not more than 0.5%.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of 0.025 M phosphoric acid, previously adjusted (with triethylamine) to a pH of 3.0 ± 0.1, and acetonitrile (87 : 13). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Ciprofloxacin Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Resolution solution—~~Dissolve a quantity of USP Ciprofloxacin Ethylenediamine Analog RS in the Standard preparation to obtain a solution containing about 0.5 mg per mL.~~

■Prepare a 0.025 mg per mL solution of USP Ciprofloxacin Ethylenediamine Analog RS in *Mobile phase.* Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with *Standard preparation* to volume, and mix.■1S (*USP30*)

Assay preparation—Transfer about 25 mg of Ciprofloxacin Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a ~~4-mm × 25-cm~~

■4.6-mm × 25-cm■1S (*USP30*)
column that contains packing L1 and is maintained at a temperature of 30 ± 1°. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the retention time for ciprofloxacin is between 6.4 and 10.8 minutes; the relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin; and~~

■■1S (*USP30*)
the resolution, *R,* between the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak is not less than 6. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency, determined from the ciprofloxacin peak, is not less than 2500 theoretical plates; the tailing factor for the ciprofloxacin peak is not more than ~~4.0;~~

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■2.5;■1S (*USP30*)
and the relative standard deviation for replicate injections is not more than 1.5%.

■[NOTE—For the purpose of identification, the relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin.]■1S (*USP30*)

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{17}H_{18}FN_3O_3 \cdot HCl$ in the portion of Ciprofloxacin Hydrochloride taken by the formula:

$$50C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Standard preparation,* calculated on the anhydrous basis; and r_U and r_S are the ciprofloxacin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ciprofloxacin Injection, *USP 29* page 518. On the basis of supporting data and comments received, it is proposed to make the following changes:

1. Insert *Mobile phase, Resolution solution, Assay preparation,* and *Chromatographic system* into the test for *Limit of ciprofloxacin ethylenediamine analog* to remove reliance on the drug substance monograph.
2. Change the concentration for the *Standard preparation* to provide more signal due to higher overall concentration and thus improve the detection sensitivity for the analog.
3. Change the *Assay preparation* and the calculation formula to reflect the change in the *Standard preparation.*
4. Insert *Mobile phase, Chromatographic system,* and *Procedure* into the *Assay* to remove reliance on the drug substance monograph.
5. See briefing under *Ciprofloxacin* for other revisions to the *Assay.*

(MD-AA: B. Davani) RTS—44062-1

Change to read:

Limit of ciprofloxacin ethylenediamine analog—

Mobile phase

■*Resolution solution, Assay preparation,*■1S (*USP30*) and *Chromatographic system*—~~Proceed~~

■Prepare■1S (*USP30*) as directed in the *Assay.* ~~*under Ciprofloxacin.*~~

■■1S (*USP30*) ~~*Standard preparation, Resolution solution,* and *Assay preparation*—Proceed as directed in the *Assay* under *Ciprofloxacin.*~~

■■1S (*USP30*) *Procedure*—Proceed as directed for *Procedure* in the *Assay.* ~~under *Ciprofloxacin.*~~

■■1S (*USP30*) Calculate the percentage of ciprofloxacin ethylenediamine analog from the chromatogram obtained from the *Assay preparation* ~~in the *Assay* under *Ciprofloxacin*~~

■■1S (*USP30*) by the formula:

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

in which 0.7 is the correction factor for ciprofloxacin ethylenediamine analog; and r_A and r_C are the responses of the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak, respectively. It contains not more than 0.5% of ciprofloxacin ethylenediamine analog.

Change to read:

Assay—

~~*Mobile phase* and *Chromatographic system*—Proceed as directed in the *Assay* under *Ciprofloxacin.*~~

■*Mobile phase*—Prepare a filtered and degassed mixture of 0.025 M phosphoric acid, previously adjusted with triethylamine to a pH of 3.0 ± 0.1, and acetonitrile (87 : 13). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).■1S (*USP30*)

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Ciprofloxacin Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about ~~0.3 mg~~

■0.5 mg■1S (*USP30*) per mL.

Resolution solution—~~Dissolve a quantity of USP Ciprofloxacin Ethylenediamine Analog RS in *Standard preparation* to obtain a solution having a concentration of about 0.25 mg per mL.~~

■Prepare a 0.025 mg per mL solution of USP Ciprofloxacin Ethylenediamine Analog RS in *Mobile phase.* Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with *Standard preparation* to volume, and mix.■1S (*USP30*)

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 25 mg of ciprofloxacin, to a ~~100 mL~~

■50-mL■1S (*USP30*) volumetric flask, dilute with *Mobile phase* to volume, and mix.

■*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 25-cm column that contains packing L1 and is maintained at a temperature of $30 \pm 1°$. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak is not less than 6. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the

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column efficiency, determined from the ciprofloxacin peak, is not less than 2500 theoretical plates; the tailing factor for the ciprofloxacin peak is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.5%. [NOTE—For the purpose of identification, the relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin.]■1S (*USP30*)

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of ciprofloxacin in each mL of the Injection taken by the formula:

~~$(331.34/367.81)(100C/V)(r_U/r_S)$~~

■$(331.34/367.81)(50C/V)(r_U/r_S)$■1S (*USP30*)

in which 331.34 and 367.81 are the molecular weights of ciprofloxacin and anhydrous ciprofloxacin hydrochloride, respectively; C is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Standard preparation,* calculated on the anhydrous basis; V is the volume, in mL, of Injection taken to prepare the *Assay preparation;* and r_U and r_S are the ciprofloxacin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

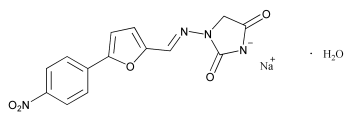
BRIEFING

Dantrolene Sodium. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedures in the tests for *Related compounds* and *Limit of dantrolene related compound A* and in the *Assay* are based on analyses performed with the Waters Symmetry C18 brand of L1 column. In the test for *Related compounds* and in the *Assay,* the typical retention time for dantrolene is about 10 minutes. In the test for *Limit of dantrolene related compound A,* the typical retention time for dantrolene related compound A is about 3.8 minutes, and dantrolene elutes at void volume at about 1.5 minutes.

(MD-PP: R. Ravichandran) RTS—42654-1

Add the following:

■Dantrolene Sodium



$C_{14}H_9N_4NaO_5 \cdot 3½H_2O$ 399.29

2,4-Imidazolidinedione, 1-[[[5-(4-nitrophenyl)-2-furanyl]-methylene]amino]-, sodium salt, hydrate (2 : 7).

1-[[5-(*p*-Nitrophenyl)furfurylidene]amino]hydantoin sodium salt hydrate [*24868-20-0*].

» Dantrolene Sodium contains not less than 90.0 percent and not more than 96.0 percent of $C_{14}H_{10}N_4O_5$, the free acid form of Dantrolene Sodium, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at room temperature.

USP Reference standards ⟨11⟩—*USP Dantrolene RS. USP Dantrolene Related Compound A RS. USP Dantrolene Related Compound B RS. USP Dantrolene Related Compound C RS. USP Dantrolene Sodium RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

C: Ignite about 200 mg: the residue meets the requirements of the flame test for *Sodium* ⟨191⟩.

Water, *Method Ia* ⟨921⟩**:** between 14.5% and 17.0%.

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

Limit of dantrolene related compound A—

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

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩.

Standard solution—Dissolve an accurately weighed quantity of *USP Dantrolene Related Compound A RS* and *USP Dantrolene Sodium RS* in dimethylformamide to obtain a solution having known concentrations of 17.5 µg per mL of dantrolene related compound A and 50 µg per mL of dantrolene sodium. Dilute with acetonitrile to obtain a solution having concentrations of about 0.35 µg per mL of dantrolene related compound A and 1 µg per mL of dantrolene sodium.

Test solution—Dilute the *Test stock solution* with acetonitrile to obtain a solution having a concentration of about 0.175 mg per mL of dantrolene sodium.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 365-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*. The tailing fator for dantrolene related compound A is not more than 1.5; and the relative standard deviation for replicate injections is not more than 5% for dantrolene related compound A. [NOTE—The dantrolene peak elutes at void volume at approximately 1.5 minutes.]

Procedure—Inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution,* record the chromatograms, and measure the response for the dantrolene related compound A peak. Calculate the percentage of dantrolene related compound A in the portion of Dantrolene Sodium taken by the formula:

$$100(r_U / r_S)(C_S / C_T)$$

in which r_U and r_S are the peak responses of dantrolene related compound A obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of dantrolene related compound A in the *Standard solution;* and C_T is the concentration, in mg per mL, of dantrolene sodium in the *Test solution:* not more than 0.15% of dantrolene related compound A is found.

Related compounds—

Mobile phase, System suitability stock solution B, Diluent, and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Dilute quantitatively the *System suitability stock solution B* with *Diluent* to obtain a solution having a known concentration of 0.25 µg per mL each of dantrolene related compound B and dantrolene related compound C.

Test solution—Use the *Assay preparation.*

Procedure—Inject equal volumes (about 20 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each of the relevant dantrolene related compounds in the portion of Dantrolene Sodium taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of dantrolene related compound B or dantrolene related compound C in the *Standard solution;* C_T is the concentration, in mg per mL, of dantrolene sodium in the *Test solution;* r_U is the individual peak response for dantrolene related compound B or dantrolene related compound C obtained from the *Test solution;* and r_S is the response of the corresponding peak

obtained from the *Standard solution.* Not more than 0.50% of dantrolene related compound B is found; and not more than 0.30% of dantrolene related compound C is found.

Assay—

Buffer—Dissolve 3.85 g of ammonium acetate in 1.0 L of water, and adjust with glacial acetic acid to a pH of 4.5 ± 0.1.

Diluent—Prepare a mixture of water and acetonitrile (50 : 50).

Solution A—Prepare a filtered and degassed mixture of water, *Buffer,* and acetonitrile (70 : 20 : 10).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Buffer* (80 : 20).

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

System suitability stock solution A—Transfer 62.5 mg of *USP Dantrolene Sodium RS,* accurately weighed, into a 50-mL volumetric flask, and dissolve in 2.5 mL of dimethylformamide. Add 2.5 mL of glacial acetic acid, and dilute with acetone to volume to obtain a solution having a known concentration of about 1.25 mg per mL of dantrolene sodium.

System suitability stock solution B—Transfer 6.3 mg each of USP Dantrolene Related Compound B RS and USP Dantrolene Related Compound C RS, accurately weighed, into a 50-mL volumetric flask, and dissolve in 2.5 mL of dimethylformamide. Add 2.5 mL of glacial acetic acid, and dilute with acetone to volume to obtain a solution having known concentrations of about 0.125 mg per mL each of dantrolene related compound B and dantrolene related compound C.

System suitability solution—Quantitatively dilute suitable volumes of *System suitability stock preparation A* and *System suitability stock preparation B* with *Diluent* to obtain a solution having concentrations of about 0.125 mg per mL of dantrolene sodium and 2.5 µg per mL each of dantrolene related compound B and dantrolene related compound C.

Standard stock preparation—Transfer 50 mg of USP Dantrolene RS, accurately weighed, into a 50-mL volumetric flask, and dissolve in 2.5 mL of dimethylformamide. Add 2.5 ml of glacial acetic acid, and dilute with acetone to volume to obtain a solution having a known concentration of about 1.0 mg per mL of dantrolene.

Standard preparation—Dilute the *Standard stock preparation* with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL of dantrolene.

Assay stock preparation—Transfer an accurately weighed quantity of dantrolene sodium into a 100-mL volumetric flask, and dissolve in 5mL of dimethylformamide. Add 5 mL of glacial acetic acid, and dilute with acetone to volume to obtain a solution having a concentration of about 1.25 mg per mL of dantrolene sodium.

Assay preparation—Dilute the *Assay stock preparation* with *Diluent* to obtain a solution having a concentration of about 0.125 mg per mL of dantrolene sodium.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 365-nm detector and a 4.6-mm × 15-cm column that contains 5-µm L1 packing. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solvent A* (%)	*Solvent B* (%)	Elution
0–10	90→60	10→40	linear gradient
10–20	60→10	40→90	linear gradient
20–25	10	90	isocratic
25–25.1	10→90	90→10	linear gradient
25.1–35	90	10	re-equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*. The resolution, *R,* between dantrolene and dantrolene related compound C is not less than 8. Chromatograph the *Standard preparation,* and

record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 1.0%. [NOTE—For the purpose of identification, the approximate relative retention times are 0.68 for dantrolene related compound B, 1.24 for dantrolene related compound C, and 1.0 for dantrolene.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the dantrolene peaks. Calculate the percentage of dantrolene ($C_{14}H_{10}N_4O_5$) in the portion of Dantrolene Sodium taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of dantrolene in the *Standard preparation;* C_U is the concentration, in mg per mL, of dantrolene sodium in the *Assay preparation;* and r_U and r_S are the peak responses for dantrolene obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Diazepam Extended-Release Capsules, *USP 29* page 674. It is proposed to require the use of USP Ethylparaben RS for the preparation of the *Internal standard solution.* The current monograph does not contain any specific system suitability criteria; this proposal introduces two system suitability criteria. It is also proposed to clarify that the relative retention times are intended for identification only.

(MD-PP: R. Ravichandran) RTS—44083-1

Change to read:

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

■*USP Ethylparaben RS.*■1S (*USP30*)

Change to read:

Assay—

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay* under *Diazepam*.

Internal standard solution—~~Transfer about 300 mg of ethylparaben to a 200-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.~~

■Dissolve an accurately weighed quantity of USP Ethylparaben RS in methanol to obtain a solution having a known concentration of about 1.5 mg per mL.■1S (*USP30*)

Standard preparation—Dissolve an accurately weighed quantity of USP Diazepam RS in methanol, quantitatively dilute with methanol to obtain a solution having a known concentration of about 1 mg per mL, and mix. Transfer 15.0 mL of this solution and 5.0 mL of *Internal standard solution* to a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Assay preparation—Weigh and mix the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the mixture, equivalent to about 15 mg of diazepam, to a 100-mL volumetric flask. Add 5.0 mL of *Internal standard solution* and about 45 mL of methanol. Shake by mechanical means for 30 minutes, dilute with methanol to volume, and mix. Centrifuge about 30 mL of this solution for 5 minutes, and filter.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. ~~The relative retention times are about 0.5 for ethylparaben and 1.0 for diazepam.~~

■The tailing factor for diazepam is not more than 2.0; and the relative standard deviation for the diazepam peak for replicate injections is not more than 2.0%. [NOTE—For the purpose of identifcation, the relative retention times are about 0.5 for ethylparaben and 1.0 for diazepam.]■1S (*USP30*)

Calculate the quantity, in mg, of diazepam ($C_{16}H_{13}ClN_2O$) in the portion of Capsules taken by the formula:

$$100C(R_U / R_S)$$

in which C is the concentration, in mg per mL, of USP Diazepam RS in the *Standard preparation;* and R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Doxepin Hydrochloride, *USP 29* page 758. It is proposed to add a test for *Related compounds* based on an isocratic reverse phase HPLC methodology. The method was validated using a Phenomenx brand of Luna C18(2) column. The typical retention times for doxepin and doxepinone are about 20 and 9.5 minutes, respectively. It is also proposed to make the following changes:

1. Replace the UV *Identification* test with an HPLC test based on a comparison of the retention times of the drug substance and the Reference Standard.

In-Process Revision

2. Delete the test for *Chloride content,* and add a qualitative *Identification* test for chloride.
3. Delete the *Melting range* test.

(MD-PP: R. Ravichandran) RTS—42805-1

Change to read:

USP Reference standards ⟨11⟩—*USP Doxepin Hydrochloride RS.* ■*USP Doxepin Related Compound A RS. USP Doxepin Related Compound B RS. USP Doxepin Related Compound C RS.*■1S (*USP30*)

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: ~~*Ultraviolet Absorption* ⟨197U⟩—~~

~~*Solution:* 50 µg per mL.~~

~~*Medium:* alcohol.~~

~~Absorptivities at 296 nm, calculated on the dried basis, do not differ by more than 3.0%.~~

■The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

C: A solution (1 in 100) in a mixture of water and alcohol (1 : 1) meets the requirements of the test for *Chloride* ⟨191⟩ in amine hydrochlorides.■1S (*USP30*)

Delete the following:

■~~**Melting range,** *Class I* ⟨741⟩: between 185° and 191°.~~■1S (*USP30*)

Delete the following:

■~~**Chloride content**—Dissolve about 100 mg, accurately weighed, in a mixture of 100 mL of water and 100 mL of alcohol. Titrate with 0.05 N silver nitrate VS, determining the endpoint potentiometrically using a silver silver sulfide sensing electrode and a double junction reference electrode containing potassium nitrate filling solution in the outer jacket and a standard filling solution in the inner jacket. Each mL of 0.05 N silver nitrate is equivalent to 1.773 mg of chloride. Not less than 10.9% and not more than 11.6% of chloride is found.~~■1S (*USP30*)

Add the following:

■**Related compounds—**

Diluted phosphoric acid—Prepare a mixture of water and phosphoric acid (10 : 1), and mix well.

Buffer—Dissolve 1.42 g of dibasic sodium phosphate in 1 L of water, adjust with *Diluted phosphoric acid* to a pH of 7.7, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *Buffer,* and acetonitrile (50 : 30 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of *Mobile phase* and 2 N sodium hydroxide (1000 : 2).

Standard solution—Dissolve accurately weighed quantities of USP Doxepin Hydrochloride RS, USP Doxepin Related Compound A RS, USP Doxepin Related Compound B RS, and USP Doxepin Related Compound C RS in *Diluent* to obtain a solution having a known concentration of about 0.001 mg of each per mL. [NOTE—Sonication for about 1 minute may be used to aid the initial dissolution of the compounds.]

Test solution—Dissolve an accurately weighed quantity of Doxepin Hydrochloride in *Diluent* to obtain a final solution having a known concentration of about 1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 30°. Chromatograph about 20 µL of the *Standard solution,* and record the peak areas as directed for *Procedure:* the resolution, *R,* between doxepin related compound A and doxepin related compound C is not less than 1.5; the resolution between doxepin related compound C and doxepin related compound B is not less than 1.5; and the S/N ratio for all the peaks is not less than 10. [NOTE—Use the approximate relative retention times given in *Table 1* for the purpose of peak identification.]

Name	Relative Retention Time (RRT)	Limit (%)
Doxepin related compound A	0.48	0.10
Doxepin related compound C	0.55	0.20
Doxepin related compound B	0.63	0.10
Doxepin hydrochloride	1.0	—
Unknown impurity	—	0.10 each

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram for up to 2.2 times the retention time of doxepin, and measure the peak responses. Calculate the percentage of each individual doxepin related compound in the portion of Doxepin Hydrochloride taken by the formula:

$$100(r_U / r_S)(C_S / C_T)$$

in which r_U is the individual peak response for each doxepin related compound obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution;* C_S is the concentration, in mg per mL, of each doxepin related compound in the *Standard solution;* and C_T is the concentration, in mg per mL, of Doxepin Hydrochloride in the *Test solution*. The related substance limits are listed in *Table 1*. [NOTE—Discard any peak with a relative retention time less than 0.25.] Use the response of the doxepin peak obtained from the *Standard solution* and the concentration of doxepin hydrochloride in the *Standard solution* to calculate the percentage of unknown individual impurities.■1S (*USP30*)

BRIEFING

Ethotoin Tablets, *USP 29* page 870. In the *Assay,* it is proposed to use a mixture of acidified water and acetonitrile as the *Diluent* instead of the *Mobile phase* in the preparation of the *Internal standard solution* to enhance the stability of the *Standard preparation* and the *Assay preparation*. It is also proposed to revise the *USP Reference standards* section to include USP Ethylparaben RS in the preparation of the *Internal standard solution*.

(MD-PP: R. Ravichandran) RTS—40023-1

Change to read:

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

■*USP Ethylparaben RS.*■1S (*USP30*)

Change to read:

Assay—

■*Diluent*—Prepare a mixture of water, acetonitrile, and phosphoric acid (750 : 250 : 1).■1S (*USP30*)

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of ~~ethylparaben~~ ■USP Ethylparaben RS■1S (*USP30*) in ~~*Mobile phase*~~ ■*Diluent*■1S (*USP30*) having a concentration of 0.02 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Ethotoin RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL. ~~To 5.0 mL of this solution add 5.0 mL of *Internal standard solution,* and mix.~~

■Immediately transfer 5 mL of this solution and 5 mL of the *Internal standard solution* to a suitable container, and mix well.■1S (*USP30*)

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of ethotoin, to a 100-mL volumetric flask. Add 75 mL of *Mobile phase,* shake vigorously for 60 minutes, dilute with *Mobile phase* to volume, mix, and ■immediately■1S (*USP30*) filter. ~~To 5.0 mL of the filtrate add 5.0 mL of the *Internal standard solution,* and mix.~~

■Without delay, transfer 5 mL of the filtrate and 5 mL of the *Internal standard solution* to a suitable container, and mix.■1S (*USP30*)

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the analyte and internal standard peaks is not less than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

In-Process Revision

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. ~~The relative retention times are about 0.5 for ethotoin and 1.0 for ethylparaben.~~

■[NOTE—For the purpose of identification, the relative retention times are about 0.5 for ethotoin and 1.0 for ethylparaben.]■1S *(USP30)*

Calculate the quantity, in mg, of $C_{11}H_{12}N_2O_2$ in the portion of Tablets taken by the formula:

$$200C(R_U / R_S)$$

in which C is the concentration, in mg per mL, of USP Ethotoin RS in the *Standard preparation;* and R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Famotidine Injection. Because there is no existing *USP* monograph for this dosage form, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Ultrasphere Silica brand of L3 column. The typical retention time reported for famotidine is about 8 minutes.

(MD-GRE: E. Gonikberg; MSA: R. Tirumalai) RTS—43694-1

Add the following:

■Famotidine Injection

» Famotidine Injection is a sterile, concentrated solution of famotidine. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of famotidine ($C_8H_{15}N_7O_2S_3$). It may contain suitable preservatives.

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass. Store in a refrigerator.

Labeling—It meets the requirements for *Labeling* under *Injections* ⟨1⟩. Label it to indicate that the Injection is to be diluted with a suitable parenteral vehicle prior to administration. Label it to indicate the name and the quantity of any added preservative.

USP Reference standards ⟨11⟩**—***USP Benzyl Alcohol RS. USP Endotoxin RS. USP Famotidine RS.*

Identification—The retention time of the famotidine peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩**—**It contains not more than 16.67 USP Endotoxin Units per mg of famotidine.

Sterility ⟨71⟩**:** meets the requirements.

pH ⟨791⟩**:** between 5.0 and 5.6.

Particulate matter ⟨788⟩**:** meets the requirements for small-volume injections.

Related compounds—

Buffer solution, Mobile phase, and *Diluent*—Proceed as directed in the *Assay.*

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

System suitability stock solution—Proceed as directed in the test for *Content of benzyl alcohol.*

System suitability solution—

IF BENZYL ALCOHOL IS PRESENT—Proceed as directed in the test for *Content of benzyl alcohol.*

IF BENZYL ALCOHOL IS NOT PRESENT—Transfer 25 mL of *System suitability stock solution* to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution,* identify the famotidine peak and other peaks based on the relative retention times listed in *Table 1*, and record the peak responses as directed for *Procedure:* the

resolution, *R,* between adjacent peaks of impurity B, impurity C, famotidine, and impurity D is not less than 1.3 for each pair of peaks.

Table 1

Name	Approximate Relative Retention Time
Benzyl alcohol (if present)	0.4
Impurity B[1]	0.7
Impurity C[2]	0.8
Famotidine	1.0
Impurity D[3]	1.3

[1] 3-[2-(Diaminomethyleneamino)-1,3-thiazol-4-ylmethylthio]-propanoic acid
[2] 3-[2-(Diaminomethyleneamino)-1,3-thiazol-4-ylmethylthio]-*N*-sulfamoyl-propanamide
[3] 3-[2-(Diaminomethyleneamino)-1,3-thiazol-4-ylmethylthio]-propanamide

Procedure—Inject about 30 µL of the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of the total of impurities B, C, and D in the portion of the Injection taken by the formula:

$$100(r_U / r_T)$$

in which r_U is the sum of the areas of peaks for impurities B, C, and D obtained from the *Test solution;* and r_T is the sum of the peak areas for famotidine, impurity B, impurity C, and impurity D obtained from the *Test solution*: not more than 5.0% of total impurities is found.

Content of benzyl alcohol *(if present)*—

Buffer solution, Mobile phase, and *Diluent*—Proceed as directed in the *Assay.*

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

System suitability stock solution—Transfer approximately 10 mg of USP Famotidine RS to a 50-mL volumetric flask, and add 1 mL of 0.1 N hydrochloric acid. Heat at 80° for 30 minutes. Allow to cool, add 2 mL of 0.1 N sodium hydroxide, and heat at 80° for an additional 30 minutes. Allow to cool, and neutralize by adding 1 mL of 0.1 N hydrochloric acid. Dilute with *Diluent* to volume, and mix (*Solution A*). Transfer about 5 mg of USP Famotidine RS to a separate 50-mL volumetric flask, add 8 mL of methanol, and sonicate to dissolve. Add 10 mL of *Solution A,* dilute with *Diluent* to volume, and mix.

System suitability solution—Transfer 25 mL of *System suitability stock solution* to a 50-mL volumetric flask. Add 1 drop (approximately 20 mg) of USP Benzyl Alcohol RS, dilute with *Diluent* to volume, and mix.

Standard solution—Dissolve accurately weighed quantities of USP Famotidine RS and USP Benzyl Alcohol RS in *Diluent* to obtain a solution having known concentrations of about 0.1 mg of famotidine per mL and about 0.09 mg of benzyl alcohol per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution,* identify the components based on their relative retention times listed in *Table 1*, and record the peak responses as directed for *Procedure:* the benzyl alcohol peak is resolved from the solvent front, and the resolution, *R,* between adjacent peaks of benzyl alcohol and famotidine impurity B is not less than 1.3. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is less than 2.0% for each peak.

Procedure—Separately inject equal volumes (about 30 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of benzyl alcohol in each mL of the Injection by the formula:

$$D(C/V)(r_U / r_S)$$

in which *D* is the volume, in mL, of the *Test solution; C* is the concentration, in mg per mL, of benzyl alcohol in the *Standard solution; V* is the volume, in mL, of the Injection taken to prepare the *Test solution;* and r_U and r_S are the peak

areas for benzyl alcohol obtained from the *Test solution* and the *Standard solution,* respectively: the content of benzyl alcohol is between 90.0% and 110.0% of the labeled amount.

Other requirements—It meets the requirements for *Volume in Container* under *Injections* ⟨1⟩.

Assay—

Buffer solution—Dissolve 13.8 g of monobasic sodium phosphate in water, and dilute with water to 1 L.

Mobile phase—Prepare a mixture of water, methanol, and *Buffer solution* (32 : 5 : 3), and adjust with 1 N sodium hydroxide to a pH of 5.3.

Diluent—Dissolve 1.36 g of monobasic potassium phosphate in 800 mL of water, adjust with 1 N sodium hydroxide to a pH of 7.0, and dilute with water to 1 L.

Standard preparation—

IF BENZYL ALCOHOL IS PRESENT—Dissolve accurately weighed quantities of USP Famotidine RS and USP Benzyl Alcohol RS in *Diluent* to obtain a solution having known concentrations of about 0.1 mg of famotidine per mL and about 0.09 mg of benzyl alcohol per mL.

IF BENZYL ALCOHOL IS NOT PRESENT—Dissolve an accurately weighed quantity of USP Famotidine RS in *Diluent* to obtain a solution having a known concentration of about 0.1 mg of famotidine per mL.

Assay preparation—Transfer an accurately measured volume of Famotidine Injection, equivalent to about 20 mg of famotidine based on the label claim, to a 200-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L3. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections for the famotidine peak is less than 2.0%.

Procedure—Separately inject equal volumes (about 30 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of famotidine ($C_8H_{15}N_7O_2S_3$) in each mL of the Injection by the formula:

$$D(C/V)(r_U/r_S)$$

in which D is the volume, in mL, of the *Assay preparation; C* is the concentration, in mg per mL, of famotidine in the *Standard preparation; V* is the volume, in mL, of the Injection taken to prepare the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S *(USP30)*

BRIEFING

Fluconazole, *USP 29* page 911 and page 1368 of *PF* 31(5) [Sept.–Oct. 2005]. It is proposed to revise the limits for total unknown impurities and total impurities in *Test 1* under *Related compounds* to correspond to those in the NDA submission. On the basis of the new information received, it is also proposed to revise the relative retention times of impurities in *Test 2* under *Related compounds.*

(MD-AA: B. Davani) RTS—43736-1

Delete the following:

■~~**Melting range** ⟨741⟩: between 138° and 142°.~~■2S *(USP29)*

Change to read:

Related compounds—▲[NOTE—On the basis of information regarding the manufacturing process, perform either *Test 1,* or *Test 2* and *Test 3*.]

TEST 1—▲*USP29*

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

System suitability solution—Use the *Standard solution*.

Standard solution—Transfer accurately weighed quantities of USP Fluconazole RS, USP Fluconazole Related Compound A RS, USP Fluconazole Related Compound B RS, and USP Fluconazole Related Compound C RS to a suitable volumetric flask, dissolve in acetonitrile, dilute quantitatively, and stepwise if necessary, with *Mobile phase* to volume, and mix to obtain a solution having known concentrations of 10 µg of each per mL.

In-Process Revision

Test solution—Transfer about 30 mg of Fluconazole, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L1. The flow rate is about 0.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* typical retention times are about 4.9 minutes for fluconazole related compound A, 8.0 minutes for fluconazole related compound B, 8.5 minutes for fluconazole related compound C, and 9.9 minutes for fluconazole; the resolution, *R,* between fluconazole related compound B and fluconazole related compound C is not less than 1.5; and the relative standard deviation of each peak for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of fluconazole related compound A, fluconazole related compound B, fluconazole related compound C, and any other impurities in the portion of Fluconazole taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Fluconazole Related Compound A RS, USP Fluconazole Related Compound B RS, USP Fluconazole Related Compound C RS, or USP Fluconazole RS, respectively, in the *Standard solution; W* is the weight, in mg, of Fluconazole taken to prepare the *Test solution;* r_U is the peak response obtained from the *Test solution;* and r_S is the average peak response of fluconazole related compound A, fluconazole related compound B, fluconazole related compound C, or fluconazole obtained from replicate injections of the *Standard solution:* ▲not more than 1.0% of any impurity with a relative retention time (RRT) of about 0.6 is found; not more than 0.2% of fluconazole related compound A or fluconazole related compound C is found; not more than 0.1% of fluconazole related compound B is found; not more than 0.1% of any other individual impurity is found; not more than ~~0.2%~~

■0.3%■1S (*USP30*)
of total ~~other~~

■unknown■1S (*USP30*)
impurities is found; and not more than ~~1.2%~~

■1.5%■1S (*USP30*)
of total impurities is found.

TEST 2—

Acetate buffer—Prepare a 0.04 M anhydrous sodium acetate solution, adjust with 1 N acetic acid to a pH of 5.0, and mix.

Solution A: filtered and degassed *Acetate buffer*.

Solution B: acetonitrile.

Solution C: methanol.

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

Diluent—Prepare a mixture of *Acetate buffer* and methanol (84 : 16).

Standard solution—Dissolve an accurately weighed quantity of USP Fluconazole RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.01 mg per mL.

System suitability solution—Dissolve suitable quantities of USP Fluconazole RS and USP Desacetyl Diltiazem Hydrochloride RS in *Diluent.* Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution containing about 0.02 mg per mL and 0.006 mg per mL, respectively.

Test solution—Transfer about 200 mg of Fluconazole, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 261-nm detector and a 4.0-mm × 10-cm column that contains packing L1. The flow rate is 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0–10	80	5	15	isocratic
10–20	80→30	5→55	15	linear gradient (*A* and *B*)
20–23	30	55	15	isocratic
23–25	30→80	55→5	15	reset composition
25–30	80	5	15	re-equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are 1.0 for fluconazole and about 1.2 for desacetyl hydrochloride; the resolution, *R,* between fluconazole and desacetyl diltiazem hydrochloride is not less than 10.0; the column efficiency for fluconazole is not less than 30,000 theoretical plates; and the tailing factor, *T,* is not more than 1.4. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is less than 5.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Fluconazole taken by the formula:

$$10{,}000(r_i/r_S)(C/W)(1/F)$$

in which r_i is the peak response of each impurity obtained from the *Test solution;* r_S is the peak response of fluconazole obtained from the *Standard solution; C* is the concentration, in mg per mL, of USP Fluconazole RS in the *Standard solution; W* is the weight, in mg, of Fluconazole taken to prepare the *Test solution;* and *F* is the relative response factor as determined from the following table.

Relative Response Factor *(F)*	Relative Retention Time (RRT)
0.72	0.17–0.37
0.85	~~1.20–1.32~~
	■0.48–0.60■1S (*USP30*)
1.21	~~0.48–0.60~~
	■0.67–0.79■1S (*USP30*)
0.96	1.14–1.18
0.97	~~0.67–0.79~~
	■1.20–1.32■1S (*USP30*)
1.0	all other peaks

Not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found.

TEST 3—

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

Test solution—Dissolve an accurately weighed quantity of Fluconazole in methanol to obtain a solution containing approximately 50 mg per mL.

Standard solutions—Dissolve an accurately weighed quantity of USP Fluconazole RS in methanol to obtain *Standard solution A* having a known concentration of about 1 mg per mL (2.0%). Quantitatively dilute portions of this solution with methanol to obtain *Standard solution B* and *Standard solution C* having known concentrations of about 0.1 mg per mL (0.2%) and 0.05 mg per mL (0.1%), respectively.

Developing solvent system—Prepare a mixture of chloroform, methanol, and ammonium hydroxide (80 : 20 : 1).

Application volume: 10 µL.

Spray reagent A—Dissolve about 170 mg of silver nitrate in 100 mL of water.

Spray reagent B (Potassium iodoplatinate solution)—Dissolve about 375 mg of chloroplatinic acid in 5 mL of 1 N hydrochloric acid. Dissolve about 5 g of potassium iodide in 50 mL of water, and

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store in a light-resistant container. Prepare a mixture of water, the potassium iodide solution, and the chloroplatinic acid solution (20 : 9 : 1).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Spray the dry plate with *Spray reagent A,* and expose the plate to 365-nm UV light for 10 to 20 minutes. Dry the plate for 20 minutes between 80° and 90°, then spray the plate with *Spray reagent B*. Allow the plate to dry. Examine the plate and compare the intensities of any secondary spots observed in the chromatogram of the *Test solution* with those of the principal spots in the chromatograms of the *Standard solutions:* no spot from the chromatogram of the *Test solution* with an R_F value of between 0.10 to 0.25 and 0.27 to 0.41 is larger or more intense than that obtained from *Standard solution B* (0.2%).▲*USP29*

BRIEFING

Fluoxetine Delayed-Release Capsules, *USP 29* page 942. It is proposed to revise the *Detector sensitivity solution* preparation to ensure that the solution will have adequate concentration to meet the signal-to-noise ratio requirement specified in the monograph. It is proposed to implement this revision via the *Fourth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of August 1, 2006.

(MD-PP: R. Ravichandran) RTS—44019-1

Change to read:

Chromatographic purity—

Ion-pair solution—Dissolve about 6.5 g of sodium 1-octanesulfonate and 2.9 g of anhydrous sodium acetate in 1 L of water, and adjust with glacial acetic acid to a pH of 5.0.

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

Degraded fluoxetine solution—Dissolve a quantity of USP Fluoxetine Hydrochloride RS in 1.0 N sulfuric acid to obtain a solution containing about 2.2 mg per mL. Heat to 85° for 3 hours, and cool to room temperature.

Fluoxetine related compound solution—Dissolve a quantity of USP Fluoxetine Related Compound C RS in *Mobile phase* to obtain a solution containing about 0.5 mg per mL.

System suitability solution—Transfer about 13.5 mg of USP Fluoxetine Hydrochloride RS to a 100-mL volumetric flask, add 2 mL of *Degraded fluoxetine solution* and 2 mL of *Fluoxetine related compound solution,* and dissolve in and dilute with *Mobile phase* to volume. Transfer 10.0 mL of this solution to a 250-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Detector sensitivity solution—~~Transfer 1 mL of the *System suitability solution* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.~~

•Transfer 2 mL of the *System suitability solution* to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume.•[4]

Test solution—Weigh and finely powder not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of fluoxetine, to a 250-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Filter before injection.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L7. The column temperature is maintained at 30°. The flow rate is about 1 mL per minute. Inject the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.49 for α,α,α-trifluoro-*p*-cresol, 0.70 for fluoxetine related compound C, and 1.0 for fluoxetine; the resolution, *R,* between α,α,α-trifluoro-*p*-cresol and fluoxetine related compound C is not less than 2.0; and the resolution, *R,* between fluoxetine related compound C and fluoxetine is not less than 6.0. Chromatograph the *Detector sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the fluoxetine peak is not less than 10.

Procedure—Inject a volume (about 50 µL) of the *Test solution* into the chromatograph, record the chromatogram for at least three times the retention time of the fluoxetine peak, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$100(r_i / r_s)$$

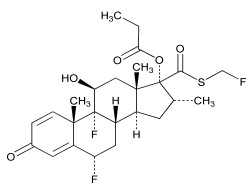
in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.2% of any individual impurity is found, and not more than 0.7% of total impurities is found.

BRIEFING

Fluticasone Propionate, *USP 29* page 960 and page 95 of *PF* 32(1) [Jan.–Feb. 2006]. On the basis of comments received, it is proposed to revise the upper limit for the drug substance in the Definition. The test for *Bromofluoromethane content* has also been deleted due to the unavailabilty of this reagent.

(AER: K. Zaidi) RTS—43189-1; 44078-1

Change to read:



$C_{25}H_{31}F_3O_5S$ 500.57

Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy-, (6α,11β,16α,17α)-*S*-(fluoromethyl) ester.

~~*S*-(Fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate~~

▲*S*-Fluoromethyl 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate▲*USP30*

[*80474-14-2*].

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Change to read:

» Fluticasone Propionate contains not less than 98.0 percent and not more than ~~100.5~~

■101.0■1S *(USP30)*
percent of $C_{25}H_{31}F_3O_5S$, calculated on the anhydrous,

▲solvent-free▲*USP30*
basis.

Delete the following:

~~■**Bromofluoromethane content**—~~

~~*Standard stock solution*—Transfer about 20 µL of bromofluoromethane to 10 mL of dimethylformamide, and mix. Dilute 10 µL of this solution with 1 mL of dimethylformamide (0.002% v/v).~~

~~*Standard solution*—Dilute 10 µL of *Standard stock solution* with 1 mL of dimethylformamide, and mix (0.00002% v/v).~~

~~*Test solution*—Dissolve 200 mg of Fluticasone Propionate in 1.0 mL of dimethylformamide.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with an electron-capture detector, a 0.32-mm × 25-m capillary column coated with a 5-µm film of phase G27 and a split injection system. The carrier gas is nitrogen, flowing at a rate of about 2.8 mL per minute. The make-up gas is nitrogen, flowing at a rate of 30 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at 40° for 3.5 minutes, then the temperature is increased at the rate of 30° per minute to 200°, and maintained at 200° for 10 minutes. The split injector (70 : 1) is maintained at a temperature of 85°, and the detector temperature is maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure.*~~

~~*Procedure*—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and measure the responses for the bromofluoromethane peaks. The intensity of bromofluoromethane peak in the chromatogram of the *Test solution* is less than the intensity of bromofluoromethane peak in the chromatogram of the *Standard solution.*~~■1S *(USP30)*

Change to read:

Content of acetone—
Internal standard solution—Prepare a 0.05% (v/v) solution of tetrahydrofuran in dimethylformamide.

Standard solution—Prepare 0.05% (v/v) of acetone in *Internal standard solution*.

Test solution—Dissolve an accurately weighed quantity of Fluticasone Propionate in *Internal standard solution* to obtain a solution having a concentration of about 50 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 25-m column coated with a 2-µm film of phase G15, and a splitless injector system. The carrier gas is nitrogen or helium, flowing at a rate of about 5.5 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at 60° for 3.5 minutes, then the temperature is increased at the rate of 30° per minute to 180°, and maintained at 180° for 3 minutes. The splitless injector temperature is maintained at 150°, and the detector temperature is maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections

▲of the *Standard solution*▲*USP30*
is not more than 5.0%.

Procedure—Separately inject equal volumes (about 0.1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and record the peak responses. Calculate the percentage of acetone (w/w) in the portion of Fluticasone Propionate taken by the formula:

$$0.05D/C(R_U/R_S)$$

in which D is the density of acetone at 20°; C is the concentration, in g per mL, of Fluticasone Propionate in the *Test solution;* and R_U and R_S are the ratios of the acetone peak response to the tetrahydrofuran peak response obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.0% (w/w) is found.

Change to read:

Assay—
0.01 M Monobasic ammonium phosphate buffer, pH 3.5—Dissolve ~~11.5 g~~

▲1.15 g▲*USP30*
of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.5 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *0.01 M Monobasic ammonium phosphate buffer, pH 3.5,* and acetonitrile (50 : 35 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve approximately ~~2.0 mg~~

▲2.5 mg▲*USP30*
of USP Fluticasone Propionate Resolution Mixture RS in 50 mL of *Mobile phase.*

Standard preparation—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Fluticasone Propionate in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a concentration of about 0.04 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Resolution solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 1.10 for fluticasone propionate related compound D and 1.0 for fluticasone propionate; and the resolution, *R,* between fluticasone propionate and fluticasone propionate related compound D is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the relative standard deviation for replicate injections

▲of the *Standard preparation*▲*USP30*
is not more than 2%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{31}F_3O_5S$ in the portion of Fluticasone Propionate taken by the formula:

$$CV(r_U/r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in mg per mL, in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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BRIEFING

Fluticasone Propionate Nasal Spray, page 97 of *PF* 32(1) [Jan.–Feb. 2006]. It is proposed to revise the tests for *Delivered dose uniformity* (within container) to specify correct concentrations of the components of the *Resolution solution.*

(AER: K. Zaidi) RTS—44076-1

Add the following:

■Fluticasone Propionate Nasal Spray

» Fluticasone Propionate Nasal Spray is a white, opaque suspension of fluticasone propionate in water. It is supplied in a form suitable for nasal administration. It contains not less than 95.0 percent and not more than 115.0 percent of the labeled amount of fluticasone propionate ($C_{25}H_{31}F_3O_5S$).

Packaging and storage—Preserve in tight, light-resistant containers. Store between 4° and 30°.

USP Reference standards ⟨11⟩**—***USP Fluticasone Propionate RS. USP Fluticasone Propionate Related Compound D RS. USP Fluticasone Propionate Related Compound F RS. USP Phenylethyl Alcohol RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩—

Test specimen—Transfer about 30 g of Nasal Spray equally into two 50-mL centrifuge tubes. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. Add 10 mL of water to each tube, insert the stopper, and shake vigorously for 2 minutes. Centrifuge at 3500 rpm for 10 minutes, and discard the supernatant. To one tube add 10 mL of methanol. Shake to disperse the residue, and transfer to the other tube. Shake the other tube for 1 minute. Centrifuge at 3500 rpm for 10 minutes. Decant the supernatant into an agate mortar. Evaporate the methanol either by carefully blowing dry with compressed air or nitrogen, or by allowing the methanol to evaporate naturally. If using an air or nitrogen line, use a suitable in-line filter to avoid contamination. Allow the residue to dry overnight in a desiccator over silica gel.

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

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.* The total aerobic microbial count does not exceed 100 cfu per g, and the total combined molds and yeasts count does not exceed 50 cfu per g.

pH ⟨791⟩**:** between 5.0 and 7.0.

Particle size—Remove the pump system after shaking the test bottle to ensure product uniformity. Transfer 1 drop of the Nasal Spray onto a clean microscope slide. Examine 10 random fields of view on the slide using 400 × magnification. Record the number of individual particles that are less than 5 µm in diameter: not less than 98% by number. Record the number of individual particles that are greater than 5 µm in diameter but less than 15 µm in diameter: not more than 1.8% by number. Record the number of individual particles that are greater than 15 µm in diameter: not more than 0.2% by number.

Foreign particulates—Shake the required number of bottles to ensure uniformity. Remove the pump system carefully to minimize contamination of the sample. Collect about 100 g of Nasal Spray, and pass it through a wetted 250-µm screen. Rinse each bottle with a portion of water equal to twice the volume of each bottle. Pass the rinse through the 250-µm screen. Visually observe the screen and filtrate for any foreign

particulates. Also examine the screen under a microscope using transmitted light: free from any visible foreign particulates greater than 250 µm.

Delivered dose uniformity (within container)—

Diluent, 0.01 M Monobasic ammonium phosphate buffer, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Resolution solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS and USP Fluticasone Propionate Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution ~~having a known concentration of about 4 µg per mL of each~~ containing 4 µg per mL of USP Fluticasone Propionate RS and 0.4 µg per mL of USP Fluticasone Propionate Related Compound D RS.

Standard solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in *Diluent* to obtain a solution having a known concentration of about 4 µg per mL.

Test solution—Wipe the pump clean. ~~and record the weight of the bottle prior to actuation.~~ Shake the bottle for 30 seconds, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations (1 dose) into the flask. Turn the flask to the upright position immediately after each actuation. Insert the stopper into the flask after collecting two actuations. ~~Weigh the bottle after sample collection.~~ Discharge actuations 3 to 48 (50-spray pack) or 3 to 118 (120-spray pack) to waste. Wipe the bottle clean, and ~~record the weight of the bottle. Collect~~ collect the last two actuations (49 and 50 or 119 and 120) in a second 25-mL volumetric flask. Turn the flask to the upright position immediately after each actuation, ~~Insert the stopper into the flask,~~ and insert the stopper into the flask. ~~and record the weight of the bottle.~~ Add 20 mL of the *Diluent* to each flask, and shake well for 10 minutes to disperse the suspension. Dilute with *Diluent* to volume, and mix thoroughly. Allow the flask to stand until the excipients have settled. Transfer a portion of the clear supernatant to an HPLC vial, and inject. Repeat this procedure with 4 additional bottles.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of $C_{25}H_{31}F_3O_5S$ per dose taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in µg per mL, in the *Standard solution; V* is the total volume of *Test solution,* in mL; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. The mean dose delivered from 10 doses is within 85% to 115% of the label claim. Not more than 1 dose is outside 80% to 120% of the label claim. No doses are outside 75% to 125% of the label claim. Test an additional 10 bottles if 2 or 3 doses are outside $\pm$20% of the label claim. The mean dose delivered from ~~30~~ 20 doses should be within 85% to 115% of the label claim. Not more than 3 doses are outside 80% to 120% of the label claim. No doses are outside 75% to 125% of the label claim.

Delivered dose uniformity (within batch)—

Diluent, 0.01 M Monobasic ammonium phosphate buffer, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Resolution solution—Prepare as directed in the test for *Delivered dose uniformity* (within container).

Standard solution—Prepare as directed in the test for *Delivered dose uniformity* (within container).

Test solution—Wipe the pump clean. ~~and record the weight of the bottle prior to actuation.~~ Shake the bottle for 30 seconds, and mechanically prime the bottle. Hold a 25-mL volumetric flask in an inverted position, and discharge the first two actuations into the flask. Turn the flask to the upright

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position immediately after each actuation. Insert the stopper into the flask after collecting two actuations (1 dose). Repeat this procedure with 9 additional bottles.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of $C_{25}H_{31}F_3O_5S$ per dose taken by the formula:

$$CV(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in µg per mL, in the *Standard solution; V* is the total volume of *Test solution,* in mL; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. The mean dose delivered from 10 doses is within 85% to 115% of the label claim. Not more than 1 dose is outside 80% to 120% of the label claim. No doses are outside 75% to 125% of the label claim. Test an additional 20 bottles if 2 or 3 doses are outside ±20% of the label claim. The mean dose delivered from the two actuations at the beginning of the 30 bottles (30 doses) is within 85% to 115% of the label claim. Not more than 3 doses are outside 80% to 120% of the label claim. No doses are outside 75% to 125% of the label claim.

Related compounds—

Solution A—Prepare a mixture of methanol and acetonitrile (77 : 23).

0.01 M Monobasic ammonium phosphate buffer—Dissolve 1.15 g of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.4 ± 0.1, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and *0.01 M Monobasic ammonium phosphate buffer* (60 : 40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of acetonitrile and 0.001 M hydrochloric acid (60 : 40).

Control solution—Prepare a solution in a mixture of *Diluent* and water (4 : 1) containing about 0.5 mg per mL of USP Phenylethyl Alcohol RS and 0.08 mg per mL of benzalkonium chloride.

System suitability solution—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS, USP Fluticasone Related Compound D RS, USP Fluticasone Propionate Related Compound F RS, and USP Phenylethyl Alcohol RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 100 µg per mL, 1.0 µg per mL, 1.0 µg per mL, and 500 µg per mL of each Reference Standard, respectively.

Test solution—Transfer accurately about 1.0 g of the Nasal Spray to a 5-mL volumetric flask, dissolve in and dilute with *Diluent* to volume. Shake the flask vigorously to dissolve. Pass through a 0.5-µm porosity filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The column is maintained at a temperature of 40°. Chromatograph the *System suitability solution,* and measure the peak responses as directed for *Procedure:* the resolution, *R,* between fluticasone propionate related compound F and phenylethyl alcohol is not less than 1.5; the resolution, *R,* between fluticasone propionate related compound D and fluticasone propionate is not less than 2; and the relative retention times and limits are as provided in *Table 1.*

Procedure—Separately inject a volume (about 50 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Nasal Spray taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks, excluding the peaks obtained from the *Control solution.*

Content of phenylethyl alcohol—

Diluent, Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Phenylethyl Alcohol RS in *Diluent* to obtain a solution having a known concentration of about 50 µg per mL.

Test solution—Use the *Assay preparation.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg per g, of phenylethyl alcohol in the portion of Nasal Spray taken by the formula:

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

in which C is the concentration, in mg per mL, of the USP Phenylethyl Alcohol RS in the *Standard solution;* W_U is the weight, in g, of the Nasal Spray taken to prepare the *Test solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively. For 50 sprays: not less than 1.75 mg per g and not more than 2.63 mg per g. For 120 sprays: not less than 1.88 mg per g and not more than 2.63 mg per g.

Content of benzalkonium chloride—

Citric acid buffer solution—Dissolve 50 g of citric acid in 200 mL of water. Adjust the solution with 2 N sodium hydroxide to a pH of 3.5 ± 0.05.

Docusate sodium titrant—Dissolve 0.22 g of docusate sodium in 100 mL of warm water, and dilute with water to make 1000 mL.

Eosin Y indicator—Dissolve about 25 mg of eosin Y in 50 mL of acetone. Add 450 mL of chloroform and 5.0 ± 0.5 g of citric acid. Shake thoroughly until no discoloration occurs. Filter the mixture to remove any undissolved citric acid. Store in an amber bottle.

Table 1

Compound	Approximate Relative Retention Time	Limit (%)
S-Fluoromethyl 17α-acetyloxy-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate/ *S*-Fluoromethyl 9α-fluoro-11β-hydroxy-16α-methyl-3,6-dioxo-17α-propionyloxyandrosta-1,4-diene-17β-carbothioate	0.7	0.3
Fluticasone propionate related compound D	1.1	0.3
6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic acid 6α,9α-difluoro-17β-(fluoromethylthio)carbonyl-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl ester	2.1	0.3
Unknown impurities	—	0.2
Total	—	1.5

Benzalkonium chloride standard stock solution—Use 50% (w/v) solution of benzalkonium chloride.*

Benzalkonium chloride standard solution—Transfer accurately about 0.4 g of *Benzalkonium chloride standard stock solution* to a 1000-mL volumetric flask. Dilute with water to volume, and mix. Sonicate for 5 minutes to dissolve.

Procedure—Pipet 10 mL of *Benzalkonium chloride standard solution* into a 250-mL glass-stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator,* and 2 mL of *Citric acid buffer solution.* Insert the stopper into the flask, and shake, releasing any build-up of pressure. Titrate with *Docusate sodium titrant* with vigorous shaking to a point when pink coloration is discharged from the chloroform layer. Perform a blank determination, substituting 10 mL of water for the *Benzalkonium chloride standard solution,* and make any necessary correction (see *Titrimetry* ⟨541⟩). Calculate the titer value of the *Docusate sodium titrant,* in µg of benzalkonium chloride per mL of *Docusate sodium titrant,* by the formula:

$$W_B / V_D$$

in which W_B is the weight, in µg, of benzalkonium chloride titrated; and V_D is the volume, in mL, of *Ducosate sodium titrant.* Transfer accurately about 10 g of Nasal Spray into a 250-mL glass-stoppered flask containing 40 mL of water, 5 mL of *Eosin Y indicator,* and 2 mL of *Citric acid buffer solution.* Repeat the procedure as given above for *Benzalkonium chloride standard solution.* To clarify the endpoint, place the flask in an ultrasonic bath for 1 to 2 minutes to separate the chloroform layer from the aqueous phase. Perform a blank determination. Calculate the concentration of benzalkonium chloride, in µg per g, in the portion of Nasal Spray taken by the formula:

$$TV/W$$

in which T is the titer value of *Ducosate sodium titrant; V* is the volume, in mL, of the *Docusate sodium titrant* used in the titration of the Nasal Spray; and W is the weight, in g, of the portion of Nasal Spray taken: not less than 160 µg per g and not more than 210 µg per g.

Assay—

Diluent—Prepare a mixture of acetonitrile and 0.001 M hydrochloric acid (60 : 40).

0.01 M Monobasic ammonium phosphate buffer—Dissolve 1.15 g of monobasic ammonium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 3.5 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *0.01 M Monobasic ammonium phosphate buffer,* and acetonitrile (50 : 35 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve accurately weighed quantities of USP Phenylethyl Alcohol RS, USP Fluticasone Propionate RS, and USP Fluticasone Propionate Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 50 µg per mL, 10 µg per mL, and 1 µg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Fluticasone Propionate RS in *Diluent* to obtain a solution having a known concentration of about 10 µg per mL.

Assay preparation—Transfer accurately about 1.0 g of the Nasal Spray to a 50-mL volumetric flask, add about 40 mL of *Diluent,* and sonicate the flask for 10 minutes. Dilute with *Diluent* to volume, and shake. Allow to stand for about 10 minutes until the supernatant is a clear solution. Inject the clear supernatant into the chromatograph.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 4.6-mm × 25-cm column that contains 5-µm packing L1, and a programmable variable wavelength detector capable of monitoring at 210 nm and 239 nm. The flow rate is about

* A suitable grade is available from Merck, Germany (www.merck.-com).

1.5 mL per minute. The column is maintained at a temperature of 40°. Chromatograph the *Resolution solution* and the *Standard preparation,* record the peak areas at 210 nm for 5 minutes, then change the wavelength to 239 nm and record the peak areas: the relative retention times are about 0.42 for phenylethyl alcohol, 1.0 for fluticasone propionate, and 1.10 for fluticasone propionate related compound D; the resolution, *R,* between fluticasone propionate and fluticasone propionate related compound D is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of fluticasone propionate ($C_{25}H_{31}F_3O_5S$) in the portion of Nasal Spray taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration of USP Fluticasone Propionate RS, in mg per mL, in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

BRIEFING

Fluvoxamine Maleate, *USP 29* page 964. On the basis of comments received, it is proposed to delete the redundant *Maleic acid* content test performed by nonaqueous titration. The *Maleic acid* content requirement as stated in the monograph is inconsistent and larger than the range stated in the Definition. Also, a *Note* has been added to clarify the purpose of including relative retention times in *Table 1*, which is included in the *Related compounds* test (see page 965 of *USP 29*).

(MD-PP: R. Ravichandran) RTS—43037-1

Delete the following:

~~■**Maleic acid**—Transfer about 800.0 mg of Fluvoxamine Maleate, accurately weighed, to a 250-mL conical flask containing 50 mL of water. Titrate with 0.1 N sodium hydroxide VS, using 0.5 mL of phenolphthalein TS as the indicator. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N sodium hydroxide VS is equivalent to 5.805 mg of maleic acid ($C_4H_4O_4$). Between 26.0% and 27.5% of maleic acid is found.~~ ■1S (*USP30*)

Change to read:

Assay—

Buffer solution—Dissolve about 5 g of 1-pentanesulfonic acid sodium salt and 0.7 g of monobasic potassium phosphate in 620 mL of water. Adjust with phosphoric acid to a pH of 3.00 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (62 : 38). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Transfer about 6 mg of Fluvoxamine Maleate to a 50-mL volumetric flask. Heat the sample at 120° for 10 minutes. Cool down to room temperature, and add 3.0 mL of 0.1 N hydrochloric acid. Heat the solution in a water bath for 10 minutes. Cool down to room temperature, add 50 mg of Fluvoxamine Maleate, and dissolve in 25 mL of *Mobile phase.* Dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Fluvoxamine Maleate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay stock preparation—Transfer an accurately weighed quantity of about 50 mg of Fluvoxamine Maleate to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer 5.0 mL of the *Assay stock preparation* to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 234-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.7 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.2 for maleic acid, 0.5 for 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone (*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime, 0.8 for the *Z*-isomer, and 1.0 for fluvoxamine maleate;~~

■ ■1S (*USP30*)
the resolution, *R,* between the *Z*-isomer and fluvoxamine maleate is not less than 3.0 and not less than 5.0 between 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime and the *Z*-isomer. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

■[NOTE—For the purpose of peak identification, the approximate relative retention times are given in *Table 1.*] ■1S (*USP30*)

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the

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responses for the fluvoxamine maleate peaks. Calculate the quantity, in mg, of $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ in the portion of Fluvoxamine Maleate taken by the formula:

$$1000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Fluvoxamine Maleate RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Indinavir Sulfate, *USP 29* page 1118. On the basis of new information and supporting data received, three revisions have been proposed: (1) It is proposed to modify the procedure in the test for *Heavy metals* ⟨231⟩, because there is a matrix effect on *Method 1* for this drug substance. This proposed revision is consistent with the New Drug Application (NDA) submission. The revision also attempts to harmonize the texts of this procedure found in *USP* and in the *European Pharmacopoeia.* (2) In the test for *Chromatographic purity,* it is proposed to move *Table 1* from the *Chromatographic system* section to the *Procedure* section. The rationale is that, although *Table 1* lists five related compounds, with corresponding relative retention times based on the indinavir peak at about 21 to 26 minutes, the *System suitability solution* does not contain all these components. The related compounds shown in the table are for information and not part of the system suitability requirement. (3) In the *Assay,* it is proposed to revise the pH range for the *Dibutyl ammonium phosphate buffer* used in the preparation of the *Mobile phase.*

(MD-AA: B. Davani) RTS—43721-1

Delete the following:

■~~**Heavy metals,** *Method 1* ⟨231⟩: 0.001%.~~ ■1S (*USP30*)

Add the following:

■**Heavy metals** ⟨231⟩—

Standard solution—Into a 50-mL color-comparison tube, pipet 2 mL of *Standard Lead Solution* (10 µg per mL), and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as an external indicator, adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Test solution—In a 50-mL color-comparison tube, dissolve 2.0 g of Indinavir Sulfate in 25 mL of water. Using a pH meter or a suitable short-range pH indicator paper as an external indicator, adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Blank solution—To a 50-mL color-comparison tube, add 25 mL of water. Using a pH meter or a suitable short-range pH indicator paper as an external indicator, adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Procedure—To each tube, add 10 mL of hydrogen sulfide TS, mix, allow to stand for 5 minutes, and view downward over a white surface: the color of the *Test solution* is not darker than that of the *Standard solution*. The intensity of the color of the *Blank solution* is less than or equal to the intensity of that of the *Test solution.* ■1S (*USP30*)

Change to read:

Chromatographic purity—

Solution A—Dissolve 0.54 g of monobasic potassium phosphate and 2.79 g of dibasic potassium phosphate in 2 L of water.

Solution B—Use acetonitrile.

Diluent—Prepare a mixture of *Solution A* and *Solution B* (1 : 1).

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

System suitability solution—Transfer about 40 mg of USP Indinavir System Suitability RS to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 50 mg of Indinavir Sulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–40	80→30	20→70	linear gradient
40–45	30	70	isocratic
45–47	30→80	70→20	linear gradient
47–52	80	20	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times, based on the indinavir peak at about 21 to 26 minutes, are listed in *Table 1;*~~

■ ■1S (*USP30*)

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the resolution, *R,* between indinavir and related compound C is greater than 1.8; and the tailing factor, determined from the indinavir peak, is greater than 0.95 and less than 2.0.

~~Table 1~~

~~Indinavir Related Compound~~	~~Approximate Relative Retention Time~~
~~A~~	~~0.18~~
~~B~~	~~0.80~~
~~C~~	~~0.98~~
~~D~~	~~1.14~~
~~E~~	~~1.30~~

■■1S (*USP30*)
Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Indinavir Sulfate taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak area response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 0.1% of any individual impurity specified in *Table 1* is found; and not more than 0.5% of total impurities is found.

■

Table 1

Indinavir Related Compound	Approximate Relative Retention Time
A	0.18
B	0.80
C	0.98
D	1.14
E	1.30

■1S (*USP30*)

Change to read:

Assay—

Dibutylammonium phosphate buffer—Transfer 20 mL of dibutyl ammonium phosphate to 1000 mL of water. While stirring, adjust with sodium hydroxide TS to a pH of 6.5 ± ~~0.05~~

■0.5.■1S (*USP30*)
Mobile phase—Prepare a filtered and degassed mixture of *Dibutylammonium phosphate buffer* and acetonitrile (11 : 9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve a suitable quantity of USP Indinavir RS, accurately weighed, in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 60 mg of Indinavir Sulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 4000 theoretical plates; the tailing factor is less than 2.0; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{36}H_{47}N_5O_4 \cdot H_2SO_4$ in the portion of Indinavir Sulfate taken by the formula:

$$(1.1598)DC(r_U/r_S)$$

in which D is the dilution factor, in mL, for the *Assay preparation; C* is the concentration, in mg per mL, of USP Indinavir RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. [NOTE—1.1598 = Indinavir Sulfate MW (711.87 g/mol)/Indinavir MW (613.80 g/mol).]

BRIEFING

Lamivudine, *USP 29* page 1225. It is proposed to specify the concentration of USP Lamivudine Resolution Mixture B RS used in the *System suitability solution* in the *Assay.*

(MD-AA: B. Davani) RTS—43858-1

Change to read:

Assay—

0.025 M Ammonium acetate solution—Transfer about 1.9 g of ammonium acetate to a 1000-mL volumetric flask, dissolve in about 900 mL of water, adjust with acetic acid to a pH of 3.8 ± 0.2, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.025 M Ammonium acetate solution* and methanol (95 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—~~Dissolve the contents of 1 vial of USP Lamivudine Resolution Mixture B RS in 2 mL of *Mobile phase.*~~

■Dissolve an accurately weighed quantity of USP Lamivudine Resolution Mixture B RS in *Mobile phase* to obtain a solution having a known concentration of about 0.25 mg per mL.■1S (*USP30*)

Standard preparation—Dissolve an accurately weighed quantity of USP Lamivudine RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.25 mg per mL.

Assay preparation—Transfer about 25 mg of Lamivudine, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 277-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 35°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between lamivudine and lamivudine diastereomer is not less than 1.5. [NOTE—The relative retention times are about 1.0 for lamivudine and 0.9 for lamivudine diastereomer.] Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

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Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the lamivudine peaks. Calculate the quantity, in mg, of $C_8H_{11}N_3O_3S$ in the portion of Lamivudine taken by the formula:

$$100C(r_U/r_S)$$

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

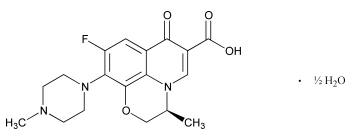
BRIEFING

Levofloxacin. Because there is no existing *USP* monograph for this drug substance, a new monograph based on the submitted data is being proposed. The HPLC procedures used in the test for *Related compounds* and in the *Assay* are based on analysis performed with a YMC-OD-A brand of L1 column. The HPLC procedure used in the test for *Enantiometric purity* is based on analysis performed with a Symmetry Shield RP18 brand of L1 column.

(MD-AA: B. Davani) RTS—43750-1

Add the following:

■Levofloxacin



$C_{18}H_{20}FN_3O_4 \cdot ½H_2O$ 370.38

7*H*-Pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo hydrate (2 : 1), (*S*)-.

(–)-(*S*)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid, hemihydrate [*138199-71-0*].

Anhydrous 361.37 [*100986-85-41*].

» Levofloxacin contains not less than 98.0 percent and not more than 102.0 percent of $C_{18}H_{20}FN_3O_4$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩**—***USP Levofloxacin RS. USP Levofloxacin Related Compound A RS. USP Levofloxacin Related Compound B RS. USP Ofloxacin RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Water, *Method I* ⟨921⟩**:** between 2.0% and 3.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

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

Related compounds—[NOTE—Solutions of Levofloxacin are not stable in light; use amber bottles.]

Solution A, Solution B, Mobile phase, and *System suitability preparation*—Prepare as directed in the *Assay.*

Levofloxacin stock solution—Dissolve an accurately weighed quantity of about 10 mg of USP Levofloxacin RS in 2 mL of acetonitrile, sonicate, and quantitatively dilute with water to 25 mL. Transfer 5 mL of this solution to a 100-mL volumetric flask, dilute with a mixture of acetonitrile and water (1 : 10) to volume, and mix.

Levofloxacin related compound B stock solution—Dissolve an accurately weighed quantity of about 10 mg of USP Levofloxacin Related Compound B RS in methanol, sonicate, and quantitatively dilute with methanol to 50 mL. Transfer 2 mL of this solution to a 10-mL volumetric flask, dilute with methanol to volume, and mix.

Standard solution—Transfer 2 mL each of *Levofloxacin stock solution* and *Levofloxacin related compound B stock solution* into the same 100-mL volumetric flask, dilute with a

mixture of acetonitrile and water (1 : 10) to volume, and mix.

Test solution—Transfer about 10 mg of Levofloxacin, accurately weighed, to a 25-mL volumetric flask, dissolve in 2 mL of acetonitrile, sonicate, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to program the chromatograph as follows in *Table 1*.

Table 1

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibrium
0–5	100	0	isocratic
5–10	100→82	0→18	linear gradient
10–15	82→40	18→60	linear gradient
15–30	40	60	isocratic
30–30.1	40→100	60→0	step gradient
30.1–38	100	0	re-equilibration

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of levofloxacin related compound B in the portion of Levofloxacin taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Levofloxacin Related Compound B RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Levofloxacin in the *Test solution;* r_U is the peak response for levofloxacin related compound B obtained from the *Test solution;* and r_S is the peak response for levofloxacin obtained from the *Standard solution*. Calculate the percentage of other levofloxacin related compounds or impurities in the portion of Levofloxacin taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Levofloxacin RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Levofloxacin in the *Test solution;* r_U is the peak response for levofloxacin related compound obtained from the *Test solution;* and r_S is the peak response for levofloxacin obtained from the *Standard solution*. The limits of related compounds or impurities meet the requirements specified in *Table 2.*

Table 2

Related Compound/ Impurity	Relative Retention Time	Limit (%)
A	0.9	0.20
B	2.9	0.13
Any other impurity	—	0.1
Total impurities	—	0.50

Enantiomeric purity—

Buffer solution—Dissolve 1.32 g of D-phenylamine and 0.75 g of copper(II)sulfate pentahydrate in about 500 mL of water, dilute with water to 1000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (85 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve in and dilute accurately weighed quantities of USP Ofloxacin RS and USP Levofloxacin RS with water to obtain a solution having a final concentration of about 0.01 mg of each per mL.

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Test solution—Transfer about 20 mg of Levofloxacin, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 2 mL into a 10-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 294-nm detector and 4.6-mm × 15-cm column that contains 3.5-µm packing L1. The flow rate is about 0.7 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between D-ofloxacin and levofloxacin is not less than 2.0. [NOTE—The relative retention times are about 0.91 for D-ofloxacin and 1.0 for levofloxacin.]

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for all the peaks. Calculate the percentage of D-ofloxacin in the portion of Levofloxacin taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 1.0% of D-ofloxacin is found.

Assay—

Buffer solution—Dissolve 3.08 g of ammonium acetate and 8.43 g of sodium perchlorate monohydrate in about 500 mL of water, and dilute with water to 1000 mL. Adjust with phosphoric acid to a pH of 2.2, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution A—Prepare a mixture of *Buffer solution* and acetonitrile (84 : 16).

Solution B—Prepare a mixture of *Buffer solution,* acetonitrile, and methanol (50 : 30 : 20).

Solution C—Transfer about 10 mg of USP Levofloxacin RS to a 25-mL volumetric flask, dissolve in 2 mL of acetonitrile, dilute with water to volume, and mix.

Solution D—Transfer about 5.0 mg of USP Levofloxacin Related Compound A RS to a 100-mL volumetric flask, dissolve in and dilute with 0.2% ammonium hydroxide in methanol to volume, and mix.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system* (see *Table 3*).

Table 3

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–5	100	0	isocratic
5–10	100→82	0→18	linear gradient
10–15	82→40	18→60	linear gradient
15–15.1	40→100	60→0	step gradient
15.1–20	40→100	60→0	re-equilibration

System suitability preparation—Transfer 5 mL of *Solution C* and 2 mL of *Solution D* to a 20-mL volumetric flask, dilute with water to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Levofloxacin RS in 2 mL of acetonitrile, sonicate, and dilute quantitatively, and stepwise if necessary, with a mixture of acetonitrile and water (1 : 10) to obtain a solution having a known concentration of about 0.02 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Levofloxacin in 2 mL of acetonitrile, sonicate, and dilute quantitatively, and stepwise if necessary, with a mixture of acetonitrile and water (1 : 10) to obtain a solution having a known concentration of about 0.02 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and 4.0-mm × 15-cm column that contains 3.0-µm packing

L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 38°. The chromatograph is programmed as shown in *Table 3.* Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between levofloxacin related compound A and levofloxacin is not less than 3.0; and the relative standard deviation for replicate injections for levofloxacin is not more than 2.0%. [NOTE—The relative retention times are about 0.9 for levofloxacin related compound A and 1.0 for levofloxacin.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{18}H_{20}FN_3O_4$ in the portion of Levofloxacin taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Levofloxacin RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

BRIEFING

Lipid Injectable Emulsion, page 416 of *PF* 31(2) [Mar.–Apr. 2005]. It is proposed to revise the lower limit of the concentration range of phospholipids in the Definition to reflect FDA-approved product specifications. Secondly, as the fatty acid composition of a given emulsion may vary, especially in oil mixtures, the test for *Fatty acid composition* has been revised to identify the individual profiles of each oil prior to emulsification. Finally, the mean droplet diameter has been changed to a universal limit of less than 500 nm, or 0.5 µm, as detailed in *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩ on page 1451 of *PF* 31(5) [Sept.–Oct. 2005].

(PPI: J. Kelly) RTS—43584-1

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Add the following:

■Lipid Injectable Emulsion

» ~~Lipid Injectable Emulsion is a sterile 10 percent, 20 percent, or 30 percent w/v oil in water emulsion in a vehicle containing glycerol in Water for Injection. The oils are Soybean Oil, Safflower Oil, Olive Oil, Medium Chain Triglycerides, or other suitable nutritional oils, or a mixture of these oils. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of the oil. It contains no antimicrobial agents. It contains Egg Phospholipids as an emulsifying agent.~~ Lipid Injectable Emulsion used in total parenteral nutrition is a sterile 10 ~~percent~~ (0.10 g per mL), 20 ~~percent~~ (0.20 g per mL), or 30 percent (0.30 g per mL) w/v emulsion in a vehicle. The vehicle contains 2.25 percent to 2.5 percent w/v Glycerin and ~~0.6 percent~~ 0.74 percent to 1.8 percent w/v parenteral Egg Phospholipids in Water for Injection. The principal oil used is Soybean Oil, which provides an ample supply of the essential fatty acids: linoleic acid and linolenic acid. Other oils, such as Safflower Oil, Medium-Chain Triglycerides, Olive Oil, Fish Oil, ~~Containing Omega-3 Acids,~~ or other suitable oils, can be mixed with Soybean Oil. Hence, Soybean Oil can be the only oil or be part of a mixture ~~containing~~ of these other oils. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of the oils. It contains no antimicrobial agents. The final products are terminally sterilized.

Packaging and storage—~~Preserve in a single-dose, glass container or glass *Pharmacy Bulk Package* (see *Injections* ⟨1⟩). Use elastomeric closures that are compatible with both the oil and water phases of the Emulsion. Store at controlled room temperature, and protect from freezing.~~ Preserve in a single-dose, Type I or Type II glass container or glass *Pharmacy bulk package* (see *Injections* ⟨1⟩). Use elastomeric closures that are compatible with both the oil and water phases of the Emulsion. Store at a temperature not below 4° (protect from freezing) or above 30° (protect from excessive heat).

Labeling—The label states the identity and the quantities of the specific oils in the Emulsion. The label states the total ~~osmolal~~ osmolar concentration (or osmolarity) in ~~mOsmol~~ mOsm per ~~kg.~~ L. The labeling provides the following information: do not use if there is evidence of excessive creaming or aggregation, if excessive free oil droplets are visible, or if there ~~are other forms of phase separation indicating that the stability of the product has been compromised.~~ are other indications of compromised integrity, such as microbial growth, present in the product.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Particle Count RS.*

Fatty acid composition—Transfer a volume of the Emulsion, equivalent to about 200 mg of lipids, to a stoppered extraction vessel, add 10 mL of ether, and mix. Add 5 g of anhydrous sodium sulfate, mix, and allow the mixture to stand until separation of the layers is complete. Wet the packing of a chromatographic silica cartridge with a few mL of ether, transfer about 5 mL of the ether layer from the extraction vessel to the column reservoir, and elute at a rate of between 5 and 10 drops per minute into a suitable vessel. Evaporate the ether from the eluant, and dissolve the residue in 5.0 mL of toluene. Transfer 1.0 mL of the toluene solution to a reaction vial, and add 0.4 mL of (*m*-trifluoromethylphenyl) trimethylammonium hydroxide in methanol. Cover, mix, and allow to stand for 30 minutes. Inject about 1 µL of this solution into a ~~gas ionization detector and~~ gas chromatograph equipped with a 0.53-mm × 50-m wide-bore, fused-silica capillary column coated with a 2.0-µm thickness of liquid phase G16 and maintained at a temperature of 200°. Helium is used as the carrier gas at a flow rate of about 10 mL per minute. Measure the ~~five~~ main peak areas of the methyl esters of the fatty acids. ~~The order of elution is palmitate, stearate, oleate, linoleate, and linolenate: their~~ The relative peak areas expressed as a percentage of the ~~five~~ main peaks are in the known ranges for the ~~oils or mixtures of oils~~ oil (e.g., Soybean Oil, USP; Safflower Oil, USP) as specified on the label. For oil mixtures, analysis of each oil should be performed to identify known peaks prior to emulsification as specified on the label.

Bacterial endotoxins ⟨85⟩—It contains not more than 0.5 USP Endotoxin Unit per mL.

pH ⟨791⟩**:** between 6.0 and 9.0.

Globule size limits—Lipid Injectable Emulsion meets the requirements of the limits specified in both *Method I* and *Method II* as directed under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩.

Limit of oil droplet mean diameters (See *Method I—Light Scattering Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light scattering, determine the mean droplet diameter (MDD): the sample meets the requirements. The intensity-weighted mean droplet diameter (MDD) for Lipid Injectable Emulsion must be ≤500 nm, or 0.5 µm, irrespective of the concentration of the dispersed lipid phase.

Limit of large globule volume-diameter (See *Method II—Light Obscuration or Extinction Method* under *Globule Size Distribution in Lipid Injectable Emulsions* ⟨729⟩)—Using the method of light obscuration, determine the size distribution of globules in the large-diameter tail of the dispersion (detection threshold ≥2.0 µm). Calculate the volume-weighted mass of lipid in the form of globules with diameters in excess of 5.0

μm per 100 mL of Emulsion. This mass does not exceed 0.05% of the dispersed phase that is ≥5.0 μm from the nominal lipid concentration stated on the label.

~~**Particulate matter** ⟨788⟩: meets the requirements for *Large Volume Injections* for single dose infusion.~~

Limit of free fatty acid—

Solvent—Prepare a mixture of heptane, isopropanol, and water (400 : 400 : 200) in a separatory funnel. Allow the phases to separate, and discard the lower phase. Filter the upper phase (heptane solution) through 40 g of anhydrous sodium sulfate. Store in a tightly-capped glass container, and use within 1 week.

Chromatographic column—Prepare a slurry of heptane and chromatographic silica gel having an average pore size of 6 nm, and activate at a temperature of 110° for not less than 1 hour prior to use. Transfer the slurry to a 2.3-cm chromatographic tube (see *Column Chromatography* under *Chromatography* ⟨621⟩), and pack to a bed height of between 5 cm and 6 cm. Wash the column with about 40 mL of heptane, and drain the heptane through the column to a level of about 0.5 cm above the silica gel bed.

Procedure—Transfer 20.0 mL of the Emulsion to a flask, freeze, and lyophilize. Dissolve the residue in ~~3 mL~~ 30 mL of *Solvent,* and transfer the solution to the column. Rinse the flask with three 30-mL portions of *Solvent,* and transfer the washings to the column, allowing each rinsing to drain to the top of the column bed before applying the next rinse. Collect a total of 120 mL of effluent. Add 10 drops of phenolphthalein TS to the effluent, bubble nitrogen through the solution, and titrate with 0.02 N alcoholic potassium hydroxide VS until the solution remains pale pink after mixing for 10 seconds. Titrate a blank using 120 mL of *Solvent.* Calculate the quantity, in mEq, of free fatty acids in the portion of Emulsion taken by the formula:

$$(V_U - V_B)N / 20C$$

in which V_U is the volume, in mL, of 0.02 N alcoholic potassium hydroxide consumed by the eluant; V_B is the volume, in mL, of 0.02 N alcoholic potassium hydroxide consumed by the blank; N is the normality of the 0.02 N alcoholic potassium hydroxide; and C is the labeled concentration, in g per mL, of the ~~sum of the individual~~ oils in the Emulsion: not more than 0.07 mEq of free fatty acids per ~~mL~~ g of Emulsion is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of isopropanol, ethyl acetate, and glacial acetic acid (179 : 20 : 1).

Standard preparation—Dissolve an accurately weighed portion of Soybean Oil (or other relevant oils used in the Emulsion) in *Mobile phase* to obtain a solution having a known concentration of about 8 mg per mL.

Assay preparation—Transfer an accurately measured portion of Emulsion, equivalent to about 800 mg of oil, ~~to a suitable container, and freeze dry. Dissolve the residue in *Mobile phase,* and quantitatively transfer~~ to a 100-mL volumetric flask with the aid of additional portions of *Mobile phase.* Dilute with *Mobile phase* to volume, and mix to obtain a solution containing about 8 mg of oil per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a ~~4.6-mm~~ 4.1-mm × 25-cm column that contains packing L21. The flow rate is about 1 mL per minute, adjusted so that the peak due to oil elutes at about 6.5 minutes. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 1.0; the tailing factor for the oil peak is not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

In-Process Revision

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of oil in the portion of Emulsion taken by the formula:

$$100C(r_U / r_S)$$

~~in which *C* is the concentration, in mg per mL, of Soybean Oil in the *Standard preparation;* and r_u and r_s are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~ in which *C* is the concentration, in mg per mL, of Soybean Oil or other relevant oils used in the Emulsion in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Loperamide Hydrochloride Oral Solution, *USP 29* page 1269. On the basis of comments received, it is proposed to provide additional information for the preparation of the *Standard preparation* in the *Assay.*

(MD-GRE: E. Gonikberg) RTS—44051-1

Change to read:

Assay—

Buffer solution—Transfer 3.0 g of monobasic potassium phosphate to a 1-L volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase—Prepare a mixture of *Buffer solution* and acetonitrile (63 : 37), and adjust with 0.9 M phosphoric acid to a pH of 3.0. Mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation— ~~Dissolve an accurately weighed quantity of USP Loperamide Hydrochloride RS in methanol, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 10 µg per mL.~~

■Dissolve an accurately weighed quantity of USP Loperamide Hydrochloride RS in methanol to obtain a solution having a known concentration of about 2 mg per mL. Quantitatively dilute this solution with water to obtain a solution having a known concentration of about 0.1 mg per mL. Further dilute this solution with *Mobile phase* to obtain a solution having a known concentration of about 10 µg of loperamide hydrochloride per mL.■1S (*USP30*)

Assay preparation—Transfer an accurately measured volume of Oral Solution, equivalent to about 1.0 mg of loperamide hydrochloride, to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, mix, and filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.0-mm × 8.0-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of loperamide hydrochloride ($C_{29}H_{33}ClN_2O_2 \cdot HCl$) in each mL of Oral Solution taken by the formula:

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

in which *C* is the concentration, in mg per mL, of USP Loperamide Hydrochloride RS in the *Standard preparation; V* is the volume of Oral Solution taken to prepare the *Assay preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Milk of Magnesia, *USP 29* page 1291. It is proposed to delete the test for *Limit of calcium* because this test is also required for raw materials used in the preparation of *Milk of Magnesia* and, therefore, provides assurance of the quality of the material.

(MD-GRE: E. Gonikberg) RTS—44052-1

Delete the following:

■~~**Limit of calcium—**~~

~~*Dilute hydrochloric acid, Lanthanum solution, Standard preparations,* and *Blank solution*—Proceed as directed in the test for *Limit of calcium* under *Magnesium Carbonate*.~~

~~*Test preparation*—Transfer the equivalent of 1.4 g of regular-strength Milk of Magnesia to a beaker, add 60 mL of *Dilute hydrochloric acid*, and stir until dissolved, heating if necessary. Transfer the solution so obtained to a 200-mL volumetric flask containing 4 mL of *Lanthanum solution*, dilute with water to volume, and mix.~~

~~*Procedure*—Proceed as directed in the test for *Limit of calcium* under *Magnesium Carbonate*. Calculate the percentage of calcium in the Milk of Magnesia taken by multiplying the concentration, in µg per mL, of calcium found in the *Test preparation* by 0.014: the limit is 0.07%.~~■1S (*USP30*)

In-Process Revision

BRIEFING

Methyldopa Oral Suspension, *USP 29* page 1396. It is proposed to delete the test for *Limit of methyldopa-glucose reaction product* because the required USP Reference Standard for this test is not available.

(MD-CV: S. Ramakrishna) RTS—44024-1

Change to read:

USP Reference standards ⟨11⟩—*USP Methyldopa RS.* ~~*USP Methyldopa-glucose Reaction Product RS.*~~

■■1S (*USP30*)

Delete the following:

■~~**Limit of methyldopa-glucose reaction product** [TO BE DETERMINED IF SUCROSE IS PRESENT]~~

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

~~*Solution A*—Dissolve a suitable, accurately weighed quantity of USP Methyldopa-glucose Reaction Product RS in 0.1 N sulfuric acid to obtain a solution having a known concentration of about 0.45 mg per mL.~~

~~*Standard solution*—Transfer about 25 mg of USP Methyldopa RS, accurately weighed, to a 25-mL volumetric flask, add 1.0 mL of *Solution A*, dilute with 0.1 N sulfuric acid to volume, and mix. The *Standard solution* has a known concentration of about 18 µg of USP Methyldopa-glucose Reaction Product RS per mL.~~

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

~~*Chromatographic system*—Use the system described under *Chromatographic system* in the *Assay.* The relative retention times for methyldopa and methyldopa-glucose reaction product are about 1.0 and 0.8, respectively. Chromatograph three replicate injections of the *Standard solution:* the resolution factor, *R,* between methyldopa and methyldopa-glucose reaction product is not less than 2.0. The relative standard deviations for three replicate injections of the *Standard solution* are not more than 2.0% and 3.0% for methyldopa and methyldopa-glucose reaction product, respectively.~~

~~*Procedure*—Proceed as directed for *Procedure* in the *Assay.* Calculate the quantity, in µg, of methyldopa equivalent to the methyldopa-glucose reaction product in each mL of the Oral Suspension taken by the formula:~~

~~$$(211.22/373.35)(250)(CD/W)(r_u/r_s)$$~~

~~in which 211.22 and 373.35 are the molecular weights of anhydrous methyldopa and methyldopa-glucose reaction product, respectively; *C* is the concentration, in µg per mL, of USP Methyldopa-glucose Reaction Product RS in the *Standard solution;* r_u and r_s are the peak responses of the methyldopa-glucose reaction product obtained from the *Test solution* and the *Standard solution,* respectively; and the other terms are as defined therein. The limit is 10.0%, based on the methyldopa content of the Oral Suspension as determined in the *Assay.*~~■1S (*USP30*)

BRIEFING

Methylprednisolone, *USP 29* page 1406. It is proposed to revise the test for *Chromatographic purity* to correct the formula provided in the *Procedure.*

(MD-PS: D. Bempong) RTS—43741-1

Change to read:

Chromatographic purity—

Mobile phase—Prepare a filtered and degassed mixture of water, tetrahydrofuran, dimethylsulfoxide, and butanol (149 : 40 : 10 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluting solution—Prepare a filtered mixture of water, tetrahydrofuran, and glacial acetic acid (72 : 25 : 3).

Standard solution—Dissolve an accurately weighed quantity of USP Methylprednisolone RS in *Diluting solution.* Dilute quantitatively, and stepwise if necessary, with *Diluting solution* to obtain a solution having a known concentration of about 0.01 mg per mL.

Test solution—Transfer about 25 mg of Methylprednisolone, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluting solution* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 20-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 800 theoretical plates; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—~~Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the amount of each impurity in the portion of Methylprednisolone taken by the formula:~~

~~$$20C(r_i/r_s),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Methylprednisolone RS in the *Standard solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the peak response obtained in the *Standard solution;*~~

■Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Methylprednisolone taken by the formula:

$$25 \times 100(C/W)(r_i/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Methylprednisolone RS in the *Standard solution; W* is the weight, in mg, of the sample taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for methylprednisolone in the *Standard solution:*■1S (*USP30*)
not more than 1.0% of any individual impurity is found, and not more than 2.0% of total impurities is found.

In-Process Revision

BRIEFING

Mitoxantrone Injection, *USP 29* page 1447. To better represent currently marketed products, it is proposed to revise the *Packaging and storage* statement to include multiple-dose containers.

(MD-ANT: B. Gilbert) RTS—43932-1; 43933-1

Change to read:

Packaging and storage—Preserve in single-dose

■or in multiple-dose■1S (*USP30*) containers, preferably of Type I glass.

BRIEFING

Morantel Tartrate, *USP 29* page 1455. On the basis of comments received, it is proposed to raise the upper limit of the *pH* from 3.2 to 3.9. Interested parties are encouraged to submit comments.

(VET: I. DeVeau) RTS—43546-1

Change to read:

pH ⟨791⟩**:** between 2.8 and ~~3.2~~

■3.9.■1S (*USP30*)
Solution—Dissolve and dilute 0.25 g to 25.0 mL in carbon dioxide-free water.

BRIEFING

Nifedipine Extended-Release Tablets, *USP 29* page 1531. It is proposed to add an identical *Test 5* to both the currently official *Drug release* section and to the delayed implementation date *Dissolution* section of this monograph because FDA recently approved a new generic version of this product. In the absence of any negative comments, it is proposed to implement this revision via the *Fourth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of August 1, 2006.

(BPC: M. Marques) RTS—44118-1

Change to read:

Drug release ⟨724⟩—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 1.*

Medium: water; 50 mL.

Apparatus 7: 15 to 30 cycles per minute. Do not use the reciprocating disk, but use a 25-cm plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue. The solution containers are 25-mm test tubes, 150 to 200 mm in length, and the water bath is maintained at 37 ± 0.5°. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.

Times: 4, 8, 12, 16, 20, and 24 hours.

Diluting solution: a mixture of methanol and water (1 : 1).

Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of methanol, dilute with water to volume, and mix to obtain a Standard stock solution. Quantitatively dilute this Standard stock solution with *Diluting solution* to obtain solutions having suitable known concentrations.

Test solution—Use portions of the solution under test, passed through a 0.4-µm filter, suitably diluted with methanol, and stepwise, if necessary, with *Diluting solution* to obtain a final mixture consisting of equal parts of methanol and water.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in the *Test solution* at each 4-hour interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm, in 0.5-cm cells. [NOTE—For the 4-hour time period, determine the absorbance at 456 nm, and use this determination to correct for excipient interference.]

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved*
4	between 5% and 17%
8	—
12	between 43% and 80%
16	—
20	—
24	not less than 80%

* The amount dissolved is expressed in terms of the labeled tablet strength rather than in terms of the labeled total contents.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Buffer concentrate—Transfer 330.9 g of dibasic sodium phosphate and 38 g of citric acid to a 1-L volumetric flask, add water to dissolve, add 10 mL of phosphoric acid, dilute with water to volume, and mix.

Medium—Mix 125.0 mL of *Buffer concentrate* and 1 L of 10% sodium lauryl sulfate solution, and dilute to 10 L. Adjust if necessary to a pH of 6.8; 900 mL.

Apparatus 2: 50 rpm, with sinkers (see *Figure 1*).

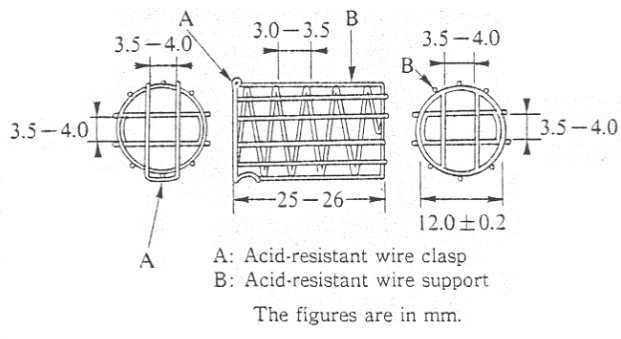


Figure 1 (printed with permission of the Japanese Pharmacopoeia)

Times: 3, 6, and 12 hours.

Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol to obtain a solution having a known concentration of about 1.11 mg per mL. Dilute quantitatively and stepwise with *Medium* to obtain a solution having a known concentration of 0.1 mg per mL.

Chromatographic system—The liquid chromatograph is equipped with a 350-nm detector and a 4.0-mm × 125-mm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at about 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of filtered portions of the *Standard solution* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved.

Tolerances—The percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) released in vivo and dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
3	between 10% and 30%
6	between 40% and 65%
12	not less than 80%

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

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Apparatus 2: 100 rpm.

Time: 1 hour.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 30% and 55%
8	not less than 60%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Apparatus 2: 100 rpm.

Time: 25 minutes.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 40% and 70%
8	not less than 70%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

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

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL for Tablets labeled to contain 60 mg, and of about 0.034 mg of USP Nifedipine RS per mL for Tablets labeled to contain 30 mg. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

In-Process Revision

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released at the times specified, conform to *Acceptance Table 1*.

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 12% and 35%
4	between 44% and 67%
12	not less than 80%

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 10% and 30%
4	between 40% and 63%
12	not less than 80%

•TEST 5—If the product complies with this test, the labeling indicates that the product meets USP *Drug Release Test 5*.

Medium: water; 50 mL.

Apparatus 7—Use a 25-cm plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue; 30 dips per minute. The solution containers are 25-mm test tubes, 150 to 200 mm in length, and the water bath is maintained at 37 $\pm$0.5°.

Time: 4, 12, and 24 hours.

Diluting solution 1—Prepare a mixture of methanol and acetonitrile (1 : 1).

Diluting solution 2—Prepare a mixture of *Diluting solution 1* and water (1 : 1).

Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Diluting solution 1,* dilute with water to volume, and mix. Quantitatively dilute this solution with *Diluting solution 2* to obtain solutions having known concentrations of 0.01 mg per mL, 0.05 mg per mL, and 0.20 mg per mL that are used at 4, 12, and 24 hours sampling, respectively.

Procedure—[NOTE—For the 4-hour time period, filter the solution under test, and determine the absorbance at 456 nm. Use this absorbance value to correct for excipient interference at the other time points.] Determine the amount of nifedipine released at each interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted, if necessary, with *Diluting solution 1* and water to obtain a final mixture of water, methanol, and acetonitrile (2 : 1 : 1), in comparison with the appropriate *Standard solution,* using 0.5-cm cells, and *Diluting solution 2* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine, released in vivo and dissolved at the times specified, conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
4	not more than 14%
12	between 39% and 75%
24	not less than 75%

•4

Change to read:

Dissolution ⟨711⟩—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1.*

Medium: water; 50 mL.

Apparatus 7 (see *Drug Release* ⟨724⟩): 15 to 30 cycles per minute. Do not use the reciprocating disk, but use a 25-cm plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue. The solution containers are 25-mm test tubes, 150 to 200 mm in length, and the water bath is maintained at 37 $\pm$ 0.5°. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.

Times: 4, 8, 12, 16, 20, and 24 hours.

Diluting solution: a mixture of methanol and water (1 : 1).

Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of methanol, dilute with water to volume, and mix to obtain a Standard stock solution. Quantitatively dilute this Standard stock solution with *Diluting solution* to obtain solutions having suitable known concentrations.

Test solution—Use portions of the solution under test, passed through a 0.4-µm filter, suitably diluted with methanol, and stepwise, if necessary, with *Diluting solution* to obtain a final mixture consisting of equal parts of methanol and water.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in the *Test solution* at each 4-hour interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm, in 0.5-cm cells. [NOTE—For the 4-hour time period, determine the absorbance at 456 nm, and use this determination to correct for excipient interference.]

In-Process Revision

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved*
4	between 5% and 17%
8	—
12	between 43% and 80%
16	—
20	—
24	not less than 80%

* The amount dissolved is expressed in terms of the labeled tablet strength rather than in terms of the labeled total contents.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Buffer concentrate—Transfer 330.9 g of dibasic sodium phosphate and 38 g of citric acid to a 1-L volumetric flask, add water to dissolve, add 10 mL of phosphoric acid, dilute with water to volume, and mix.

Medium—Mix 125.0 mL of *Buffer concentrate* and 1 L of 10% sodium lauryl sulfate solution, and dilute to 10 L. Adjust if necessary to a pH of 6.8; 900 mL.

Apparatus 2: 50 rpm, with sinkers (see *Figure 1*).

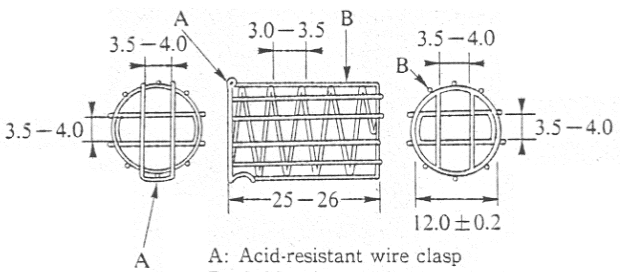


Figure 1

Times: 3, 6, and 12 hours.

Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol to obtain a solution having a known concentration of about 1.11 mg per mL. Dilute quantitatively and stepwise with *Medium* to obtain a solution having a known concentration of 0.1 mg per mL.

Chromatographic system—The liquid chromatograph is equipped with a 350-nm detector and a 4.0-mm × 125-mm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column is maintained at about 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of filtered portions of the *Standard solution* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved.

Tolerances—The percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) released in vivo and dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
3	between 10% and 30%
6	between 40% and 65%
12	not less than 80%

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

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Apparatus 2: 100 rpm.

Time: 1 hour.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm, using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 30% and 55%
8	not less than 60%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Apparatus 2: 100 rpm.

Time: 25 minutes.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm, using filtered portions of the solution under test, in comparison with the *Standard solution,* using *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 40% and 70%
8	not less than 70%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

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

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL for Tablets labeled to contain 60 mg, and of about 0.034 mg of USP Nifedipine RS per mL for Tablets labeled to contain 30 mg. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released at the times specified, conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 12% and 35%
4	between 44% and 67%
12	not less than 80%

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 10% and 30%
4	between 40% and 63%
12	not less than 80%

•TEST 5—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 5*.

Medium: water; 50 mL.

Apparatus 7 (see *Drug Release* ⟨724⟩)—Use a 25-cm plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue; 30 dips per minute. The solution containers are 25-mm test tubes, 150 to 200 mm in length, and the water bath is maintained at 37 $\pm$0.5°.

Time: 4, 12, and 24 hours.

Diluting solution 1—Prepare a mixture of methanol and acetonitrile (1 : 1).

Diluting solution 2—Prepare a mixture of *Diluting solution 1* and water (1 : 1).

Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Diluting solution 1,* dilute with water to volume, and mix. Quantitatively dilute this solution with *Diluting solution 2* to obtain solutions having known concentrations of 0.01 mg per mL, 0.05 mg per mL, and 0.20 mg per mL that are used at 4, 12, and 24 hours sampling, respectively.

Procedure—[NOTE—For the 4-hour time period, filter the solution under test, and determine the absorbance at 456 nm. Use this absorbance value to correct for excipient interference at the other time points.] Determine the amount of nifedipine released at each interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted, if necessary, with *Diluting solution 1* and water to obtain a final mixture of water, methanol, and acetonitrile (2 : 1 : 1), in comparison with the appropriate *Standard solution,* using 0.5-cm cells, and *Diluting solution 2* as the blank.

(Official April 1, 2006)

Tolerances—The cumulative percentages of the labeled amount of nifedipine, released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
4	not more than 14%
12	between 39% and 75%
24	not less than 75%

•4

BRIEFING

Nimodipine, *USP 29* page 1535. It is proposed to revise the test for *Related compounds* to simplify the procedures for preparing Standard solutions and to correct the formula provided in the *Procedure.* An incorrect reference provided in *Identification* test *B* has also been corrected.

(MD-CV: D. Bempong) RTS—43759-1; 43760-1; 43760-2; 43793-1; 43793-2

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of *Standard solution 1,* as obtained in the test for ~~*Chromatographic purity.*~~

■*Related compounds.*■1S *(USP30)*

Change to read:

Related compounds—

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and tetrahydrofuran (3 : 1 : 1).

Standard solution 1—~~Transfer about 40 mg of USP Nimodipine RS, accurately weighed, to a 25-mL volumetric flask, dissolve in 2.5 mL of tetrahydrofuran, dilute with *Mobile phase* to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 2.0 mL of this second solution to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~

■Transfer an accurately weighed quantity of USP Nimodipine RS to a suitable volumetric flask, dissolve in a volume of tetrahydrofuran equivalent to about 10% of the volume of the volumetric flask, and dilute with *Mobile phase* to volume to obtain a solution containing about 1.6 mg per mL. Dilute an aliquot of this solution with *Mobile phase* to obtain a solution having a known concentration of about 3.2 µg per mL.■1S *(USP30)*

Standard solution 2—~~Transfer about 20.0 mg of USP Nimodipine Related Compound A RS, accurately weighed, to a 25-mL volumetric flask, dissolve in 2.5 mL of tetrahydrofuran, dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~

■Transfer accurately weighed quantities of USP Nimodipine RS and USP Nimodipine Related Compound A RS to a suitable volumetric flask, dissolve in a volume of tetrahydrofuran equivalent to about 10% of the volume of the volumetric flask, and dilute with *Mobile phase* to volume to obtain a solution containing 0.8 mg per mL each of USP Nimodipine RS and USP Nimodipine Related Compound A RS. Dilute an aliquot of this solution with *Mobile phase* to obtain a solution having a known concentration of about 1.6 µg per mL each of USP Nimodipine RS and USP Nimodipine Related Compound A RS.■1S *(USP30)*

~~*Standard solution 3*—Transfer 2.5 mL of *Standard solution 1* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~

~~*Standard solution 4*—Transfer 1.0 mL of *Standard solution 2* and 1.0 mL of *Standard solution 3* to a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~

■■1S *(USP30)*

Test solution—Transfer about 40 mg of Nimodipine, accurately weighed, to a 25-mL volumetric flask, dissolve in 2.5 mL of tetrahydrofuran, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 4.6-mm × 12.5-cm column that contains packing L1. The flow rate is about 2 mL per minute. The column temperature is maintained at 40°. Chromatograph ~~*Standard solution 4,*~~

■*Standard solution 2,*■1S *(USP30)* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.9 for nimodipine related compound A and 1.0 for nimodipine;~~

■■1S *(USP30)* the resolution, *R,* between nimodipine related compound A and nimodipine is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

■[NOTE—For the purpose of identification, the relative retention times are about 0.9 for nimodipine related compound A and 1.0 for nimodipine.]■1S *(USP30)*

Procedure—Separately inject equal volumes (about 20 µL) of *Standard solution 1,*~~*Standard solution 4,*~~

■*Standard solution 2,*■1S *(USP30)* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. [NOTE—Record the chromatogram of the *Test solution* for a period of time equivalent

In-Process Revision

to four times the retention time of nimodipine.] ~~Calculate the percentage of each impurity in the portion of Nimodipine taken by the formula:~~

~~$100C(r_i/r_s)$~~

~~in which C is the concentration, in mg per mL, of USP Nimodipine Related Compound A RS in *Standard solution 4;* r_i is the peak response of each impurity obtained from the *Test solution;* and r_s is the peak response of nimodipine related compound A obtained from *Standard solution 4:* not more than 0.1% of nimodipine related compound A is found; not more than 0.2% of any other individual impurity is found; and not more than 0.5% of total impurities is found.~~

■Calculate the percentage of nimodipine related compound A in the portion of Nimodipine taken by the formula:

$$(100/1000)(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in µg per mL, of USP Nimodipine Related Compound A RS in *Standard solution 2;* C_T is the concentration, in mg per mL, of nimodipine in the *Test solution;* and r_U and r_S are the peak responses of nimodipine related compound A obtained from the *Test solution* and *Standard solution 2,* respectively: not more than 0.1% of nimodipine related compound A is found. Calculate the percentage of any other impurity in the portion of Nimodipine taken by the formula:

$$(100/1000)(C_S/C_T)(r_i/r_S)$$

in which C_S is the concentration, in µg per mL, of USP Nimodipine RS in *Standard solution 1;* C_T is the concentration, in mg per mL, of nimodipine in the *Test solution;* r_i is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of nimodipine obtained from *Standard solution 1*: not more than 0.2% of any other impurity is found; and not more than 0.5% of total impurities is found.■1S (*USP30*)

BRIEFING

Paclitaxel, *USP 29* page 1624. It is proposed to revise the test for *Related compounds* to add *Test 3* for materials produced by fermentation. *Test 3* will require the new USP Paclitaxel Impurity Mixture RS. The liquid chromatographic procedure in this test is based on analyses performed with the YMC-Pack ODS-A brand of L1 column. The typical retention time for Paclitaxel is about 27 minutes.

(MD-OOD: F. Mao) RTS—43952-1

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Paclitaxel RS. USP Paclitaxel Related Compound A RS. USP Paclitaxel Related Compound B RS.*

■*USP Paclitaxel Impurity Mixture RS.*■1S (*USP30*)

Change to read:

Related compounds—

TEST 1 (FOR MATERIAL LABELED AS ISOLATED FROM NATURAL SOURCES)—If the material complies with this test, the labeling indicates that it meets USP *Related compounds Test 1.*

Diluent—Prepare as directed in the *Assay.*

Solution A—Prepare filtered and degassed acetonitrile.

Solution B—Prepare filtered and degassed water.

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

System suitability solution—Dissolve accurately weighed quantities of USP Paclitaxel Related Compound A RS and USP Paclitaxel Related Compound B RS in methanol to obtain a solution having known concentrations of about 10 µg of each per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard solution—Dissolve, with the aid of sonication, an accurately weighed quantity of USP Paclitaxel RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 5 µg per mL.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L43. The flow rate is about 2.6 mL per minute. The column temperature is maintained at 30°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–35	35	65	isocratic
35–60	35→80	65→20	linear gradient
60–70	80→35	20→65	linear gradient
70–80	35	65	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.78 for paclitaxel related compound A and 0.86 for paclitaxel related compound B (relative to the retention time for paclitaxel obtained from the *Test solution*); and the resolution, *R,* between paclitaxel related compound A and paclitaxel related compound B is not less than 1.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

In-Process Revision

Procedure—Inject a volume (about 15 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$100(Fr_i / r_U)$$

in which F is the relative response factor for each impurity peak (see *Table 1* for values); r_i is the peak area for each individual impurity; and r_U is the peak area for paclitaxel.

Table 1

Relative Retention Time	Relative Response Factor *(F)*	Name	Limit (%)
0.24	1.29	Baccatin III	0.2
0.53	1.00	10-Deacetylpaclitaxel	0.5
0.57	1.00	7-Xylosylpaclitaxel	0.2
0.78	1.26	Cephalomannine (paclitaxel related compound A)	a_1[1]
0.78	1.26	2″,3″-Dihydrocephalomannine	a_2[1]
0.86	1.00	10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B)	0.5
1.10	1.00	Benzyl analog[3]	b_1[2]
1.10	1.00	3″,4″-Dehydropaclitaxel C	b_2[2]
1.40	1.00	7-Epicephalomannine	0.3
1.85	1.00	7-Epipaclitaxel	0.5

[1] Resolution may be incomplete for these peaks, depending upon the relative amounts present; the sum of a_1 and a_2 is not more than 0.5%.
[2] Resolution may be incomplete for these peaks, depending upon the relative amounts present; the sum of b_1 and b_2 is not more than 0.5%.
[3] The following chemical name is assigned to the related compound Benzyl analog: Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(2-phenylacetylamino)propanoic acid.

In addition to not exceeding the limits for paclitaxel related impurities in *Table 1,* not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities is found.

TEST 2 (FOR MATERIAL LABELED AS PRODUCED BY A SEMISYNTHETIC PROCESS)—If the material complies with this test, the labeling indicates that it meets USP *Related compounds Test 2.*

Diluent—Use acetonitrile.

Solution A—Use a filtered and degassed mixture of water and acetonitrile (3 : 2).

Solution B—Use filtered and degassed acetonitrile.

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

System suitability solution—Dissolve accurately weighed quantities of USP Paclitaxel RS and USP Paclitaxel Related Compound B RS in *Diluent,* shaking and sonicating if necessary, to obtain a solution having known concentrations of about 0.96 mg and 0.008 mg per mL, respectively.

Test solution—Transfer about 10 mg of Paclitaxel, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, shaking and sonicating if necessary, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–20	100	0	isocratic
20–60	100→10	0→90	linear gradient
60–62	10→100	90→0	linear gradient
62–70	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.94 for paclitaxel related compound B and 1.0 for paclitaxel; the resolution, *R,* between paclitaxel related compound B and paclitaxel is not less than 1.2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Diluent* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Disregard any peaks due to the *Diluent.* Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$100(Fr_i / r_s)$$

in which F is the relative response factor for each impurity (see *Table 2* for values); r_i is the peak area for each impurity obtained from the *Test solution;* and r_s is the sum of the areas of all the peaks obtained from the *Test solution.*

Table 2

Relative Retention Time	Relative Response Factor *(F)*	Name	Limit (%)
0.11	1.24	10-Deacetylbaccatin III	0.1
0.20	1.29	Baccatin III	0.2
0.42	1.39	Photodegradant[2]	0.1
0.47	1.00	10-Deacetylpaclitaxel	0.5
0.80	1.00	2-Debenzoylpaclitaxel-2-pentenoate	0.7
0.92[1]	1.00	Oxetane ring opened, acetyl and benzoyl[2]	x_1
0.92[1]	1.00	10-Acetoacetylpaclitaxel	x_2
0.94[1]	1.00	10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B)	x_3
1.37	1.00	7-Epipaclitaxel	0.4
1.45	1.00	10,13-Bissidechainpaclitaxel[2]	0.5
1.54	1.00	7-Acetylpaclitaxel	0.6
1.80	1.75	13-Tes-baccatin III	0.1
2.14	1.00	7-Tes-paclitaxel	0.3

[1] Resolution may be incomplete for these peaks, depending upon the relative amounts present; the sum of x_1, x_2, and x_3 is not more than 0.4%.
[2] The following chemical names are assigned to the related compounds Photodegradant; Oxetane ring opened, acetyl and benzoyl; and 10,13-Bissidechainpaclitaxel:

Photodegradant
(1*R*,2*R*,4*S*,5*S*,7*R*,10*S*,11*R*,12*S*,13*S*,15*S*,16*S*)-2,10-diacetyloxy-5,13-dihydroxy-4,16,17,17-tetramethyl-8-oxa-3-oxo-12-phenylcarbonyloxypentacyclo[11.3.1.$0^{1,11}$.$0^{4,11}$.$0^{7,10}$]heptadec-15-yl
(2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoate

Oxetane ring opened, acetyl and benzoyl migrated
(1*S*,2*S*,3*R*,4*S*,5*S*,7*S*,8*S*,10*R*,13*S*)-5,10-diacetyloxy-1,2,4,7-tetrahydroxy-8,12,15,15-tetramethyl-9-oxo-4-(phenylcarbonyloxymethyl)tricyclo[9.3.1.$0^{3,8}$]pentadec-11-en-13-yl
(2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoate

10,13-Bissidechainpaclitaxel
Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoic acid, 10-ester with (2*S*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoic acid

In addition to not exceeding the limits for paclitaxel related impurities in *Table 2,* not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities is found.

■TEST 3 (FOR MATERIAL LABELED AS PRODUCED BY A PLANT CELL FERMENTATION PROCESS)—If the material complies with this test, the labeling indicates that it meets USP *Related compounds Test 3.*

Solution A—Prepare a filtered and degassed mixture of water and acetonitrile (3 : 2).

Solution B—Prepare filtered and degassed acetonitrile.

In-Process Revision

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

System suitability solution—Dissolve USP Paclitaxel Impurity Mixture RS in acetonitrile, sonicating if necessary, to obtain a solution having a known concentration of about 1 mg per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Paclitaxel RS in acetonitrile, sonicating if necessary, to obtain a solution having a known concentration of about 1 mg per mL.

Test solution—Transfer about 10 mg of Paclitaxel, accurately weighed, to a 10-mL volumetric flask. Dissolve in and dilute with acetonitrile to volume, sonicating if necessary, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L1. The flow rate is about 1.2 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–28	100	0	isocratic
28–33	100→98	0→2	linear gradient
33–58	98→10	2→90	linear gradient
58–60	10	90	isocratic
60–63	10→100	90→0	linear gradient
63–70	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between paclitaxel and benzyl analog is not less than 1.8. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%. [NOTE—For the purpose of peak identification, the approximate relative retention times are given in *Table 3*. The relative retention times are measured versus Paclitaxel.]

Table 3

Name	Relative Retention Time	Limit (%)
Propyl analog[1]	0.54	0.2
Cephalomannine (Paclitaxel related compound A)	0.76	0.5
sec-Butyl analog[2]	0.81	0.2
n-Butyl analog[3]	0.89	0.1
Benzyl analog	1.10	0.4
Baccatin VI	1.23	0.2
Pentyl analog[4]	1.31	0.2
7-Epipaclitaxel	1.51	0.4

[1] The following chemical name is assigned to the related compound Propyl analog: Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-(propanoylamino)propanoic acid.
[2] The following chemical name is assigned to the related compound *sec*-Butyl analog: Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-(2-methylbutanoylamino)-3-phenylpropanoic acid.
[3] The following chemical name is assigned to the related compound *n*-Butyl analog: Baccatin III 13-ester with (2*S*,3*S*)-3-(butanoylamino)-2-hydroxy-3-phenylpropanoic acid.
[4] The following chemical name is assigned to the related compound Pentyl analog: Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-(pentanoylamino)-3-phenylpropanoic acid.

Procedure—Inject a volume (about 12 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for all the peaks. Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$100(r_i / r_U)$$

in which r_i is the response of each individual impurity; and r_U is the sum of the areas of all the peaks obtained from the *Test solution*. In addition to not exceeding the limits for Paclitaxel

related impurities in *Table 3,* not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities is found.■1S (*USP30*)

BRIEFING

Pentobarbital Sodium Injection, *USP 29* page 1680. It is proposed to replace the nonspecific gravimetric assay with a specific stability-indicating HPLC assay. The method is based on the HPLC method used for the Pentobarbital and Pentobarbital Sodium monographs. The method was verified using the Phenomenex Gemini C18 brand of L1 column. The typical retention time for pentobarbital is about 12 minutes. Consequently, the *Identification* test has been revised to use retention time by HPLC.

(MD-PP: R. Ravichandran) RTS—44094-1

Change to read:

Identification— ~~The residue obtained in the *Assay* responds to *Identification* test *A* under *Pentobarbital Sodium*.~~

■The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*■1S (*USP30*)

Change to read:

Assay— ~~Pipet a volume of Injection, equivalent to about 500 mg of pentobarbital sodium, into a separator, and dilute with water to about 15 mL. To the solution add 2 mL of hydrochloric acid, shake, and completely extract the liberated pentobarbital with 25-mL portions of chloroform. Test for completeness of extraction by extracting with an additional 10-mL portion of chloroform and evaporating the solvent: not more than 0.5 mg of residue remains. Filter each extract through a pledget of chloroform-washed cotton, or other suitable filter, into a tared beaker, and finally wash the separator and the filter with several small portions of chloroform. Evaporate the combined filtrate and washings on a steam bath with the aid of a current of air, add 10 mL of ether, again evaporate, dry the residue at 105° for 2 hours, cool, and weigh. The weight of the residue, multiplied by 1.097, represents the weight of pentobarbital sodium ($C_{11}H_{17}N_2NaO_3$).~~

■*Mobile phase, Standard preparation,* and *Chromatographic system*—Proceed as directed in the *Assay* under *Pentobarbital.*

Assay preparation—Quantitatively dilute a suitable volume of Pentobarbital Sodium Injection with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{11}H_{17}N_2NaO_3$ in the portion of Pentobarbital Sodium Injection taken by the formula:

$$100(248.25/226.27)(C_S/C_U)(r_U/r_S)$$

in which 248.25 and 226.27 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; C_S is the concentration, in mg per mL, of USP Pentobarbital RS in the *Standard preparation;* C_U is the final concentration, in mg per mL, of the *Assay preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Potassium Perchlorate, *USP 29* page 1775. Because of the low-volume production of this article and the low cost of a high-quality ACS reagent, it is proposed to remove the requirement for USP Potassium Perchlorate RS and use the reagent instead. The proposed changes appear in the *USP Reference standards* section and the *Assay.* It is also proposed to make appropriate related changes in the general chapter *USP Reference Standards* ⟨11⟩ and in the *Reagents* section of *USP–NF.*

(RMI: A. Wilk) RTS—43829-1

Delete the following:

■~~**USP Reference standards** ⟨11⟩ *USP Potassium Perchlorate RS.*~~■1S (*USP30*)

In-Process Revision

Change to read:

Assay—

Mobile phase—Transfer 16.6 g of phthalic acid to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Transfer 10.0 mL of this solution to a 1000-mL flask, dilute with water to volume, and mix. Adjust with about 450 mg of lithium hydroxide to a pH of 4.5, filter, and degas.

Standard preparation—Transfer about 50 mg of ~~USP Potassium Perchlorate RS~~

■potassium perchlorate,■1S *(USP30)*
accurately weighed, to a 50-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Using about 50 mg of Potassium Perchlorate, accurately weighed, proceed as directed for the *Standard preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector and a 4.6-mm × 7.5-cm column that contains 6-µm packing L23. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $KClO_4$ in the portion of Potassium Perchlorate taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of ~~USP Potassium Perchlorate RS~~

■potassium perchlorate■1S *(USP30)*
in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Prednisolone Sodium Phosphate, *USP 29* page 1791. It is proposed to add USP Prednisolone Sodium Phosphate RS and to replace the current *Identification* test *A* with *Infrared Absorption* ⟨197K⟩.

(MD-PS: D. Bempong) RTS—43947-1

Change to read:

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

■*USP Prednisolone Sodium Phosphate RS.*■1S *(USP30)*

Change to read:

Identification—

A: ~~Place 5 mL of the *Assay preparation* obtained as directed in the *Assay*, in a glass-stoppered, 100-mL volumetric flask, mix with 5 mL of *Alkaline phosphatase solution* prepared as directed in the *Assay*, and add 50 mL of methylene chloride. Insert the stopper, and allow to stand, with occasional gentle inversion (about once every 15 minutes), for 2 hours. Filter the methylene chloride layer through a dry paper, and evaporate 25 mL of the filtrate to dryness: the residue so obtained responds to *Identification* test *A* under *Prednisolone*.~~

■*Infrared Absorption* ⟨197K⟩.■1S *(USP30)*

B: The residue from the ignition of about 20 mg of it responds to the tests for *Sodium* ⟨191⟩ and for *Phosphate* ⟨191⟩.

BRIEFING

Promethazine Hydrochloride, *USP 29* page 1824. It is proposed to delete the thin-layer chromatographic procedure in the test for *Related substances* and replace it with a stability-indicating HPLC procedure. The HPLC procedure is based on analyses performed with the 5-µm Luna C18(2) brand of L1 column. The typical retention time for promethazine is 20 minutes.

(MD-PS: D. Bempong) RTS—43743-1

Change to read:

USP Reference standards ⟨11⟩—*USP Promethazine Hydrochloride RS.*

■*USP Promethazine Related Compound A RS.*■1S *(USP30)*

Change to read:

Related substances—

~~*Standard preparation* and *Standard dilutions*—Dissolve an accurately weighed quantity of USP Promethazine Hydrochloride RS in methylene chloride to obtain a solution containing 10.0 mg per mL (*Standard preparation*). Prepare a series of quantitative dilutions of the *Standard preparation* in methylene chloride to contain 0.2, 0.1, 0.05, and 0.025 mg per mL (*Standard dilutions*) corresponding to 2.0%, 1.0%, 0.5%, and 0.25% of impurities, respectively.~~

~~*Test solution*—Dissolve 100 mg, accurately weighed, of Promethazine Hydrochloride in 10.0 mL of methylene chloride.~~

~~*Procedure*—Using a 20- × 20-cm thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of silica gel mixture, apply 10-µL portions of the *Test preparation,* the *Standard preparation,* and each of the *Standard dilutions* 2.5 cm from the lower edge of the plate. Develop the plate in an unsaturated tank containing a mixture of ethyl acetate, acetone, alcohol, and ammonium hydroxide (90 : 45 : 2 : 1). After the solvent has moved not less than 10 cm, air-dry the plate, and view under short-~~

In-Process Revision

~~wavelength UV light: the R_F value of the principal spot obtained from the *Test preparation* corresponds to that from the *Standard preparation*. Estimate the concentration of any other spots observed in the lane for the *Test preparation* by comparison with the *Standard dilutions:* the sum of the impurities is not greater than 2.0%, and no single impurity is greater than 1.0%.~~

▪*Buffer solution*—Dissolve 1.35 g of monobasic potassium phosphate in 500 mL of water, and adjust with triethylamine to a pH of 7.0 ± 0.5.

Mobile phase—Prepare a mixture containing 450 mL of *Buffer solution,* 350 mL of acetonitrile, and 200 mL of methanol. Pass the mixture through a 0.45-µm membrane filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve suitable quantities of USP Promethazine Hydrochloride RS and USP Promethazine Related Compound A RS in *Mobile phase,* and dilute quantitatively with *Mobile phase,* to obtain a solution having known concentrations of about 1.0 µg per mL and 0.4 µg per mL, respectively.

Test solution—Transfer 20 mg of Promethazine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, add about 50 mL of *Mobile phase,* and shake to dissolve. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 25°, and the samples are maintained at about 4° in a refrigerated autosampler. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between promethazine related compound A and promethazine is not less than 2.0; and the relative standard deviation for replicate injections, calculated for promethazine, is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than two times the retention time of promethazine. Record the chromatograms, and measure the peak responses. Calculate the percentage of promethazine related compound A in the portion of Promethazine Hydrochloride taken by the formula:

$$100(C_S / C_U)(r_A / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Promethazine Related Compound A RS in the *Standard solution;* C_U is the concentration of Promethazine Hydrochloride, in mg per mL, in the *Test solution;* r_A is the peak response for promethazine related compound A obtained from the *Test solution;* and r_S is the peak response for promethazine related compound A obtained from the *Standard solution*. Calculate the percentage of any other impurity in the portion of Promethazine Hydrochloride taken by the formula:

$$100(1/F)(C_S / C_U)(r_i / r_S)$$

in which F is the relative response factor (see accompanying table for values) for each impurity; C_S is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard solution;* C_U is the concentration of Promethazine Hydrochloride, in mg per mL, in the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for promethazine obtained from the *Standard solution*. The limits are as specified in the accompanying table.

In-Process Revision

Compound Name	Relative Retention Time	Relative Response Factor (*F*)	Limit (w/w, %)
Promethazine sulfoxide[1]	about 0.13	0.23	0.2
Promethazine related compound A (phenothiazine)	about 0.8	—	0.2
Promethazine hydrochloride	1.0	—	—
Isopromethazine hydrochloride[2]	about 1.6	1.0	0.5
Individual unknown impurity	—	1.0	0.10
Total impurities	—	—	1.0

[1] (2*RS*)-*N,N*-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine *S*-oxide.
[2] (2*RS*)-*N,N*-dimethyl-2-(10*H*-phenothiazin-10-yl)propan-1-amine.

■1S (*USP30*)

BRIEFING

Promethazine Hydrochloride Tablets, *USP* 29 page 1826. It is proposed to replace the UV spectrophotometric method in the *Assay* with a stability-indicating liquid chromatographic (LC) method. It is also proposed to add a test for *Related compounds* that is based on this LC method and to add a USP Reference Standard for use in this test. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the 5-µm Luna C18(2) brand of L1 column. The typical retention time for promethazine is 20 minutes. In addition, minor editorial style changes have been made.

(MD-PS: D. Bempong) RTS—43138-1

Change to read:

USP Reference standards ⟨11⟩—*USP Promethazine Hydrochloride RS.*

■*USP Promethazine Related Compound A RS.*■1S (*USP30*)

NOTE—Throughout the following procedures, protect

■from light■1S (*USP30*)
the test or assay specimens, the Reference ~~Standard~~

■Standards,■1S (*USP30*)
and solutions containing them by conducting the procedures without delay, and under subdued light or using low-actinic glassware.

Add the following:

■Related compounds—

Buffer solution and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution—Dissolve suitable quantities of USP Promethazine Hydrochloride RS and USP Promethazine Related Compound A RS in *Mobile phase,* and dilute with *Mobile phase* to obtain a solution having known concentrations of about 1.0 µg per mL and 0.4 µg per mL, respectively.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 20 mg of promethazine hydrochloride, to a 100-mL volumetric flask, and add about 50 mL of *Mobile phase*. Sonicate for about 1 minute, and shake by mechanical means for 5 minutes. Cool to room temperature, dilute with *Mobile phase* to volume, mix, and pass through a 0.45-µm nylon filter, discarding the first 10 mL of filtrate.

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between promethazine related compound A and promethazine is not less than 2.0; and the relative standard deviation for replicate injections, calculated for promethazine, is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than two times the retention time of promethazine.

Record the chromatograms, and measure the peak responses. Calculate the percentage of promethazine related compound A in the portion of Tablets taken by the formula:

$$100(C_S / C_U)(r_A / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Promethazine Related Compound A RS in the *Standard solution;* C_U is the concentration of promethazine hydrochloride (based on the label claim), in mg per mL, in the *Test solution;* r_A is the peak response of promethazine related compound A obtained from the *Test solution;* and r_S is the peak response of promethazine related compound A obtained from the *Standard solution.* Calculate the percentage of any other impurity in the portion of Tablets taken by the formula:

$$100(1/F)(C_S/C_U)(r_i / r_S)$$

in which F is the relative response factor (see accompanying table for values) for each impurity; C_S is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard solution;* C_U is the concentration of promethazine hydrochloride (based on the label claim), in mg per mL, in the *Test solution;* r_i is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of promethazine obtained from the *Standard solution.* The limits are as specified in the accompanying table.

Change to read:

Assay—

~~*Buffered palladium chloride solution*~~ ~~Transfer 500 mg of palladium chloride to a 250-mL beaker, add 5 mL of hydrochloric acid, and warm on a steam bath. Add 200 mL of hot water in small quantities while stirring until solution is complete. Cool, dilute with water to 500 mL, and mix. Transfer 25 mL of this solution to a 500-mL volumetric flask. Add 50 mL of 1 N sodium acetate and 48 mL of 1 N hydrochloric acid, dilute with water to volume, and mix.~~

~~*Standard preparation*~~ ~~Transfer about 31 mg of USP Promethazine Hydrochloride RS, accurately weighed, to a low-actinic 250-mL volumetric flask. Dissolve in 0.1 N hydrochloric acid, dilute with 0.1 N hydrochloric acid to volume, and mix.~~

~~*Assay preparation*~~ ~~Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6.25 mg of promethazine hydrochloride, to a low-actinic 125-mL separator. Add 20 mL of saturated potassium chloride solution, 10 mL of 1 N sodium hydroxide, and 10 mL of methanol, and extract the promethazine with three 20-mL portions of *n* heptane. Filter the heptane extracts through anhydrous sodium sulfate and collect them in a low-actinic 125-mL separator. Extract the promethazine from the *n* heptane solution with three 15-mL portions of 0.1 N hydrochloric acid, collect the acid extracts in a low-actinic 50-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.~~

~~*Procedure*~~ ~~Into separate test tubes, pipet 2-mL portions of the *Standard preparation,* the *Assay preparation,* and 0.1 N hydrochloric acid to provide a blank. Add 3.0 mL of *Buffered palladium chloride solution* to each tube, and mix. Concomitantly determine the absorbances of the solutions at the wavelength of maximum absorbance at about 470 nm, using a suitable spectrophotometer, and using the blank in the reference cell. Calculate the quantity, in mg, of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) in the portion of Tablets taken by the formula:~~

~~$$50C(A_U / A_S)$$~~

~~in which C is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard preparation;* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively.~~

Compound Name	Relative Retention Time	Relative Response Factor (F)	Limit (w/w, %)
Promethazine sulfoxide[1]	about 0.13	0.23	0.2
Promethazine related compound A (phenothiazine)	about 0.8	—	0.2
Promethazine hydrochloride	1.0	—	—
Isopromethazine hydrochloride[2]	about 1.6	1.0	0.5
Individual unknown impurity	—	1.0	0.2
Total impurities	—	—	1.0

[1] (2RS)-*N,N*-Dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine *S*-oxide.
[2] (2RS)-*N,N*-Dimethyl-2-(10*H*-phenothiazin-10-yl)propan-1-amine. ■1S (*USP30*)

In-Process Revision

■*Buffer solution*—Dissolve 1.35 g of potassium phosphate monobasic in 500 mL of water, and adjust with triethylamine to a pH of 7.0 ± 0.5.

Mobile phase—Mix 450 mL of *Buffer solution,* 350 mL of acetonitrile, and 200 mL of methanol. Pass through a 0.45-µm membrane filter, and degas. Make adjustments if necessary (see *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Promethazine Hydrochloride RS in *Mobile phase,* and dilute with *Mobile phase* to obtain a solution having a known concentration of about 4 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 50 mg of promethazine hydrochloride, to a 250-mL volumetric flask, and add about 100 mL of *Mobile phase*. Sonicate for 30 minutes with intermittent shaking, and shake by mechanical means for an additional 30 minutes. Dilute with *Mobile phase* to volume, mix, and pass through a 0.45-µm nylon filter, discarding the first 10 mL of filtrate. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 25°, and the samples are maintained at 4° in a refrigerated autosampler. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses of the promethazine peaks. Calculate the quantity, in mg, of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) in the portion of Tablets taken by the formula:

$$(250)50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Pyridoxine Hydrochloride Injection, *USP 29* page 1870. On the basis of comments received, it is proposed to revise the *Procedure,* subsection *(a),* in the *Assay* to extend the time period just prior to determining the absorbance of the *Standard preparation* and the *Assay preparation.* The additional time allows for the maximum formation of the derivative that results from the coupling reaction between pyridoxine and 2,6-dichloroquinine, thus decreasing the variability of the results.

(DSN: L. Evans) RTS—40767-1

Change to read:

Assay—

Ammonium chloride–ammonium hydroxide buffer—Dissolve 16 g of ammonium chloride in 70 mL of water, add 16 mL of ammonium hydroxide, dilute with water to 100 mL, mix, and filter.

Chlorimide solution—Dissolve 40 mg of 2,6-dichloroquinone-chlorimide in 100 mL of isopropyl alcohol. Store the solution in a refrigerator, and use within 1 month. Do not use the solution if it has become pink.

Standard stock solution—Dissolve a suitable quantity of USP Pyridoxine Hydrochloride RS, accurately weighed, in 0.1 N hydrochloric acid, quantitatively dilute with the same solvent to obtain a solution having a known concentration of about 0.1 mg per mL, and mix. Keep the solution in an amber bottle, in a cool place.

Standard preparation—In a 100-mL volumetric flask dilute 10.0 mL of *Standard stock solution* with water to volume, and mix. Prepare this solution daily as needed.

Assay preparation—Dilute an accurately measured volume of Injection, equivalent to about 100 mg of pyridoxine hydrochloride, quantitatively and stepwise with water to a concentration of about 10 µg of pyridoxine hydrochloride per mL.

Procedure—

(a) Pipet 5 mL of the clear *Assay preparation* into a flask, add 25.0 mL of isopropyl alcohol, and mix. Pipet 5 mL of the isopropyl alcohol dilution into a glass-stoppered, 25-mL graduated cylinder or test tube; and add in succession, mixing after each addition, 1.0 mL of *Ammonium chloride–ammonium hydroxide buffer,* 1.0 mL of sodium acetate solution (1 in 5), and 1.0 mL of water. Cool to about 25°, then add 1.0 mL of *Chlorimide solution,* and shake vigorously for 10 seconds, accurately timed. ~~Sixty~~

■Ninety■1S *(USP30)* seconds, accurately timed, after the addition of the *Chlorimide solution,* determine the absorbance at the wavelength of maximum absorbance at about 650 nm, with a suitable spectrophotometer, using water as the blank. [NOTE—Make the reading promptly to avoid errors due to fading of the color.] Designate the absorbance as A_U.

(b) Repeat procedure *(a),* but substitute 1.0 mL of boric acid solution (1 in 20) for the 1.0 mL of water. Designate the absorbance as A_U'.

(c) Repeat procedure *(a),* but substitute 5.0 mL of the *Standard preparation* for the 5.0 mL of the *Assay preparation.* Designate the absorbance as A_S.

(d) Repeat procedure *(c),* but substitute 1.0 mL of boric acid solution (1 in 20) for the 1.0 mL of water. Designate the absorbance as A_S'.

Calculate the quantity, in mg, of Pyridoxine Hydrochloride ($C_8H_{11}NO_3 \cdot HCl$) in each mL of the Injection taken by the formula:

$$10(C/V)(A_U - A_U')/(A_S - A_S')$$

in which C is the concentration, in µg per mL, of USP Pyridoxine Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of Injection taken; and the other terms are as defined above.

BRIEFING

Quazepam Tablets, *USP 29* page 1875. It is proposed to require the use of USP Ethylparaben RS for the preparation of the *Internal standard solution*. It is also proposed to clarify that the relative retention times are intended for identification only.

(MD-PP: R. Ravichandran) RTS—44082-1

In-Process Revision

Change to read:

USP Reference standards ⟨11⟩**—**

■*USP Ethylparaben RS.*■1S *(USP30)*
USP Quazepam RS. USP Quazepam Related Compound A RS.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (7 : 3). Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Dissolve an accurately weighed quantity of ~~ethylparaben~~ ■USP Ethylparaben RS■1S *(USP30)* in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution containing about 0.19 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Quazepam RS in *Internal standard solution,* and dilute quantitatively, and stepwise if necessary, with *Internal standard solution* to obtain a solution having a known concentration of about 1.5 mg of quazepam per mL.

Assay preparation—Weigh and finely powder not fewer than 10 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 15 mg of quazepam, to a 50-mL screw-capped centrifuge tube. Add 10.0 mL of *Internal standard solution,* and centrifuge for 30 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.4 for ethylparaben and 1.0 for quazepam,~~

■■1S *(USP30)* the resolution, *R,* between ethylparaben and quazepam is not less than 5.5; and the relative standard deviation for replicate injections is not more than 2.0%.

■[NOTE—For identification purposes, the relative retention times are about 0.4 for ethylparaben and 1.0 for quazepam.]■1S *(USP30)*

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of quazepam ($C_{17}H_{11}ClF_4N_2S$) in the portion of Tablets taken by the formula:

$$10C(R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Quazepam RS in the *Standard preparation;* and R_U and R_S are the ratios of the peak response of quazepam to that of ethylparaben obtained from the *Assay preparation* and the *Standard preparation,* respectively.

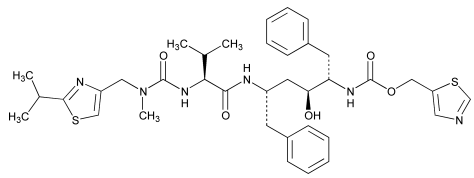
BRIEFING

Ritonavir, page 788 of *PF* 31(3) [May–June 2005]. It is proposed to change the method for *Identification* test *A* from ⟨197S⟩ to ⟨197⟩, because ⟨197S⟩ signifies that a solution is examined in 0.1-mm cells, whereas no cell was used in the IR procedure. Additionally, a change is proposed for the *Chromatographic system* section of the *Related compounds* test to clarify the peak-to-valley ratio for the system suitability requirement. Minor editorial changes have also been made.

(MD-AA: B. Davani) RTS—43853-1

Add the following:

■Ritonavir



$C_{37}H_{48}N_6O_5S_2$ 720.94

2.4.7.12-Tetraazatridecan-13-oic acid, 10-hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-5-thiazolylmethyl ester [5*S*-(5*R**,8*R**,10*R**,11*R**)]-.

5-Thiazolylmethyl [(α*S*)-α-[(1*S*,3*S*)-1-hydroxy-3-[(2*S*)-2-[3-[(2-isopropyl-4-thiazolyl)methyl]-3-methylureido]-3-methylbutyramido]-4-phenylbutyl]phenethyl]carbamate [*155213-67-5*].

» Ritonavir contains not less than 97.0 percent and not more than 102.0 percent of $C_{37}H_{48}N_6O_5S_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store between 5° and 30°.

USP Reference standards ⟨11⟩**—***USP Ritonavir RS. USP Ritonavir Related Compounds Mixture RS.*

Change to read:

Identification—

A: *Infrared Absorption* ⟨~~197S~~⟩ ■⟨197⟩—■1S *(USP30)*

Test specimen—Dissolve 50 mg of Ritonavir in 1.0 mL of chloroform. Add 1 drop of this solution to the surface of a potassium bromide or a sodium chloride disk, and evaporate to dryness.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* is within 2% of the retention time of the major peak in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

C: *X-Ray diffraction* ⟨941⟩—The X-ray diffraction pattern conforms to that of USP Ritonavir RS.

Heavy metals, *Method II* ⟨231⟩**:** not more than 0.002%, using 1.0 g of Ritonavir and 2 mL of *Standard Lead Solution* (10 ppm Pb) in the *Standard Preparation.*

Water, *Method I* ⟨921⟩**:** not more than 0.5%, determined on 0.500 g.

Residue on ignition ⟨281⟩**:** not more than 0.2%, determined on 1.0 g.

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

Change to read:

Related compounds—[NOTE—Ritonavir is ~~alkaline~~ ■alkali■1S *(USP30)* sensitive. All glassware should be prerinsed with distilled water prior to use to remove residual detergent contamination.]

Monobasic potassium phosphate solution (0.03M), Diluent, Solution A, Solution B, and *Mobile phase*—Prepare as directed in the *Assay.*

Standard stock solution and *Intermediate stock solution*—Prepare as directed for *Standard stock preparation* and *Intermediate standard preparation* in the *Assay.*

Ritonavir identity standard solution—Transfer about 50 mg of USP Ritonavir Related Compounds Mixture RS, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Standard solution—Transfer 5.0 mL of the *Intermediate standard solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. [NOTE—This solution may be used for 48 hours if stored at room temperature.]

Test solution—Transfer about 50 mg of Ritonavir, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L26 and is maintained at a constant temperature of about 60°. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibrium
0–60	100	0	isocratic
60–120	100→0	0→100	gradient
120.1	0→100	100→0	step gradient
120.1–155	100	0	isocratic

The run time for the *Standard solution* is 40 minutes, and the run time for the *Test solution* is 155 minutes. Chromatograph the *Ritonavir identity standard solution* and the *Standard solution,* and record the responses as directed for *Procedure:* the retention time of ritonavir is between 30 and 35 minutes; the resolution, *R,* between impurity E and impurity F (see *Table 1)* in the *Ritonavir identity standard solution* is not less than 1.0; the ratio of peak (H_p) to valley (H_v) of ■Ritonavir and■1S *(USP30)* impurity N (regioisomer) is not less than 1; the capacity factor, *k′,* using the main component peak of the first *Standard solution* injection, is not less than 13; the column efficiency, using the main component peak of the first *Standard solution* injection, is not less than 5000 theoretical plates; the tailing factor, using the main component peak of

Table 1. Approximate Relative Retention Time (RRT) for Known Related Impurities

Impurity Identity	Common Name	Response Factor	RRT
A + B	Mixture of 2,4-Wing acid and monoacyl valine	—	0.07
C	Monoacylacetamide	—	0.15
D	5-Wing diacyl	1.37	0.24
E	Oxidation impurity	—	0.36
F	Acid hydrolysis product	0.73	0.39
G	Ritonavir hydroperoxide	—	0.45
H	Acid/base by-product	0.76	0.47
I	Ethyl analog	—	0.64
J + K	Mixture of Boc-monoacyl and monoacyl isobutyl carbamate	0.74	0.81
L	Base cyclization product	0.53	0.87
M	2,4-Wing isobutyl ester	—	0.94
N	Regioisomer	—	1.05
O	Isomer #2	—	1.11
P	Di-monoacyl urea	—	1.14
Q	Isomer #4	—	1.23
R	Isomer #1	—	1.32
S	Di-monoacyl valine urea	—	1.62
T	2,4-Wing diacyl	0.73	2.87
U	Triacyl impurity	—	3.20

In-Process Revision

the first *Standard solution* injection, is between 0.8 and 1.2; and the relative standard deviation of the peak area response of the main component peak, for replicate injections of the *Standard solution,* is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Diluent, Ritonavir identity standard solution, Standard solution,* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of each impurity in the portion of Ritonavir taken by the formula:

$$0.0025(W_S / W_T)\ (R_T / R_S)(1/F)P$$

in which W_S is the the weight, in mg, of USP Ritonavir RS taken to prepare the *Standard solution;* W_T is the weight, in mg, of Ritonavir taken to prepare the *Test solution;* R_T is the area of the impurity peak obtained from the *Test solution;* R_S is the average peak area of ritonavir obtained from the the six injections of the *Standard solution;* F is the response factor for the impurity (see values in *Table 1*); and P is the purity, in percentage, of USP Ritonavir RS taken to prepare the *Standard solution.* Not more than 0.3% of impurity E and O is found; not more than 0.2% of impurity T is found; not more than 0.1% of any other impurity is found; and not more than 1.0% of total impurities is found.

Assay—

Monobasic potassium phosphate solution (0.03 M)—Dissolve about 8.2 g of monobasic potassium phosphate in 2.0 L of water. Mix well, and pass through a nylon membrane filter having a 0.45-µm porosity.

Diluent—Prepare a mixture of *Monobasic potassium phosphate solution (0.03M)* and acetonitrile (1 : 1). Mix well, and pass through a nylon membrane filter having a 0.45-µm porosity.

Solution A—Prepare a mixture of the filtered *Monobasic potassium phosphate solution (0.03 M),* acetonitrile, tetrahydrofuran (inhibitor-free), and *n*-butanol (69 : 18 : 8 : 5).

Solution B—Prepare a mixture of acetonitrile, the filtered *Monobasic potassium phosphate solution (0.03 M)*, tetrahydrofuran (inhibitor-free), and *n*-butanol (47 : 40 : 8 : 5).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Because of the high dependence of retention time and selectivity on the *Mobile phase* composition, the volumes should be accurately measured. Excessive or continued helium sparging must be avoided. Store the *Mobile phase* in a tightly sealed container when not in use.]

Standard stock preparation—Transfer about 100 mg of USP Ritonavir RS, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix. [NOTE—This solution may be kept for 5 days if refrigerated.]

Intermediate standard preparation—Transfer 5.0 mL of the *Standard stock preparation* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard preparation—Transfer 25.0 mL of the *Intermediate standard preparation* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Assay preparation—Transfer 5.0 mL of the *Test solution,* prepared as directed in the test for *Related compounds,* to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Dilute 25.0 mL of this solution with *Diluent* to 100 mL, and mix.

Chromatographic system—Proceed as directed in the test for *Related compounds.* The run time for the *Standard preparation* and *Assay preparation* is 40 minutes. Chromatograph the *Standard preparation,* and record the responses as directed for *Procedure:* the capacity factor, k', using the main component peak of the first *Standard preparation* injection, is not less than 13; the column efficiency, using the main component peak of the first *Standard preparation* injection, is not less than 5000

theoretical plates; the tailing factor, using the main component peak of the first *Standard preparation* injection, is between 0.8 and 1.2; and the relative standard deviation of the peak area response of the main component peak, for replicate injections of the *Standard preparation,* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage, on the as-is basis, of $C_{37}H_{48}N_6O_5S_2$ in the portion of Ritonavir taken by the formula:

$$0.5(W_S / W_T)(r_T / r_S)P$$

in which W_S is the weight, in mg, of USP Ritonavir RS taken to prepare the *Standard preparation;* W_T is the weight, in mg, of Ritonavir taken to prepare the *Assay preparation;* r_T is the peak area of the impurity obtained from the chromatogram of the *Assay preparation;* r_S is the average peak area of ritonavir obtained from the chromatograms of the five injections of the *Standard preparation;* and P is the purity, in percentage, of USP Ritonavir RS taken to prepare the *Standard preparation.*

Calculate the percentage, on the anhydrous basis, of $C_{37}H_{48}N_6O_5S_2$ in the portion of Ritonavir taken by the formula:

$$100A/(100 - B)$$

in which A is the percentage of $C_{37}H_{48}N_6O_5S_2$ on the as-is basis, as calculated above, and B is the percentage of water content.■1S (*USP29*)

In-Process Revision

BRIEFING

Ropivacaine Hydrochloride Injection. Because there is no existing *USP* monograph for this dosage form, a new monograph is being proposed. The HPLC procedure used in the test for *Limit of 2,6-dimethylaniline* is based on analysis performed with an XTerra MS C18 brand of L1 column, and related compound A and ropivacaine elute at approximately 1.4 minutes and 2.5 minutes, respectively. The HPLC procedure used in the test for *Enantiomeric purity* is based on analysis performed with a Chiral-AGP brand of L41 column, and the typical retention times are approximately 9 minutes and 12 minutes for related compound B (*R* enantiomer) and ropivacaine (*S* enantiomer), respectively. The HPLC procedure used in the *Assay* is based on analysis performed with a µBondapak C18 brand of L1 column, and the typical retention time for ropivacaine is approximately 4 minutes.

(MD-PS: D. Bempong) RTS—42217-1

Add the following:

■Ropivacaine Hydrochloride Injection

» Ropivacaine Hydrochloride Injection is a sterile solution of Ropivacaine Hydrochloride in Water for Injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ropivacaine hydrochloride ($C_{17}H_{26}N_2O \cdot HCl$).

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type 1 glass or of suitable plastic.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Ropivacaine Hydrochloride RS. USP Ropivacaine Related Compound A RS. USP Ropivacaine Related Compound B RS.*

Identification—

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

B: The retention time of the major peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *System suitability solution,* as obtained in the test for *Enantiomeric purity.*

Bacterial endotoxins ⟨85⟩—It contains not more than 60 USP Endotoxin Units per g of ropivacaine hydrochloride.

Particulate matter ⟨788⟩**:** meets the requirements for small-volume injections.

Sterility ⟨71⟩—It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*.

pH ⟨791⟩**:** between 4.0 and 6.0.

Limit of 2,6-dimethylaniline (ropivacaine related compound A, base)—

pH 8.0 Buffer solution—Prepare as directed in the *Assay.*

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

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

Test solution—Dilute accurately the Injection with *Mobile phase* to a concentration of 2.0 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 3.9-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ropivacaine related compound A and ropivacaine is not less than 5; and the signal-to-noise ratio for ropivacaine related compound A is not less than 10.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of ropivacaine related compound A base in the portion of Ropivacaine Hydrochloride taken by the formula:

$$0.1(121.18/157.64)C_S/C_T(r_i/r_S)$$

in which 121.18 is the molecular weight of ropivacaine related compound A base (2,6-dimethylaniline); 157.64 is the molecular weight of USP Ropivacaine Related Compound A RS; C_S is the concentration, in µg per mL, of ropivacaine related compound A in the *Standard solution;* C_T is the concentration, in mg per mL, of ropivacaine hydrochloride in the *Test solution;* and r_i and r_S are the ropivacaine related compound A peak areas obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.01% of ropivacaine related compound A base is found.

Enantiomeric purity—

pH 7.2 Buffer solution—Transfer 7.5 mL of 1 M sodium phosphate monobasic solution and 28.5 mL of 0.5 M sodium phosphate dibasic dihydrate solution into a 1-L volumetric flask, and dilute with water to volume. Adjust the resulting solution to a pH of 7.2, if necessary.

Mobile phase—Transfer 35 mL of isopropyl alcohol into a 500-mL volumetric flask, dilute with *pH 7.2 Buffer solution* to volume, mix, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve suitable quantities of USP Ropivacaine Hydrochloride RS and USP Ropivacaine Related Compound B RS in water, and dilute quantitatively, and stepwise, with water to obtain a solution containing about 75 µg per mL and 0.75 µg per mL, respectively.

Test solution—Dilute the Injection with *Mobile phase* to a concentration of about 75 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4-mm × 10-cm column that contains packing L41. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ropivacaine related compound B (*R* enantiomer) and ropivacaine (*S* enantiomer) is not less than 1.5. [NOTE—For the purpose of identification, the relative retention times are about 0.75 for ropivacaine related compound B and 1.0 for ropivacaine.]

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of ropivacaine related compound B (*R* enantiomer) in the portion of ropivacaine hydrochloride taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of ropivacaine related compound B (*R* enantiomer); and r_s is the sum of the peak responses of ropivacaine (*S* enantiomer) and ropivacaine related compound B (*R* enantiomer) obtained from the *Test solution:* not more than 2.0% of ropivacaine related compound B (*R* enantiomer) is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

pH 8.0 Buffer solution—Transfer 1.3 mL of 1 M sodium phosphate monobasic solution and 32.5 mL of 0.5 M sodium phosphate dibasic dihydrate solution to a 1-L volumetric flask. Dilute with water to volume, and mix. Adjust the resulting solution to a pH of 8.0, if necessary.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *pH 8.0 Buffer solution* (60 : 40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve accurately weighed quantities of USP Ropivacaine Hydrochloride RS and USP Ropivacaine Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise, with *Mobile phase* to obtain a solution having known concentrations of about 0.25 mg per mL of USP Ropivacaine Hydrochloride RS and about 0.26 µg per mL of USP Ropivacaine Related Compound A RS.

Assay preparation—Dilute accurately the Injection with *Mobile phase* to a concentration of about 0.25 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 3.9-mm × 15-cm column that contains 5- or 10-µm packing L1. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections, calculated for the ropivacaine peak, is not more than 1.0%; and the resolution, *R,* between ropivacaine related compound A and ropivacaine is not less than 5.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ropivacaine hydrochloride ($C_{17}H_{26}N_2O \cdot HCl$) in each mL of Injection taken by the formula:

$$C(D / V)(r_U / r_S)$$

in which *C* is the concentration, in mg per mL, of USP Ropivacaine Hydrochloride RS in the *Standard preparation; D* is the dilution factor for the *Assay preparation; V* is the volume of Injection taken, in mL; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S *(USP30)*

BRIEFING

Spironolactone and Hydrochlorothiazide Tablets, *USP 29* page 2001. It is proposed to modify the chromatographic procedure used in the test for *Dissolution.* Using the current chromatographic procedure, sodium lauryl sulfate coelutes with hydrochlorothiazide. The gradient HPLC method being proposed provides a better separation betweeen sodium lauryl sulfate, spironolactone, and hydrochlorothiazide. The new chromatographic method was developed and validated using a Luna C18 brand of L1 packing.

(BPC: M. Marques) RTS—43904-1

In-Process Revision

Change to read:

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid containing 0.1% sodium lauryl sulfate; 900 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Determine the amounts of Spironolactone and Hydrochlorothiazide dissolved using the following method.

Standard solution—Prepare a solution of USP Spironolactone RS and USP Hydrochlorothiazide RS in a mixture of methanol and *Medium* (1 : 1) having accurately known concentrations of about 0.0125 mg of each per mL.

Test solution—Transfer a 5.0-mL portion of the solution under test to a 10-mL volumetric flask, dilute with methanol to volume, and mix.

~~*Mobile phase, Chromatographic system,* and *Procedure*—Proceed as directed in the *Assay.*~~

■*Solution A*—Use acetonitrile.

Solution B—Transfer about 4.5 g of monobasic potassium phosphate to a 1-L volumetric flask containing about 500 mL of water. Dissolve in and dilute with water to volume, and mix.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	25	75	equilibration
0–10	25→75	75→25	linear gradient
10–18	75	25	isocratic
18–25	75→25	25→75	linear gradient

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between hydrochlorothiazide and spironolactone is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Proceed as directed in the *Assay,* injecting 20 µL of each solution.■1S (*USP30*)

Tolerances—Not less than 75% *(Q)* of each of the labeled amounts of $C_{24}H_{32}O_4S$ and $C_7H_8ClN_3O_4S_2$ is dissolved in 60 minutes.

BRIEFING

Triclosan, *USP 29* page 2197 and page 1408 of *PF* 31(5) [Sept.–Oct. 2005]. On the basis of the supporting data, in the *Assay* it is proposed to revise the concentration of the *Standard preparation* to be consistent with the concentration of the *Assay preparation.*

(MD-AA: B. Davani) RTS—44091-1

Change to read:

USP Reference standards ⟨11⟩—

■*USP 2,4-Dichlorophenol RS. USP Parachlorophenol RS.*■1S (*USP29*)
USP Triclosan RS.

■*USP Triclosan Related Compounds Mixture A RS.*■1S (*USP29*)

Change to read:

Limit of monochlorophenols and 2,4-dichlorophenol—

Phosphate buffer—Transfer about 1.38 g of anhydrous monobasic sodium phosphate and about 1.42 g of dibasic sodium phosphate to a 1-L volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Phosphate buffer* (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Quantitatively dissolve accurately weighed quantities of ~~4-chlorophenol and 2,4-dichlorophenol~~

■USP Parachlorophenol RS and USP 2,4-Dichlorophenol RS■1S (*USP29*)
in acetonitrile, dilute with an equal volume of water, and mix. Transfer a portion of this solution to a suitable container, and dilute quantitatively, and stepwise if necessary, with a mixture of acetonitrile and water (1 : 1) to obtain a solution having known concentrations of about 0.5 µg of ~~4-chlorophenol~~

■parachlorophenol■1S (*USP29*)
and 0.1 µg of 2,4-dichlorophenol per mL.

Test solution—Transfer about 250 mg of Triclosan, accurately weighed, to a 25-mL low-actinic volumetric flask, dissolve in 20 mL of acetonitrile, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a coulometric electrochemical detector with electrode 1 set at 0.45 V and electrode 2 set at 0.75 V, both having a positive (oxidative) polarity, and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 9.0% for 2,4-dichlorophenol.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. The peak responses for ~~4-chlorophenol~~

■parachlorophenol■1S (*USP29*)
and 2,4-dichlorophenol in the chromatogram of the *Test solution* are not greater than the corresponding peaks in the chromatogram of the *Standard solution*.

In-Process Revision

Change to read:

Limit of 1,3,7-trichlorodibenzo-*p*-dioxin, 2,8-dichlorodibenzo-*p*-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and glacial acetic acid (70 : 30 : 0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Standard solution*—Transfer accurately weighed quantities of 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran to a volumetric flask, add accurately measured volumes of 1,3,7-trichlorodibenzo-*p*-dioxin and 2,8-dichlorodibenzo-*p*-dioxin, and dissolve in methanol. Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having concentrations of about 0.5, 1.0, 0.5, and 1.0 µg per mL, respectively.~~

■■1S (*USP29*)
Test solution—Transfer about 2.0 g of Triclosan, accurately weighed, to a screw-capped centrifuge tube, add 5 mL of 2 N potassium hydroxide, and shake for 10 minutes to dissolve. Add 3 mL of *n*-hexane, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to a suitable container, add another 3 mL of *n*-hexane to the aqueous layer, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to the previous extract, discard the aqueous layer, add 3 mL of 2 N potassium hydroxide to the combined organic layers, shake for 10 minutes, and allow the phases to separate. Discard the aqueous layer, add another 3 mL of 2 N potassium hydroxide to the combined organic layers, shake for 10 minutes, and allow the phases to separate. Transfer the organic layer to a suitable container, and evaporate with the aid of a stream of nitrogen to dryness. Dissolve the residue in 1.0 mL of methanol, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the ~~*Standard solution,*~~

■USP Triclosan Related Compounds Mixture A RS,■1S (*USP29*) and record the peak responses as directed for *Procedure:* the relative retention times are about 0.59 for 2,8-dichlorodibenzofuran, 0.71 for 2,8-dichlorodibenzo-*p*-dioxin, 0.88 for 2,4,8-trichlorodibenzofuran, and 1.0 for 1,3,7-trichlorodibenzo-*p*-dioxin; and the relative standard deviation for replicate injections is not more than 15.0%, determined from the 2,8-dichlorodibenzo-*p*-dioxin peak.

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. ~~The peak responses for 2,8-dichlorodibenzofuran, 2,8-dichlorodibenzo-*p*-dioxin, 2,4,8-trichlorodibenzofuran, and 1,3,7-trichlorodibenzo-*p*-dioxin obtained from the *Test solution* are not greater than the corresponding peaks obtained from the *Standard solution*~~

■Calculate the concentration of each analyte in the portion of Triclosan taken by the formula:

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

in which C is the concentration, in µg per mL, of the respective analyte in the USP Triclosan Related Compounds Mixture A RS; W is the weight, in g, of Triclosan taken; and r_i and r_S are the peak responses for the respective analyte obtained from the *Test solution* and the USP Triclosan Related Compounds Mixture A RS, respectively: not more than 0.25 ppm of 2,8-dichlorodibenzofuran is found; not more than 0.5 ppm of 2,4,8-trichlorodibenzofuran is found; not more than 0.25 ppm of 1,3,7-trichlorodibenzo-*p*-dioxin is found; and not more than 0.5 ppm of 2,8-dichlorodibenzo-*p*-dioxin is found.■1S (*USP29*)

Change to read:

Assay—

Standard preparation—Dissolve an accurately weighed quantity of USP Triclosan RS in ~~dichloromethane~~

■ethyl acetate,■1S (*USP30*) and dilute quantitatively, and stepwise if necessary, with ~~dichloromethane~~

■ethyl acetate■1S (*USP30*) to obtain a solution having a known concentration of about ~~4.0~~

■0.4■1S (*USP30*) mg per mL.

Assay preparation—Transfer about 40 mg of Triclosan, accurately weighed, to a ~~10-mL~~

■100-mL■1S (*USP30*) volumetric flask, dissolve in and dilute with ~~dichloromethane~~

■ethyl acetate■1S (*USP30*) to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 15-m capillary column with phase G3. The carrier gas is helium maintained at about 6 psi. The injection port temperature is maintained at 34° and is increased rapidly to 200° immediately after the injection, the column temperature is maintained at 34°, and the detector temperature is maintained at 260°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about ~~0.5~~

■2.0■1S (*USP30*) µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, increase the column temperature by 20° per minute to 140°, then increase the column temperature by 4° per minute to 240°, maintain this temperature for not less than 5 minutes, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{12}H_7Cl_3O_2$ in the portion of Triclosan taken by the formula:

~~$10C(r_U / r_S)$~~

■$100C(r_U / r_S)$■1S (*USP30*)

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

In-Process Revision

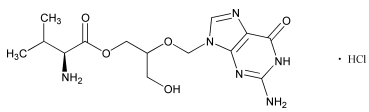
BRIEFING

Valganciclovir Hydrochloride; Valganciclovir Tablets. Because there are no existing *USP* monographs for this drug substance and dosage form, new monographs based on submitted data are being proposed. The gas chromatographic procedure in the test for the *Limit of isopropyl alcohol* is based on analyses performed with the DB624, 3.0-µm brand of G43 column. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Zorbax SB, 3.5-µm brand of L1 column. The liquid chromatographic procedure in the test for *Enantiomeric purity of valganciclovir* is based on analyses performed with the Daicel Crownpak CR(+), 5-µm brand of L## (see *Chromatography* ⟨621⟩) column.

(MD-AA: B. Davani) RTS—43282-1

Add the following:

■Valganciclovir Hydrochloride



$C_{14}H_{22}N_6O_5 \cdot HCl$ 390.82

L-Valine, ester with 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine, monohydrochloride.

L-Valine, 2-[(2-amino-1,6-dihydro-6-oxo-9*H*-purin-9-yl)methoxy]-3-hydroxypropyl ester, monohydrochloride [*175865-59-5*].

» Valganciclovir Hydrochloride contains not less than 97.0 percent and not more than 102.0 percent of $C_{14}H_{22}N_6O_5 \cdot HCl$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩**—***USP Valganciclovir Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩.

Solution: 10 µg per mL.

Medium: methanol.

C: A solution in water (1 in 20) meets the requirements of the tests for *Chloride* ⟨191⟩.

Water, *Method I* ⟨921⟩**:** not more than 8.0%, a 100-mg specimen being used.

Residue on ignition ⟨281⟩**:** not more than 0.10%, a 1-g specimen being used.

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

Limit of isopropyl alcohol—

Internal standard solution—Transfer 100 µL of 1,4-dioxane to a 100-mL volumetric flask, dilute with dimethylformamide to volume, and mix.

Standard stock solution—Transfer 1.0 mL of isopropyl alcohol and 0.1 mL of toluene to a 100-mL volumetric flask, dilute with dimethylformamide to volume, and mix. [NOTE—Toluene is used to verify the system suitability.]

Standard solution—Transfer 2.0 mL of the *Internal standard solution* to a vial. Add 100 µL of *Standard stock solution* to the *Internal standard solution,* and mix.

System suitability solution—Use the *Standard solution.*

Test solution—Transfer between 90 mg to 100 mg of Valganciclovir Hydrochloride, accurately weighed, to a vial. Add 2.0 mL, accurately measured, of *Internal standard solution,* and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m capillary column coated with a 3.0-µm phase G43. The carrier gas is helium, flowing at a rate of about 10.5 mL per minute, and the split ratio is (1 : 15). The chromatograph is programmed as follows. Initially the column temperature is maintained at 40° for 10 minutes, and then the temperature is increased at a rate of 25° per minute to 240°. [NOTE—Condition the column at 240° after each injection for approximately 15 minutes.] The

In-Process Revision

injection port temperature is maintained at about 250°, and the detector temperature is maintained at about 300°. Chromatograph the *System suitability solution* as directed for *Procedure:* the resolution, *R,* between 1,4-dioxane and toluene is not less than 8; the column efficiency, using the 1,4-dioxane peak, is not less than 6000 theoretical plates; and the relative standard deviation of the response area ratios of the isopropyl alcohol peak to the 1,4-dioxane peak for replicate injections is not more than 15%.

Procedure—Separately inject equal volumes (about 0.5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentages of isopropyl alcohol in the portion of Valganciclovir Hydrochloride taken by the formula:

$$100(VC/W)(R_U/R_S)$$

in which V is the volume, in mL, of the *Test solution; C* is the concentration, in mg per mL, of isopropyl alcohol in the *Standard solution; W* is the weight, in mg, of Valganciclovir Hydrochloride taken; and R_U and R_S are the peak area ratios of isopropyl alcohol to the internal standard obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.0% of isopropyl alcohol is found.

Related compounds—

TEST 1—

Solution A—Use *0.01 M Monobasic ammonium phosphate,* prepare as directed in the *Assay.*

Solution B—Use methanol.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system* (see *Table 1*). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The chromatograph is programmed as shown in *Table 1.*

Table 1

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	92	8	isocratic
5–15	92→80	8→20	linear gradient
15–30	80→30	20→70	linear gradient

[NOTE—Equilibrate the column with starting *Mobile phase* for at least 15 minutes between injections.] The column temperature is maintained at 25°, and the flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the first peak of valganciclovir and the methoxymethylguanine peak is not less than 1.0, and the resolution, *R,* between the two peaks for valganciclovir (*R* and *S* esters of L-valine) is not less than 3.0; the column efficiency determined using the second peak of valganciclovir is not less than 8000 theoretical plates; and the tailing factor for the second peak of valganciclovir is not more than 1.4. [NOTE—The typical retention time for the second peak of valganciclovir is between 5 and 8.5 minutes.]

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. The approximate relative retention times for each individual impurity are listed in *Table 3*. Calculate the percentage of each impurity in the portion of Valganciclovir Hydrochloride taken by the formula:

$$100(r_i/F_i)/(\Sigma r_i/F_i)$$

in which the r_i is the area response for each impurity, and F_i is the relative response factor for each individual component listed in *Table 3*: The impurities meet the requirements as specified in *Table 3*.

TEST 2—

Solution A—Dilute 2.5 mL of triethylamine with water to 1000 mL, and adjust with trifluoroacetic acid to a pH of 3.0 ± 0.05. Pass this solution through a filter having a 0.45-µm porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution B—Use methanol.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system* (see *Table 2*). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The chromatograph is programmed as follows in *Table 2.*

Table 2

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	93	7	isocratic
10–20	93→70	7→30	linear gradient

[NOTE—Equilibrate the column with starting *Mobile phase* for at least 15 minutes between injections.] The column temperature is maintained at 30°, and the flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the two peaks for valganciclovir (*R* and *S* esters of L-valine) is not less than 1.3; the column efficiency determined using the second peak of valganciclovir is not less than 8000 theoretical plates; and the tailing factor for the second peak of valganciclovir is not more than 1.2. [NOTE—The typical retention time for the second peak of valganciclovir is between 6 and 9 minutes.]

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of ganciclovir mono-*N*-methyl valinate impurity in the portion of Valganciclovir Hydrochloride taken by the formula:

$$100(r_i / F_i)/(\Sigma r_i / F_i)$$

in which R_i is the sum of the area responses of ganciclovir mono-*N*-methyl valinate impurity (diastereomers); and F_i is the relative response factor for this impurity and valganciclovir as given in *Table 3*. The impurity limits meet the requirements specified in *Table 3*.

Diastereomer ratio—Using the chromatogram for *Test 1* in the test for *Related compounds,* calculate the percentage of valganciclovir (*R* and *S* esters of L-valine) by the following formulas:

$$100[r_A (r_A + r_B)]$$

$$100[r_B (r_A + r_B)]$$

in which r_A and r_B are the peak responses for valganciclovir (*R* and *S* esters of L-valine), respectively. The diastereomer ratio is (45 : 55) to (55 : 45).

Enantiomeric purity of valganciclovir—

Mobile phase—Dissolve 16.2 g of perchloric acid in 1000 mL of water, and mix. Pass this solution through a filter having a 0.5-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 5 mg of USP Valganciclovir Hydrochloride RS and 0.5 mg of D-valine esters to a 25-mL volumetric flask, dissolve in and dilute with 0.001 N hydrochloric acid to volume, and mix.

Table 3

Component	Common Name	Test Number	Relative Retention Time	Relative Response Factor	Maximum Limit (%)
Valganciclovir	Valganciclov	1, 2	1.00	1.00	—
A[a]	Ganciclovir	1	0.42	1.4	1.5
B[a]	Guanine	1	0.28	1.9	0.25
C[a]	Methoxymethylguanine	1	0.81	1.0	0.3
D[a, b]	Isovalganciclovir	1	1.26	1.0	0.5
E[a]	Monoacetoxyganciclovir	1	1.36	1.3	0.15
F (other identified impurity)	Bis-valine easter of ganciclovir	1	1.61	0.71	0.1
G[a, b]	Homologue of valganciclovir	1	1.66	1.0	0.25
H	—	1	1.47	1.3	0.1
I	—	1	1.52	1.4	0.1
J (other identified impurity)	Ganciclovir monopropionate	1	2.09	1.1	0.15
K[a]	Valganciclovir dimer (stereoisomer A)	1	2.49	1.0	0.1
L[a]	Valganciclovir dimer (stereoisomer B)	1	2.52	1.0	0.1
M[a]	Valganciclovir dimer (stereoisomer C)	1	2.54	1.0	0.1
N[a, b]	Ganciclovir mono-*N*-methyl valinate	2	1.2	1.0	0.3
Other identified impurity	—	1	—	1.0	0.1 individual; 0.25 total
Unidentified impurity	—	1 and 2	—	1.0	0.1 individual; 0.25 total
Total of all impurities	—	1 and 2	—	—	3.0

[a] Specified impurity
[b] Reported as the sum of diastereomers

In-Process Revision

Test solution—Transfer about 10 mg of Valganciclovir Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with 0.001 N hydrochloric acid to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.0-mm × 15-cm column that contains packing L## (see *Chromatography* ⟨621⟩). The column temperature is maintained at ambient temperature, and the flow rate is about 0.8 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the second peak of the D-valine ester pair and the first peak of the valganciclovir pair is not less than 3.5; and the column efficiency determined using the second peak of valganciclovir is not less than 1800 theoretical plates.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the enantiomeric purity, in percent, by the following formula:

$$100[r_S / (r_S + r_{IM})]$$

in which r_S is the sum of the peak responses of valganciclovir (*R* and *S* esters of L-valine) and r_{IM} is the sum of the peak responses of the enantiomeric impurities (*R* and *S* esters of D-valine), respectively. The enantiomeric purity is not less than 97.0%.

Assay—

0.10 M Monobasic ammonium phosphate solution—Dissolve 11.5 g of monobasic ammonium phosphate in about 900 mL of water, adjust with phosphoric acid (85%) to a pH of 2.8 ± 0.2, dilute with water to obtain 1000 mL of solution, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.10 M Monobasic ammonium phosphate* and methanol (92 : 8). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 10 mg of USP Valganciclovir Hydrochloride RS and 0.5 mg of methoxymethylguanine to a 50-mL volumetric flask, dissolve in and dilute with 0.001 N hydrochloric acid to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Valganciclovir Hydrochloride RS in 0.001 N hydrochloric acid, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.2 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Valganciclovir Hydrochloride in 0.001 N hydrochloric acid, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a concentration of about 0.2 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The column temperature is maintained at 25°, and the flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* meets the system suitability requirements as specified for *Test 1* in the test for *Related compounds.* Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation of the correction factor (C_F) for replicate injections is not more than 1.0%. [NOTE—C_F is calculated as directed below in the *Procedure*.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage, on the anhydrous and solvent-free basis, of $C_{14}H_{22}N_6O_5 \cdot HCl$ in the portion of Valganciclovir Hydrochloride taken by the formula:

$$100[(r_U / W_U)(C_F)(100) / (100 - S_U)]$$

in which r_U is the peak response (sum of two peaks for valganciclovir diastereomers) obtained from the *Assay preparation;* W_U is the weight, in mg, of Valganciclovir Hydrochloride in the *Assay preparation;* C_F is the correction factor; and S_U is the total percent of solvent and water in the test sample.

The C_F is calculated using the following formula:

$$(W_S / R_S)(100 - S_S/100)$$

in which W_S is the weight, in mg, of USP Valganciclovir Hydrochloride RS in the *Standard preparation;* R_S is the area response (sum of two peaks for valganciclovir diastereomers) obtained from the *Standard preparation;* and S_S is the total percent of solvent and water in USP Valganciclovir Hydrochloride RS. ■1S (*USP30*)

BRIEFING

Valganciclovir Tablets—See briefing under *Valganciclovir Hydrochloride*. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Zorbax SB-Phenyl 3.5-µm brand of L11 column.

(MD-AA: B. Davani; BPC: M. Marques) RTS—43284-1

In-Process Revision

Add the following:

■Valganciclovir Tablets

» Valganciclovir Tablets contain not less than 93.0 percent and not more than 110.0 percent of the labeled amount of valganciclovir ($C_{14}H_{22}N_6O_5$).

Packaging and storage—Preserve in tight containers. Store at 25°C, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Valganciclovir Hydrochloride RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Spectral range: 200–350 nm.

Solution: 10 µg per mL.

Medium: 0.001M hydrochloric acid.

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

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Standard solution—Expose the USP Valganciclovir RS to ambient conditions overnight, and determine the water content prior to use. Accurately weigh an amount equivalent to approximately 100 mg of valganciclovir free base, transfer to a 20-mL volumetric flask, dilute with *Medium* to volume, and mix.

Working standard solution—Transfer 5.0 mL of the *Standard solution* to a 50-mL volumetric flask, dilute with *Medium* to volume, and mix well. Pass a portion of this solution through a 10-µm polyethylene filter, discarding the first 2 mL.

Test solution—Pass 10 mL of the solution under test through a 10-µm polyethylene filter, discarding the first 2 mL.

Procedure—Determine the amount of $C_{14}H_{22}N_6O_5$ dissolved by UV absorption at the wavelength of maximum absorbance at about 254 nm on portions of the *Test solution,* suitably diluted with *Medium,* if necessary, in comparison

with the *Working standard solution,* using a 0.02-cm quartz cell. Calculate the weight of valganciclovir free base by the formula:

$$W_S\left(\frac{100 - W_C}{100}\right) \times 0.91 \times P$$

in which W_S is the weight, in mg, of USP Valganciclovir RS taken to prepare the *Standard solution;* W_C is the water content of the USP Valganciclovir RS; 0.91 is the conversion factor from valganciclovir hydrochloride to valganciclovir free base; and P is the purity, in decimals, of the USP Valganciclovir RS. Calculate the amount, in percentage, of valganciclovir released by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of valganciclovir free base in the *Working standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances: Not less than 80% (Q) of the labeled amount of valganciclovir is dissolved in 30 minutes.

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

PROCEDURE FOR CONTENT UNIFORMITY—

Mobile phase, Diluent, Resolution Solution, and *Chromatographic System*—Proceed as directed in the *Assay.*

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

Test solution—Transfer 1 Tablet to a 100-mL volumetric flask, add about 80 mL of *Diluent,* and sonicate until the Tablet is fully disintegrated. Dilute with *Diluent* to volume, mix, and allow the solution to settle. Pipet 3.0 mL of the top portion of the resulting solution into a 200-mL volumetric flask, dilute with *Diluent* to volume, and mix. Pass a portion of the solution through a filter having a 0.45-µm or finer porosity, and use the filtrate, discarding the initial 2 mL.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of valganciclovir ($C_{14}H_{22}N_6O_5$) in the Tablet taken by the formula:

$$W_S(r_U/r_S)(0.91)(100 - S_S/100)(D_U/D_S)$$

in which W_S is the weight, in mg, of USP Valganciclovir Hydrochloride RS taken to prepare the *Standard solution;* r_U and r_S are the sum of the peak responses of valganciclovir obtained from the *Test solution* and the *Standard solution,* respectively; 0.91 is the conversion factor for valganciclovir hydrochloride to valganciclovir free base; S_S is the percent of water in the USP Valganciclovir Hydrochloride RS; and D_U and D_S are the dilution factors of the *Test solution* and *Standard solution,* respectively.

Related compounds—

Mobile phase, Diluent, Resolution Solution, and *Chromatographic System*—Proceed as directed in the *Assay.*

Standard Solution—Use the *Standard preparation* in the *Assay.*

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 450 mg of valganciclovir, to a 1000-mL volumetric flask, add about 800 mL of *Diluent,* and sonicate until the Tablet is fully disintegrated. Dilute with *Diluent* to volume, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate, discarding the initial 2 mL.

Procedure—Inject a volume (about 50 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of ganciclovir and guanine in the portion of Tablets taken by the formula:

$$W_S(r_U/r_S)(0.91)(1/FL)(100 - S_S/100)(D_U/D_S)(W_A/W_U)(100)$$

in which W_S is the weight, in mg, of USP Valganciclovir Hydrochloride RS taken to prepare the *Standard solution;* r_U is the guanine or ganciclovir peak response obtained from the *Test solution;* r_S is the sum of the peak responses of the valganciclovir diastereomers obtained from the *Standard solution;* 0.91 is the conversion factor for valganciclovir hydrochloride to valganciclovir free base; F is the relative response factor, 1.9 and 1.4, for guanine and ganciclovir, respectively; L is the labeled amount, in mg, of valganciclovir in each Tablet; S_S is the percent of water in the USP Valganciclovir Hydrochloride RS; D_U and D_S are the dilution factors of the *Test solution* and *Standard solution,* respectively; W_A is the average weight, in mg, of a Tablet; and W_U is the weight, in mg, of the powdered Tablet taken to prepare the *Test solution.* Not more than 2.0% of ganciclovir and not more than 1.0% of guanine are found.

Calculate the individual unidentified and identified impurities listed in *Table 1* using the formula:

$$100(r_i/r_s)$$

in which r_i is the peak response for each impurity/degradant, and r_s is the sum of the responses of all the peaks: not more than 0.2% of each unidentified individual impurity is found; not more than 0.5 % of total unidentified impurity/degradant is found; and not more than 3.5% of total impurities including all the degradation products is found.

Table 1:

Name	Component	Approximate Relative Retention time
Guanine	Degradant	0.51
Ganciclovir	Degradant	0.66
Valganciclovir 1	Active	1.00
Valganciclovir 2	Active	1.07
Ganciclovir-mono-*N*-methyl valinate 1	Impurity	1.21
Ganciclovir-mono-*N*-methyl valinate 2	Impurity	1.30
Methoxymethylguanine	Impurity	1.45
Isovalganciclovir 1	Impurity	1.55
Isovalganciclovir 2	Impurity	1.61
Ganciclovir Divalinate	Impurity	2.13
Monoacetoxyganciclovir	Impurity	2.31
Isomonochloroganciclovir	Impurity	2.52
Homologue 1	Impurity	2.69
Homologue 2	Impurity	2.77

Assay—

Solution A—Dilute 2.5 mL of triethylamine with water to 1000 mL, and adjust with trifluoroacetic acid to a pH of 3.0 ± 0.05.

Solution B—Use methanol.

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and *Solution B* (93 : 7). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Dilute 1.0 mL of 1 M hydrochloric acid with water to 1.0 L, and mix.

Resolution solution—Dissolve suitable quantities of ganciclovir mono-*N*-methylvaline and USP Valganciclovir Hydrochloride RS in *Diluent* to obtain a solution containing about 0.1 µg per mL and 78 µg per mL, respectively.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Valganciclovir Hydrochloride RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.3 mg per mL.

Standard preparation—Pipet 6.0 mL of *Standard stock preparation* into a 20-mL volumetric flask. Dilute with *Diluent* to volume, and mix well. Pass a portion of the solution through a filter having a 0.45-µm or finer porosity, and use the filtrate, discarding the initial 2 mL.

Assay preparation—Transfer five Tablets into a 500–mL volumetric flask, add about 300 mL of *Diluent,* and shake well until the Tablets are fully disintegrated. Dilute with *Diluent* to volume, mix, and allow the solution to settle. Transfer 3.0 mL of the supernatant into a 200-mL volumetric flask, and dilute with *Diluent* to volume. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate, discarding the initial 2 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *Resolution solution* as directed for *Procedure:* the resolution, *R,* between the second diastereomeric valganciclovir peak and the first ganciclovir mono-*N*-methylvaline peak is not less than 2. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency for the second diastereomeric valganciclovir peak is not less than 3000 theoretical plates; the tailing factor for the second diastereomeric valganciclovir peak is not more than 3; and the relative standard deviation for the total areas for the two valganciclovir peaks for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of valganciclovir ($C_{14}H_{22}N_6O_5$) in the portion of Tablets taken by the formula:

$$W_S(r_U / r_S)(0.91)(100 - S_S/100)(D_U / D_S)$$

in which W_S is the weight, in mg, of USP Valganciclovir Hydrochloride RS taken to prepare the *Standard preparation;* r_U and r_S are the sum of the peak responses for the valganciclovir diastereomers obtained from the *Assay preparation* and the *Standard preparation,* respectively; 0.91 is the conversion factor for valganciclovir hydrochloride to valganciclovir free base; S_S is the percent of water in the USP Valganciclovir Hydrochloride RS; and D_U and D_S are the dilution factors of the *Assay preparation* and *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Valproic Acid Injection, page 1412 of *PF* 31(5) [Sept.–Oct. 2005]. To allow additional time for public review and comment, the adoption of this monograph has been postponed from the *First Supplement* to *USP 29–NF 24* to the *First Supplement* to *USP 30–NF 25*. The official date for the previously proposed monograph title, *Valproic Acid Injection,* has likewise been postponed from October 1, 2007, to October 1, 2008. The use of this title will be permitted as of April 1, 2007, but it will not become mandatory until October 1, 2008. The 18-month extension is intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the terminology.

(NOM: L. Paul) RTS—44110-1

Add the following:

■Valproic Acid Injection

(Title for this new monograph—to become official October 1, 2008)

» Valproic Acid Injection is a sterile aqueous solution of sodium valproate, formed from the interaction of Valproic Acid and Sodium Hydroxide, in Water for Injection, and one or more suitable buffering or sequestering agents. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of valproic acid ($C_8H_{16}O_2$). Valproic Acid Injection contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose *Containers for Injection* as described under *Injections* ⟨1⟩, preferably of Type I glass. Store at controlled room temperature, excursions allowed between 15° and 30°.

Labeling—Label it to state the name and quantity of any buffering or sequestering agent used.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Valproic Acid RS.*

Identification—

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

B: It meets the requirements of the tests for *Sodium* ⟨191⟩.

Bacterial endotoxins ⟨85⟩—It contains not more than 23 USP Endotoxin Units per mL of Injection.

Sterility ⟨71⟩—It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product To Be Examined.*

pH ⟨791⟩**:** between 7.0 and 9.0.

Particulate matter ⟨788⟩—It meets the requirements for small-volume injections.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Internal standard solution—Dissolve a quantity of biphenyl in methylene chloride to obtain a solution containing 5 mg per mL.

Standard stock preparation—Prepare a solution of USP Valproic Acid RS in *Internal standard solution* having a concentration of about 8 mg per mL.

Standard preparation—Transfer 5.0 mL of *Standard stock preparation* into a 50-mL volumetric flask, and dilute with methylene chloride to volume.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to 400 mg of valproic acid, into a suitable container; add about 20 mL of 5% (v/v) hydrochloric acid; shake by mechanical means for 2 minutes; add 50.0 mL of *Internal standard solution;* and shake by mechanical means for 1 hour. Allow the phase to separate (approximately 1 hour). The bottom organic layer remains cloudy, and at times a slight emulsion may persist. If an emulsion forms, break it up by stirring it with a glass rod. Pipet 5 mL of the extract from the bottom organic layer into a 50-mL volumetric flask, and dilute with methylene chloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 1.8-m glass column packed with 10% phase G34 on 80- to 100-mesh support S1A. The column temperature is maintained at about 155°, the injection port temperature is maintained at about 275°, and the detector block temperature is maintained at about 300°. Dry helium is used as the carrier gas, at a flow rate of about 20 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the resolution, *R,* between the valproic acid

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and biphenyl peaks is not less than 3.0; and the relative standard deviation of the peak area ratios for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for the valproic acid and biphenyl peaks. Calculate the quantity, in mg, of valproic acid in the volume of Injection taken by the formula:

$$C(R_U / R_S)\, D$$

in which C is the concentration, in mg per mL, of USP Valproic Acid RS in the *Standard preparation;* R_U and R_S are the peak area ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively; and D is the appropriate dilution factor used to prepare the *Assay preparation.* ■1S (*USP30*)

BRIEFING

Verapamil Hydrochloride, *USP 29* page 2244. It is proposed to revise the test for *Chromatographic purity,* because the current method is not intended to test for verapamil related compound D, and it cannot be eluted out of the column using the existing method. The proposed revision is based on a modification of the procedure described in the monograph in the *European Pharmacopoeia* 5.2. The liquid chromatographic procedure uses a Supelco Discovery RP amide column packed with end-capped palmitamidopropyl silyl silica gel of 5-µm particle size. The *USP Reference standards* section and *Identification* test *B* are also revised accordingly.

(MD-CV: S. Ramakrishna) RTS—44077-1

Change to read:

USP Reference standards ⟨11⟩—*USP Verapamil Hydrochloride RS. USP Verapamil Related Compound B RS.*

■*USP Verapamil Related Compound D RS.* ■1S (*USP30*)

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak for verapamil in the chromatogram of the ~~*Test preparation*~~

■*Test solution* ■1S (*USP30*)
corresponds to that in the chromatogram of ~~*Standard preparation B,*~~

■the *Standard solution,* ■1S (*USP30*)
as obtained in the test for *Chromatographic purity.*

C: It responds to the tests for *Chloride* ⟨191⟩.

Change to read:

Chromatographic purity—

~~*Aqueous solvent mixture*—Prepare a 0.015 N sodium acetate solution containing about 33 mL of glacial acetic acid per L.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of *Aqueous solvent mixture,* acetonitrile, and 2-aminoheptane (70 : 30 : 0.5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparations*—Dissolve an accurately weighed quantity of USP Verapamil Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain *Standard preparation A* and *Standard preparation B* having known concentrations of about 5.6 and 9.4 µg per mL, respectively.~~

~~*Test preparation*—Prepare a solution of Verapamil Hydrochloride in *Mobile phase* having a known concentration of about 1.9 mg per mL.~~

~~*System suitability solution*—Dissolve suitable quantities of USP Verapamil Hydrochloride RS and USP Verapamil Related Compound B RS in *Mobile phase* to obtain a *System suitability solution* having known concentrations of about 1.9 and 1.5 mg, respectively, in each mL.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩): The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 12.5- to 15-cm column that contains packing L1. The flow rate is about 0.9 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.88 for verapamil related compound B and 1.0 for verapamil; the resolution, *R,* between the verapamil related compound B and verapamil peaks is not less than 1.5, and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 10 µL) of *Standard preparations A* and *B* and the *Test preparation* into the chromatograph, and allow the *Test preparation* to elute for not less than four times the retention time for verapamil. Record the chromatograms, and measure all the peak responses. The sum of the peak responses, other than that of verapamil, from the *Test preparation* is not greater than the verapamil peak response obtained from *Standard preparation B* (0.5%); and no single peak response is greater than that of the verapamil peak response obtained from *Standard preparation A* (0.3%).~~

■*Buffer solution*—Dissolve 6.97 g of dibasic potassium phosphate in 1 L of water, and adjust with phosphoric acid to a pH of 7.2.

Solution A—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (63 : 37).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (67 : 33).

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

System suitability solution—Dissolve an accurately weighed quantity of USP Verapamil Hydrochloride RS, USP Verapamil Related Compound B RS, and USP Verapamil Related Compound D RS in *Solution A* to obtain a solution having known concentrations of about 0.025 mg per mL each of verapamil hydrochloride, verapamil related compound B, and verapamil related compound D.

Standard solution—Transfer about 25 mg of USP Verapamil Hydrochloride RS, accurately weighed, to a 10-mL volumetric flask, dilute with *Solution A* to volume, and mix. Quantitatively dilute further with *Solution A* to obtain a final concentration of 2.5 µg per mL.

Test solution—Transfer about 25 mg of Verapamil Hydrochloride, accurately weighed, to a 10-mL volumetric flask, dilute with *Solution A* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 25-cm column containing packing L60 (see *Chromatography* ⟨621⟩). The flow rate is about 1.5 mL per minute. Initially equilibrate the column for about 60 minutes with *Solution A.* The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–9	100→70	0→30	linear gradient
9–18	70→0	30→100	linear gradient
18–50	0	100	isocratic
50–51	0→100	100→0	linear gradient
51–61	100	0	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the peaks for verapamil related compound B and verapamil is not less than 5.0; and verapamil related compound D elutes out from the column.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Verapamil Hydrochloride taken by the formula:

$$100(C_S/C_U)(r_i/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Verapamil Hydrochloride RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Verapamil Hydrochloride in the *Test solution;* r_i is the peak response for each individual impurity obtained from the *Test solution;* and r_S is the peak response of verapamil hydrochloride obtained from the *Standard solution:* not more than 0.1% of verapamil related compound B, not more than 0.1% of verapamil related compound D, not more than 0.1% of any other individual impurity, and not more than 0.3% of total impurities is found. [NOTE—Disregard any impurity less than 0.01%.]■1S *(USP30)*

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 24* page 3257 and page 1664 of *PF* 31(6) [Nov.–Dec. 2005]. It is proposed to add *Coconut Oil* to the *Coating Agent* and *Emulsifying and/or Solubilizing Agent* categories and *Polyvinyl Acetate* to the *Coating Agent, Desiccant,* and *Tablet Binder* categories to complement the proposed new monographs for *Coconut Oil* and *Polyvinyl Acetate,* respectively, which appear elsewhere in this issue of *PF.*

(EM2) RTS—43401-1; 43513-1

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Change to read:

Coating Agent

■Amino Methacrylate Copolymer■2S (*NF24*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose, Sodium
Cellaburate
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Cellulose Acetate Phthalate (see Cellacefate)

■Coconut Oil■1S (*NF25*)
Copovidone

■Corn Syrup Solids■2S (*NF24*)

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Maltodextrin
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol

■Polyvinyl Acetate■1S (*NF25*)
Polyvinyl Acetate Phthalate
Shellac
Starch, Pregelatinized Modified
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Desiccant
Calcium Chloride
Calcium Sulfate

■Polyvinyl Acetate■1S (*NF25*)
Silicon Dioxide

Change to read:

Emollient
Alkyl (C12-15) Benzoate
Hydrogenated Soybean Oil

▲Oleyl Oleate▲*NF25*

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Carbomer Copolymer
Carbomer Interpolymer
Cholesterol

■Coconut Oil■1S (*NF25*)
Diethanolamine (Adjunct)
Diethylene Glycol Stearates
Ethylene Glycol Stearates
Glyceryl Distearate
Glyceryl Monolinoleate
Glyceryl Monooleate
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)

▲Oleyl Oleate▲*NF25*
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
Polyoxyl Lauryl Ether
Polyoxyl Stearyl Ether
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Cetostearyl Sulfate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Sorbitan Sesquioleate
Sorbitan Trioleate
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:

Humectant

■Corn Syrup Solids■2S (*NF24*)

■Erythritol■2S (*NF24*)
Glycerin
Hexylene Glycol

■Maltitol■2S (*NF24*)
Propylene Glycol
Sorbitol
Sorbitol Sorbitan Solution

■Tagatose■1S (*NF24*)

Change to read:

Polymer Membrane

■Amino Methacrylate Copolymer■2S (*NF24*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Cellaburate
Cellulose Acetate

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

■Gamma Cyclodextrin■2S (*NF24*)
Sodium Tartrate

Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol

▲Canola Oil▲*NF25*
Caprylocaproyl Polyoxylglycerides
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
▲Lauroyl Polyoxylglycerides▲*NF24*
Linoleoyl Polyoxylglycerides
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Polyoxylglycerides
Peanut Oil
Polyethylene Glycol
Polyethylene Glycol Monomethyl Ether
Propylene Glycol
Sesame Oil
Stearoyl Polyoxylglycerides
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
Alamic Acid
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carbomer Copolymer
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

■Corn Syrup Solids■2S (*NF24*)
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate
Maltodextrin
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
Starch, Corn
Starch, Potato
Starch, Tapioca
Starch, Wheat
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent
Acesulfame Potassium
Aspartame
Aspartame Acesulfame

■Corn Syrup Solids■2S (*NF24*)
Dextrates
Dextrose
Dextrose Excipient

■Erythritol■2S (*NF24*)
Fructose
Galactose

■Maltitol■2S (*NF24*)
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible

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Sugar, Confectioner's
Syrup

■Tagatose■1S (*NF24*)

Change to read:

Tablet Binder
Acacia
Alginic Acid

■Amino Methacrylate Copolymer■2S (*NF24*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
Copovidone

■Corn Syrup Solids■2S (*NF24*)
Dextrin

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■2S (*NF24*)
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Low-Substituted Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Maltodextrin
Maltose
Methylcellulose
Polyethylene Oxide

■Polyvinyl Acetate■1S (*NF25*)
Povidone
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Syrup

Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered

■Corn Syrup Solids■2S (*NF24*)
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose, Monohydrate

■Maltitol■2S (*NF24*)
Maltodextrin
Maltose
Mannitol
Sorbitol
Starch
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tonicity Agent

■Corn Syrup Solids■2S (*NF24*)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

■Corn Syrup Solids■2S (*NF24*)
Dextrose
Peppermint Water
Sorbitol Solution
Syrup
OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil

▲Canola Oil▲*NF25*
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Valerian, *USP 29* page 2384. The USP Powdered Valerian RS is proposed for deletion from the *USP Reference standards* section because of the unavailability of this Reference Standard. Affected also is *Identification* test *B,* which uses this Reference Standard, and the accompanying *Notes* in *Identification* test *A.* In the absence of any significant adverse comment, it is proposed to implement the above revisions via the *Third Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of June 1, 2006.

In the *Packaging and storage* section, it is proposed to include a storage temperature. In the test for *Extractable matter,* changes are proposed to simplify the procedure: alcohol 70 percent is used instead of a mixture of 12 g of alcohol and 8 g of water, and measurements of the liquids are in volume instead of by weight. In the section *Microbial enumeration,* revisions to change the limits are proposed to be consistent with those in *USP* General Chapter *Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements* ⟨2023⟩.

(DSB: M. Sharaf) RTS—44023-1; 43959-1

Change to read:

Packaging and storage—Store in tight containers, protected from light and moisture,

■and store at room temperature.■1S *(USP30)*

Change to read:

USP Reference standards ⟨11⟩—~~*USP Powdered Valerian RS.*~~

••3
USP Valerenic Acid RS.

Change to read:

Identification—

A: Transfer about 0.2 g of freshly powdered Valerian to a test tube, add 5 mL of methylene chloride, shake several times, and allow to stand for 5 minutes. Filter, wash the filter with 2 mL of methylene chloride, and combine the filtrate and washings in one container. Heat the combined filtrate and washings on a water bath for the minimum time required to evaporate the solvent, and dissolve the residue in 0.2 mL of methylene chloride. ~~[NOTE—Retain a portion of this solution for use in *Identification* test *B.*]~~

••3

To about 0.1 mL of this solution, add 3 mL of a mixture of equal volumes of glacial acetic acid and 25% hydrochloric acid, and shake several times: a blue color develops within 15 minutes.

~~**B:** *Thin-Layer Chromatographic Identification Test* ⟨201⟩—~~
~~*Adsorbent:* 0.50-mm layer of chromatographic silica gel.~~
~~*Test solution:* solution reserved from *Identification* test *A.*~~
~~*Standard solution:* prepared similarly to the *Test solution* except to begin with 0.2 g of USP Powdered Valerian RS.~~
~~*Application volume:* duplicate 20-µL portions, applied as 20-mm × 3-mm bands.~~
~~*Developing solvent system*—Develop the plates twice in a mixture of toluene and ethyl acetate (75 : 25), each time allowing the solvent front to ascend 10 cm above the line of application. Remove the plate from the developing chamber, mark the solvent front, and allow the plate to air-dry. Spray the plate with a mixture of hydrochloric acid and acetic acid (8 : 2), and heat at 110° for 10 minutes. Remove the plate from the oven, cool, and visually examine the plate: the chromatogram of each solution shows a blue-to-blue-black zone due to valtrate and isovaltrate at an R_F value of about 0.75; a light brown to dark brown zone due to didrovaltrate at an R_F value of about 0.65; and a blue-to-blue-black zone due to acevaltrate at an R_F value of about 0.55.~~

•••3
~~*C:*~~

•**B:**•3
The retention time of the valerenic acid peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *Standard solution,* as obtained in the test for *Content of valerenic acid.*

Change to read:

Extractable matter—Mix 2 g of Valerian, carefully dried at 40°, and coarsely powdered, with ~~a mixture of 12 g of alcohol and 8 g of water~~

■20 mL of 70 percent alcohol,■1S *(USP30)*
and allow to stand for 2 hours, shaking frequently. Filter, evaporate ~~5 g~~

■5 mL■1S *(USP30)*
of the filtrate on a water bath to dryness, and dry the residue at 105°. The weight of the dried residue is not less than 100 mg (20%).

Change to read:

Microbial enumeration ⟨2021⟩—The total bacterial count does not exceed ~~10,000~~

■10^5■1S *(USP30)*
cfu per g, the total combined molds and yeasts count does not exceed ~~100~~

■10^3■1S *(USP30)*
cfu per g,

■bile-tolerant Gram-negative bacteria does not exceed 10^3,■1S *(USP30)*
and it meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* ~~and for absence of *Staphylococcus aureus.*~~

■■1S *(USP30)*

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BRIEFING

Powdered Valerian, *USP 29* page 2385. In the section for *Packaging and storage,* it is proposed to include a storage temperature. In the section for *Botanic characteristics,* an editorial correction is made.

It is proposed to delete the USP Powdered Valerian RS from the *USP Reference standards* section because this Reference Standard is unavailable. In the absence of any significant adverse comment, it is proposed to implement this revision via the *Third Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of June 1, 2006.

(DSB: M. Sharaf) RTS—44023-2; 43959-2

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light and moisture,

■and store at room temperature.■1S (*USP30*)

Change to read:

Labeling—The label states the Latin binomial and, following the official name, the parts of the plant ~~source~~

■■1S (*USP30*)
from which the article was derived.

Change to read:

USP Reference standards ⟨11⟩~~*— USP Powdered Valerian RS.*~~

•■
USP Valerenic Acid RS.

Change to read:

Botanic characteristics—

Diagnostic structures: Numerous fragments of parenchyma cells containing globules of volatile oil and starch granules; fragments of scalariform and reticulate thickened vessels and tracheids and strongly ~~liquefied~~

■lignified■1S (*USP30*)
narrow fibers; fragments of periderm and of piliferous layer with root hairs; numerous starch granules, rarely simple, mostly compounds of 2 to 6 components, spheroidal, plano-convex, 3 to 20, mostly 8 to 12 µm, in diameter with a central hilum, the starch granules being 7 to 30 µm in diameter.

BRIEFING

Valerian Tablets, *USP 29* page 2386. In the *Packaging and storage* section, it is proposed to include a storage temperature. It is proposed to add USP Fluorescein RS to the *USP Reference standards* section because it is used in the *Standard solution* of the *Identification* test, which is cross referenced to *Powdered Valerian Extract*.

(DSB: M. Sharaf) RTS—44025-1

Change to read:

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

■and store at room temperature.■1S (*USP30*)

Change to read:

USP Reference standards ⟨11⟩—

■*USP Fluorescein RS.*■1S (*USP30*)
USP Valerenic Acid RS.

MONOGRAPHS (NF)

BRIEFING

Alfadex, *NF 24* page 3268. It is proposed to make the following revisions to this monograph: add a *Packaging and storage* section; replace the test for *Loss on drying* with a *Water* test that will affect how to prepare the *Test solutions* in the tests for *Reducing sugars* and *Light-absorbing impurities* and the preparation of the *Standard preparation,* the *System suitability preparation,* and the *Assay stock preparation* in the *Assay;* also in the *Assay,* revise the *Chromatographic system* to exclude the relative retention times for alfadex, betadex, and gamma cyclodextrin from the suitability parameters but add the data for identification purposes in a *Note;* add a filtration step to the *Test solution* in the test for *Light-absorbing impurities;* and delete the tests for *Organic volatile impurities* and *Residual solvents.*

(EM2: H. Wang) RTS—43989-1

Change to read:

» Alfadex is composed of six alpha-(1-4) linked D-glucopyranosyl units. It contains not less than 98.0 percent and not more than 101.0 percent of $(C_6H_{10}O_5)_6$, calculated on the ~~dried~~

■anhydrous■1S (*NF25*)
basis.

Add the following:

■**Packaging and storage**—Preserve in tight containers. No storage requirements specified.■1S (*NF25*)

Delete the following:

■~~**Loss on drying** ⟨731⟩—Dry 1.0 g of it at 120° for 2 hours: it loses not more than 10.0% of its weight.~~■1S (*NF25*)

Add the following:

■**Water,** *Method I* ⟨921⟩**:** not more than 11.0%.■1S (*NF25*)

Change to read:

Reducing sugars—

Cupric solution—Dissolve 15 g of cupric sulfate in water to make 100 mL.

Tartrate solution—Dissolve 2.5 g of anhydrous sodium carbonate, 2.5 g of potassium sodium tartrate, 2.0 g of sodium bicarbonate, and 20 g of anhydrous sodium sulfate in water to make 100 mL.

Cupric–tartaric solution—Immediately before use, mix 1 part of *Cupric solution* with 25 parts of *Tartrate solution.*

Ammonium molybdate reagent—Mix 10 mL of a solution of disodium arsenate (6 in 100), 50 mL of a solution of ammonium molybdate (1 in 10), and 90 mL of diluted sulfuric acid, and dilute with water to 200 mL.

Test solution—Transfer about 1.0 g of Alfadex, accurately weighed,

■and calculated on the anhydrous basis,■1S (*NF25*)
to a 100-mL volumetric flask, dissolve in and dilute with water that has been previously boiled and cooled to room temperature, to volume, and mix. To 1 mL of this solution add 1 mL of *Cupric–tartaric solution.* Heat on a water bath for 10 minutes, then cool to room temperature. Add 10 mL of *Ammonium molybdate reagent,* and allow to stand for 15 minutes.

Standard solution—Prepare as directed for the *Test solution,* at the same time, except to use 1 mL of a solution containing 20 mg of glucose per L.

Procedure—Concomitantly measure the absorbance of the *Test solution* and the *Standard solution* at the wavelength of maximum absorbance at 740 nm relative to that of water, with a suitable spectrophotometer. The absorbance of the *Test solution* is not greater than that of the *Standard solution* (0.2%).

Change to read:

Light-absorbing impurities—

Test solution—Transfer about 1.0 g of Alfadex, accurately weighed,

■and calculated on the anhydrous basis,■1S (*NF25*)
to a 100-mL volumetric flask, dissolve in and dilute with water, which has been previously boiled and cooled to room temperature, to volume, ~~and mix~~

■mix, and pass through a 0.2-µm filter.■1S (*NF25*)

Procedure—Determine the absorbance of the *Test solution* in a 1-cm cell with a suitable spectrophotometer, after correcting for the blank: between 230 nm and 350 nm, the absorbance is not greater than 0.10; and between 350 nm and 750 nm, the absorbance is not greater than 0.05.

Delete the following:

■~~**Organic volatile impurities,** *Method IV* ⟨467⟩**:** meets the requirements.~~■1S (*NF25*)

Delete the following:

■~~**Residual solvents** ⟨467⟩**:** meets the requirements.~~
~~(Official January 1, 2007)~~■1S (*NF25*)

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—~~Transfer 25 mg of USP Alpha Cyclodextrin RS, accurately weighed, to a 25-mL volumetric flask, and dissolve in and dilute with water to volume.~~

■Dissolve an accurately weighed quantity of USP Alpha Cyclodextrin RS in water to obtain a solution having a known concentration of about 1.0 mg per mL, calculated on the anhydrous basis.■1S (*NF25*)

System suitability preparation—~~Transfer 25 mg of USP Beta Cyclodextrin RS, 25 mg of USP Gamma Cyclodextrin RS, and 50 mg of USP Alpha Cyclodextrin RS, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix.~~

■Dissolve accurately weighed quantities of USP Alpha Cyclodextrin RS, USP Beta Cyclodextrin RS, and USP Gamma Cyclodextrin RS in water to obtain a solution having known concentrations of about 1.0 mg per mL for USP Alpha Cyclodextrin RS, calculated on the anhydrous basis, about 0.5 mg of each per mL for USP Beta Cyclodextrin RS and USP Gamma Cyclodextrin RS, each calculated on the anhydrous basis.■1S (*NF25*)

Assay stock preparation—Transfer 250 mg of Alfadex, accurately weighed,

■and calculated on the anhydrous basis,■1S (*NF25*)
to a 25-mL volumetric flask, and dissolve in water with the aid of heat. Cool, and dilute with water to volume.

Assay preparation—Transfer 5.0 mL of the *Assay stock preparation* to a 50-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 4.6-mm × 25-cm column that contains ~~10 µm~~

■5-µm■1S (*NF25*)
packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability preparation,* and record the chromatograms for about 3.5 times the retention time of alpha

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cyclodextrin. Record the peak responses as directed for *Procedure:* ~~the retention time of alpha cyclodextrin is about 4.5 minutes; the relative retention times are about 1.0 for alpha cyclodextrin, about 2.2 for beta cyclodextrin, and about 0.7 for gamma cyclodextrin;~~

■■1S (*NF25*)
the resolution, *R,* between the gamma cyclodextrin and alpha cyclodextrin peaks is not less than 1.5; and for the alpha cyclodextrin peak, the relative standard deviation for replicate injections is not more than 2.0%.

■[NOTE—For the purpose of identification, the relative retention times are about 1.0 for alpha cyclodextrin, about 2.2 for beta cyclodextrin, and about 0.7 for gamma cyclodextrin.]■1S (*NF25*)

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $(C_6H_{10}O_5)_6$ in the portion of Alfadex taken by the formula:

~~$2500(C/W)(R_U/R_S)$~~

■$2500(C/W)(r_U/r_S)$■1S (*NF25*)

in which *C* is the concentration, in mg per mL, of alpha cyclodextrin in the *Standard preparation;* ~~calculated on the dried basis, as determined from the concentration of USP Alpha Cyclodextrin RS corrected for the declared moisture content;~~

■■1S (*NF25*)
W is the weight, in mg, of alpha cyclodextrin taken to prepare the *Assay stock preparation;* and ~~R_U and R_S~~

■r_U and r_S■1S (*NF25*)
are the peak responses of the alpha cyclodextrin peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Coconut Oil. Because there is no existing *NF* monograph for this article, it is proposed to add a new monograph based on the *Coconut Oil, Refined* monograph in the *European Pharmacopoeia, Fifth Edition,* page 1339; and the *Coconut Oil (Unhydrogenated)* monograph in the *Food Chemicals Codex, Fifth Edition,* page 119.

(EM2: H. Wang; NOM: L. Paul) RTS—43401-1

Add the following:

■Coconut Oil

Coconut oil.

Coconut oil [*8001-31-8*].

» Coconut oil is the refined fixed oil obtained from the seeds of *Cocos nucifera* Linné (Fam. Palmae).

Packaging and storage—Preserve in tight, light-resistant, well-filled containers. No storage requirement specified.

Identification—It meets the requirements of the test for *Fatty acid composition*.

Melting range ⟨741⟩**:** between 23° and 26°.

Acid value ⟨401⟩**:** not more than 0.5, determined on 20.0 g.

Peroxide value ⟨401⟩**:** not more than 5.0.

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

Fatty acid composition—Coconut Oil exhibits the following composition profile of fatty acids, as determined in the section *Fatty Acid Composition* under *Fats and Fixed Oils* ⟨401⟩:

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
6	0	≤1.5
8	0	5.0–11.0
10	0	4.0–9.0
12	0	40.0–50.0
14	0	15.0–20.0
16	0	7.0–12.0
18	0	1.5–5.0
20	0	≤0.2
16	1	≤1.0
18	1	4.0–10.0
18	2	1.0–3.0
18	3	≤0.2
20	1	≤0.2

Water, *Method I* ⟨921⟩**:** not more than 0.1%, 50 mL of chloroform being used as the solvent instead of 35 to 40 mL of methanol.

Arsenic, *Method II* ⟨211⟩**:** not more than 0.5 µg per g.

Alkaline impurities—Mix 10 mL of freshly distilled acetone and 0.3 mL of water, and add 0.05 mL of bromophenol blue TS. Neutralize the solution if necessary with 0.01 N hydrochloric acid or 0.01 N sodium hydroxide. Add 10 mL of Coconut Oil, shake, and allow to stand. Titrate with 0.01 N hydrochloric acid VS to change the color of the upper layer to yellow: not more than 0.1 mL of 0.01 N hydrochloric acid VS is required.■1S (*NF25*)

BRIEFING

Polyethylene Oxide, *NF 24* page 3398. On the basis of data, validation, and comments received, it is proposed to make the following changes:

1. Add "No storage requirements specified" to the test for *Packaging and storage.*
2. Add two new Reference Standards to the *USP Reference standards* section.
3. Add the phrase "using a suitable viscometer with appropriate validation" to the viscosity test under *Identification.* A rotational viscometer is suggested in this test by some manufacturers.
4. Replace the test for *Heavy metals, Method II* ⟨231⟩ with an ICP–AES method.
5. In the test for *Limit of free ethylene oxide,* the *Test preparation* response in the plot is included and the best straight line is drawn to include all five points.
6. Delete the tests for *Residual solvents* and *Organic volatile impurities.*

(EM2: H. Wang) RTS—43701-1

Change to read:

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

■No storage requirements specified.■1S (*NF25*)

Change to read:

USP Reference standards ⟨11⟩**—***USP Polyethylene Oxide RS.*

■*USP Multi-Metal Elements RS. USP Tin RS.*■1S (*NF25*)

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen: previously dried in vacuum at room temperature to constant weight.

B: The aqueous isopropyl alcohol solution viscosity, determined ■using a suitable viscometer with appropriate validation■1S (*NF25*) at 25° and in a concentration as directed in the labeling, falls within the viscosity range indicated by the labeling.

Delete the following:

■~~**Heavy metals,** *Method II* ⟨231⟩**: 0.001%.**~~■1S (*NF25*)

Add the following:

■**Heavy metals—**

Multi-element standard stock solution—Pipet 1.0 mL of USP Multi-Metal Elements RS into a 10-mL volumetric flask, add 0.1 mL of nitric acid, dilute with water to volume, and mix. This solution contains 10 µg of each metal element per mL.

Tin standard stock solution—Pipet 0.5 mL of USP Tin RS into a 25-mL volumetric flask, add 13 mL of hydrochloric acid, dilute with water to volume, and mix. This solution contains 20 µg of tin per mL.

Standard stock solution—Transfer 1.0 mL of *Multi-element standard stock solution* and 0.5 mL of *Tin standard stock solution* to a 20-mL volumetric flask, add 0.5 mL of nitric acid, dilute with water to volume, and mix. This solution contains 0.5 µg of each metal element per mL.

Standard solutions—Transfer 0 mL, 1 mL, 2 mL, and 5 mL of *Standard stock solution* to separate 25-mL volumetric flasks, add 1 mL of sulfuric acid and 5 mL of nitric acid to each flask, dilute the contents of each flask with water to volume, and mix. These solutions contain about 0 µg, 0.02 µg, 0.04 µg, and 0.1 µg of each metal element per mL, respectively.

Test solution—[Caution—When using high-pressure-resistant digestion vessels and microwave laboratory equipment, the safety precautions and operating instructions given by the manufacturers must be followed.] Transfer 0.5 g of Polyethylene Oxide, accurately weighed, to

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a dry high-pressure-resistant digestion vessel (fluoropolymer or quartz glass), and add 1 mL of sulfuric acid and 5 mL of nitric acid to the vessel. Digest Polyethylene Oxide in the microwave digestion equipment using the following time program: 10% power at 65 W for 5 minutes; 15% power at 95 W for 5 minutes; 20% power at 130 W for 5 minutes; and 25% power at 160 W for 5 minutes. After completing the digestion, allow the vessel to cool to room temperature. Open the vessel, transfer the solution to a 25-mL volumetric flask by rinsing the digestion vessel with water, dilute with water to volume, and mix.

Procedure—The inductively coupled plasma–atomic emission spectrometer (ICP–AES) is set up for Cd, Co, Cr, Cu, Mn, Mo, Ni, Pb, Sb, and Sn at the wavelengths of 226.5 nm, 228.6 nm, 267.7 nm, 324.8 nm, 257.6 nm, 202.0 nm, 231.6 nm, 220.4 nm, 217.6 nm, and 190.0 nm, respectively. The radio frequency (RF) power is 1.35 kW, the argon torch flow is about 14 L per minute, the argon auxiliary flow is about 0.5 L per minute, the argon nebulizer gas pressure is about 26 psi, and the integration time is about 25 seconds. Concomitantly analyze the *Standard solutions* and the *Test solution* by introducing the solutions into the ICP–AES and recording the reading of each metal element. Plot the absorbances of the *Standard solutions* versus concentration, in µg per mL, of each metal element, and draw the straight line best fitting the four plotted points. From the graph so obtained, determine the concentration, *C,* in µg per mL, of each metal element in the *Test solution*. Calculate the quantity, in µg, of each metal element in the portion of Polyethylene Oxide taken by the formula:

$$25C/W$$

in which *W* is the weight, in g, of Polyethylene Oxide taken to prepare the *Test solution*: not more than 1 µg per g is found.■1S (*NF25*)

Change to read:

Limit of free ethylene oxide—

Standard stock solution—[Caution—Ethylene oxide is toxic and flammable. Prepare solutions of it in a well-ventilated fume hood.] Using the special handling described in the following, complete the preparation. Ethylene oxide is a gas at room temperature. It is usually stored in a lecture-type gas cylinder or small metal pressure bomb. Chill the cylinder in a refrigerator before use. Transfer about 5 mL of the liquid ethylene oxide to a cold, 10-mL serum vial. Seal the vial, and store in a refrigerator. Transfer about 40 g of acetone, accurately weighed, to a tared 50-mL serum vial that is capable of being tightly sealed with a polytef-lined septum and a metallic crimp cap. Seal the vial, and accurately weigh it. Using a gas-tight gas chromatographic syringe that has been chilled in a refrigerator, transfer about 60 µL of the liquefied ethylene oxide to the same vial. Weigh the vial, and determine the amount added by weight difference. This solution contains about 1 µg of ethylene oxide per µL. [NOTE—This solution may be kept for 1 week in the crimp-sealed serum vial, stored in a freezer.]

Standard preparations—To four separate, tared 50-mL serum vials that are capable of being tightly sealed with polytef-lined septa and metallic crimp caps, transfer 1.0 g of the Polyethylene Oxide under test. Seal the vials. To the separate vials, transfer 2.0 µL, 4.0 µL, 6.0 µL, and 8.0 µL of the *Standard stock solution*, and mix. These vials contain about 2 µg, 4 µg, 6 µg, and 8 µg of ethylene oxide, respectively, from the *Standard stock solution*. Heat the vials at 100° for 30 minutes, and cool to room temperature.

Test preparation—Transfer about 1 g of the Polyethylene Oxide under test, accurately weighed, to a tared 50-mL serum vial that is capable of being tightly sealed with a polytef-lined septum and a metallic crimp cap. Weigh the vial, and determine the amount of Polyethylene Oxide added by weight difference. Seal the vial, heat at 100° for 30 minutes, and cool to room temperature.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 10-m capillary column bonded with a 20-µm layer of phase G45, and a split injection system. The carrier gas is helium, flowing at a rate of about 15 mL per minute. The makeup gas is also helium, with a split flow rate of about 15 mL per minute. The injection port and detector temperatures are maintained at about 200° and 250°, respectively. The column temperature is maintained at about 70° for 5 minutes after injection, then programmed to increase at a rate of 10° per minute to about 200° and to maintain this temperature for 5 minutes. Inject 300 µL of the gaseous headspace from the vial of *Standard preparation* that contains about 6 µg of ethylene oxide from the *Standard stock solution* into the gas chromatograph, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5%.

■[NOTE—Multiple vials are prepared for replicate injections.]■1S (*NF25*)

Procedure—[NOTE—A headspace apparatus that automatically transfers the measured amount of gaseous headspace may be used to perform the injections.] Using a gas-tight syringe, separately inject equal volumes (about 300 µL) of the gaseous headspace of each of the *Standard preparations* and the *Test preparation* into the gas chromatograph, record the chromatograms, and measure the areas of the peak responses. Determine by a retention time comparison whether ethylene oxide is detected in the *Test preparation*. Plot the responses of

■the *Test preparation* and■1S (*NF25*)
the *Standard preparations* versus the content, in µg, of ethylene oxide in each vial, as furnished by the *Standard stock solution;* draw the straight line best fitting the ~~four~~

■five■1S (*NF25*)
points; and calculate the correlation coefficient for the line.

■[NOTE—The content of ethylene oxide, as furnished by the *Standard stock solution,* is 0 µg in the *Test preparation*.]■1S (*NF25*)

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A suitable system is one that yields a line having a correlation coefficient of not less than 0.99. Extrapolate the line until it intercepts the content axis on the negative side. From the intercept, determine the total amount, T_U, in µg, of ethylene oxide in the *Test preparation*. Calculate the percentage of ethylene oxide in the portion of Polyethylene Oxide taken by the formula:

$$100(T_U / W)$$

in which W is the weight, in µg, of Polyethylene Oxide taken to prepare the *Test preparation:* the limit is 0.001%.

Delete the following:

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

★~~*NF24*~~■1S (*NF25*)

Delete the following:

■~~**Residual solvents** ⟨467⟩**:** meets the requirements.~~

~~(Official January 1, 2007)~~■1S (*NF25*)

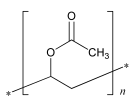
BRIEFING

Polyvinyl Acetate. Because there is no existing *NF* monograph for this article, a new monograph, based on the *Poly(vinyl acetate)* monograph in the *European Pharmacopoeia, Fifth Edition,* page 2271; the *Polyvinyl Acetate* monograph in the *Food Chemicals Codex, Fifth Edition,* page 349; and the *Polyvinyl Acetate* monograph in the *Japanese Pharmaceutical Excipients Directory 1996,* page 398, is being proposed.

(EM2: H. Wang; NOM: L. Paul) RTS—43513-1

Add the following:

■Polyvinyl Acetate



$(C_4H_6O_2)_n$

Vinyl acetate homopolymer.

Vinyl acetate resin [*9003-20-7*].

» Polyvinyl acetate is a thermoplastic polymer, represented by the formula:

$$(C_4H_6O_2)_n$$

in which the value of n lies between approximately 100 and 17,000.

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

Labeling—Label it to indicate its viscosity value.

USP Reference standards ⟨11⟩—*USP Polyvinyl Acetate RS. USP Vinyl Acetate RS.*

Identification—

A: Dissolve about 100 mg in 2.5 mL of acetone, place two drops on a potassium bromide plate, and dry to evaporate the solvent: the IR absorption spectrum of polyvinyl acetate exhibits maxima corresponding to the same wavelengths as that of a similar preparation of USP Polyvinyl Acetate RS, treated in the same manner.

B: Saponify 0.5 g in a mixture of 25.0 mL of 0.5 N alcoholic potassium hydroxide and 25.0 mL of water. The solution so obtained meets the requirements of the tests for *Acetate* ⟨191⟩.

Viscosity—Suspend 50.0 g in 100 mL of ethyl acetate in a borosilicate glass flask with a ground-glass neck. Heat under a reflux condenser with constant stirring for 30 minutes. Allow to cool. Pass through a tared sintered glass filter (No. 16), wash the residue with 50.0 mL of ethyl acetate, and pour the filtrate into a 250-mL graduated flask. Dilute with ethyl acetate to 250 mL. Resume stirring to obtain a homogenous solution of 20% (w/v) polyvinyl acetate in ethyl acetate. Determine the viscosity of this solution immediately at 20 ± 0.1° by using a rolling ball viscosimeter: between 85% and 115% of the value stated on the label is found.

Loss on drying ⟨731⟩—Dry 1.0 g at 100° to 105°, to constant weight: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Acid value ⟨401⟩**:** not more than 2.0, determined on 5.0 g dissolved in 50.0 mL of alcohol by shaking for 3 hours.

Ester value ⟨401⟩—Saponify 0.5 g in a mixture of 25.0 mL of 0.5 N alcoholic potassium hydroxide VS and 25.0 mL of water. Proceed as directed under *Saponification Value* ⟨401⟩, beginning with "Heat the flask on a steam bath". The ester value, calculated from the *Saponification Value* and the *Acid Value,* is between 615 and 675.

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

Residual peroxides—Place 0.85 g in a borosilicate glass flask with a ground-glass neck. Add 10.0 mL of ethyl acetate, and heat under a reflux condenser with constant agitation. Allow to cool. Replace the air in the container with oxygen-free nitrogen, and add a solution of 1.0 mL of glacial acetic acid and 0.5 g of sodium iodide in 40.0 mL of water. Shake thoroughly, and allow to stand protected from light for 20 minutes. Titrate with 0.005 N sodium thiosulfate VS until the yellow color is discharged. Carry out a blank titration. The difference between the titration volumes is not greater than 1.0 mL; and not more than 100 ppm, calculated as hydrogen peroxide, is found.

Free vinyl acetate—

Standard stock solution—Transfer 15.0 mL of dimethylformamide to a 20-mL vial, add 45.0 µL of USP Vinyl Acetate RS and 50.0 µL of butyraldehyde, and dilute with dimethylformamide to volume. Dilute 1.0 mL of the solution with dimethylformamide to 10 mL.

Standard solution—Transfer about 0.2 g of Polyvinyl Acetate, accurately weighed, to a 20-mL vial, and add 1.0 mL of the *Standard stock solution*. Close the vial, and secure it with a stopper. Swirl, avoiding contact between the stopper and the liquid.

Test solution—Transfer about 0.2 g of Polyvinyl Acetate, accurately weighed, to a 20-mL vial, and add 1.0 mL of dimethylformamide. Close the vial, and secure it with a stopper. Swirl, avoiding contact between the stopper and the liquid.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 25-m fused-silica capillary column coated with a 0.32-µm layer of stationary phase G36. Use static headspace conditions with an equilibration temperature of 60°, an equilibration time of 20 minutes, and a transfer line temperature of 120°, with nitrogen as the carrier gas. The injection port temperature is maintained at 120°, the detector temperature is maintained at 180°, and the column temperature is maintained at 155°. Nitrogen is used as the carrier gas, flowing at a rate of about 20 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between vinyl acetate and butyraldehyde is not less than 2.0; and the signal-to-noise ratio for vinyl acetate is not less than 5.

Procedure—Separately inject equal volumes (about 1.6 mL) of the gaseous phase of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of vinyl acetate in the portion of Polyvinyl Acetate taken by the formula:

$$(0.931 V r_u) / [2000(W_u r_s - W_s r_u)]$$

in which 0.931 is the density, in g per mL, of vinyl acetate; V is the volume, in µL, of vinyl acetate used to prepare the *Standard stock solution;* W_u and W_s are the weights, in g, of Polyvinyl Acetate used to prepare the *Test solution* and the *Standard solution,* respectively; and r_s and r_u are the vinyl acetate peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.3% of vinyl acetate is found. ■1S (*NF25*)

BRIEFING

Tribasic Sodium Phosphate, *NF 24* page 3425. On the basis of comments received, it is proposed to revise the test for *Loss on ignition* to indicate that the calculation is performed with respect to the weight of the material before it is dried.

(EM1: C. Sheehan) RTS—44045-1

Change to read:

Loss on ignition ⟨733⟩~~—Dry a portion at 100° for 5 hours. Ignite about 2 g, accurately weighed, of the dried sample at about 800° for 30 minutes: calculated on the dried basis,~~

■Weigh accurately about 2 g, dry at 110° for 5 hours, then ignite at about 800° for 30 minutes:■1S (*NF25*)
the anhydrous form loses not more than 2.0% of its weight, the monohydrate loses between 8.0% and 11.0% of its weight, and the dodecahydrate loses between 45.0% and 57.0% of its weight.

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**1**⟩ **Injections,** *USP 29* page 2455, the *Sixth Interim Revision Announcement* on page 1599 of *PF* 31(6) [Nov.–Dec. 2005], and page 1428 of *PF* 31(5) [Sept.–Oct. 2005]. The The U.S. Food and Drug Administration (FDA) is amending its regulations to change the labeling requirements for aluminum in large- and small-volume parenterals and pharmacy bulk packages used in total parenteral nutrition (TPN). The Parenteral Products—Industrial (PPI) Expert Committee has decided to adopt these labeling requirements to comply with the Code of Federal Regulations (21 CFR 201.323). However, there are some inconsistencies between the proposed USP aluminum labeling section and the Code of Federal Regulations (21 CFR 201.323). Therefore, the committee proposes, in the *Labels and Labeling* section of this chapter, to revise the subsection *Aluminum in Large-Volume Injections, Small-Volume Injections, and Pharmacy Bulk Packages PBPs) Used in Total Parenteral Nutrition (TPN) Therapy* to make the section consistent with the CFR content; this includes changes on aluminum content labeling, changing the term ''injections'' to ''parenterals'', and changing the terms ''SVI[s]'' and ''LVI[s]'' to ''SVP[s]'' and ''LVP[s]''. Additionally, the committee proposes a revised text for *Packaging and Storage* in the *Packaging* section that describes which large-volume parenterals (LVPs) are exempt from the 1-L restriction.

(PPI: J. Kelly) RTS—42879-1; 43505-1

Change to read:

LABELS AND LABELING

Labeling

NOTE—See definitions of ''label'' and ''labeling'' in *Labeling* in the section *Preservation, Packaging, Storage, and Labeling* of the *General Notices and Requirements.*

The label states the name of the preparation; in the case of a liquid preparation, the percentage content of drug or amount of drug in a specified volume; in the case of a dry preparation, the amount of *active* ingredient; the route of administration; a statement of storage conditions and an expiration date; the name and place of business of the manufacturer, packer, or distributor; and an identifying lot number. The lot number is capable of yielding the complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing, and labeling operations.

Where the individual monograph permits varying concentrations of active ingredients in the large-volume parenteral, the concentration of each ingredient named in the official title is stated as if part of the official title, e.g., Dextrose Injection 5%, or Dextrose (5%) and Sodium Chloride (0.2%) Injection.

The labeling includes the following information if the complete formula is not specified in the individual monograph: (1) In the case of a liquid preparation, the percentage content of each ingredient or the amount of each ingredient in a specified volume, except that ingredients added to adjust to a given pH or to make the solution isotonic may be declared by name and a statement of their effect; and (2) in the case of a dry preparation or other preparation to which a diluent is intended to be added before use, the amount of each ingredient, the composition of recommended diluent(s) [the name(s) alone, if the formula is specified in the individual monograph], the amount to be used to attain a specific concentration of active ingredient and the final volume of solution so obtained, a brief description of the physical appearance of the constituted solution, directions for proper storage of the constituted solution, and an expiration date limiting the period during which the constituted solution may be expected to have the required or labeled potency if it has been stored as directed.

Containers for Injections that are intended for use as dialysis, hemofiltration, or irrigation solutions and that contain a volume of more than 1 L are labeled to indicate that the contents are not intended for use by intravenous infusion.

Injections intended for veterinary use are labeled to that effect.

The container is so labeled that a sufficient area of the container remains uncovered for its full length or circumference to permit inspection of the contents.

■STRENGTH AND TOTAL VOLUME FOR SINGLE- AND MULTIPLE-DOSE INJECTABLE DRUG PRODUCTS

For single-dose and multiple-dose injectable drug products, the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses. For containers holding a volume of less than 1

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mL, the strength per fraction of a mL should be the only expression of strength. Strength per single mL should be expressed as mg/mL, not mg/1 mL.

The following formats are acceptable for contents of greater than 1 mL:

Total strength/total volume: 500 mg/10 mL

Strength/mL: (50 mg/mL)

or

Total strength/total volume: 25,000 Units/5 mL

Strength/mL: (5,000 Units/mL)

The following format is acceptable for contents of less than 1 mL: 12.5 mg/0.625 mL

There are, however, some exceptions to expressing strength per total volume. In certain cases, the primary and prominent expression of the total drug content per container would not be effective in preventing medication errors (e.g., insulin). An example is the use of lidocaine or other similar drugs used as a local anesthetic where the product is ordered and administered by percentage (e.g., 1%, 2%) or a local anesthetic in combination with epinephrine that is expressed as a ratio (e.g., 1 : 100,000). In such cases, the total strength should be expressed: for example, 1% (100 mg/10 mL). Dry solids, which need to be reconstituted, should follow the same format, with the exception that only the total strength of the drug should be listed, not the strength/total volume or strength/mL.■2S (*USP29*)

(Official February 1, 2009)

~~▲Aluminum in Large-Volume Injections (LVIs), Small-Volume Injections (SVIs), and Pharmacy Bulk Packages (PBPs) Used in Total Parenteral Nutrition (TPN) Therapy~~

■Aluminum in Large-Volume Parenterals (LVPs), Small-Volume Parenterals (SVPs), and Pharmacy Bulk Packages (PBPs) Used in Total Parenteral Nutrition (TPN) Therapy■1S (*USP30*)

~~(a) The aluminum content of LVIs used in TPN therapy must not exceed 25 µg per L).~~

~~(b) The package insert of LVIs used in TPN therapy must state that the drug product contains no more than 25µg of aluminum per L. This information must be contained in the "Precautions" section of the labeling of all LVIs used in TPN therapy.~~

~~(c) If the maximum amount of aluminum in SVIs and PBPs is 25µg or less, instead of stating the act amount of aluminum that each may contain, as in paragraph (d), the immediate container label for SVIs and PBPs used in the preparation or in the administration of TPN injections (with exceptions as noted below) and injectable emulsions may state: "Contains no more than 25µg/L of aluminum."If the SVI or PBP is a lyophilizsed powder, the immediate container label may state the following; if the SVI or PBP is a lyophilized powder used in the preparation of TPN injections and injectable emulsions, the immediate container label must state the following: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more tha 25 µg/L."~~

~~(d) The maximum level of aluminum at expiry must be stated on the immediate container label of all SVIs and PBPs used in the preparation or the administration of TPN injectionsand injectable emulsions. The aluminum content must be stated as follows: "Contains no more than __ µg/L of aluminum". This maximum amount of aluminum be stated as the highest one of the following three levels:~~

■(a) The aluminum content of LVPs used in TPN therapy must not exceed 25 µg per L (µg/L).

(b) The package insert of LVPs used in TPN therapy must state that the drug product contains no more than 25 µg of aluminum per L. This information must be contained in the "Precautions" section of the labeling of all LVPs used in TPN therapy.

(c) If the maximum amount of aluminum in SVPs and PBPs is 25 µg per L (µg/L) or less, instead of stating the exact amount of aluminum that each contains, as in paragraph (d), the immediate container label for SVPs and PBPs used in the preparation of TPN parenterals (with exceptions as noted below) may state: "Contains no more than 25 µg/L of aluminum". If the SVP or PBP is a lyophilized powder, the immediate container label may state the following: "When reconstituted in accordance with the package insert instructions, the concentration of aluminum will be no more than 25 µg/L".

(d) The maximum level of aluminum at expiry must be stated on the immediate container label of all SVPs and PBPs used in the preparation of TPN parenterals and injectable emulsions. The aluminum content must be stated as follows: "Contains no more than __ µg/L of aluminum". The immediate container label of all SVPs and PBPs that are lyophilized powder used in the preparation of TPN solutions must contain the following statement: "When reconstituted in accordance with the package insert in-

structions, the concentration of aluminum will be no more than __ µg/L." This maximum amount of aluminum must be stated as the highest one of the following three levels:■1S (*USP30*)

(1) The highest level for the batches produced during the last three years
(2) The highest level for the latest five batches
(3) The maximum level in terms of historical levels, but only until completion of production of the first five batches after ~~the effective date of~~

■July 26, 2004.■1S (*USP30*)

The package insert for all LVPs, SVPs, and PBPs used in the preparation ~~or administration~~

■■1S (*USP30*)

of TPN products must contain a warning statement. This warning must be contained in the "Warning" section of the labeling and must state the following: "WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg per kg per day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of TPN products." ~~and of the lock flush solutions used in their administration.~~▲*USP29*

■■1S (*USP30*)

Change to read:

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements.* Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate.*

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation,* in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. •For containers with a nominal volume of 2 mL or less, the contents of a sufficient number of containers may be pooled to obtain the volume required for the measurement, provided that a separate, dry syringe assembly is used

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for each container.•6 The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1- and 2-mL containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. •Cool to between 20° and 25°•6 before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

Printing on Ferrules and Cap Overseals

Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: ''Warning'', ''Dilute Before Using'', ''Paralyzing Agent'', ''I.M. Use Only'', ''Chemotherapy'', etc.

The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.

•(Postponed indefinitely)•5

~~Printing on Ferrules and Cap Overseals~~

▪Labeling on Ferrules and Cap Overseals▪2S (*USP29*)

~~Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: ''Warning'', ''Dilute Before Using'', ''Paralyzing Agent'', ''I.M. Use Only'', ''Chemotherapy'', etc.~~

~~The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.~~

~~(Official October 1, 2005)~~

▪Only cautionary statements are to appear on the top (circle) surface of the ferrule or cap overseal of a vial containing an injectable product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements include but are not limited to the following: ''Warning'', ''Dilute Before Using'', ''Paralyzing Agent'', ''I.M. Use Only'', and ''Chemotherapy''.

The text must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may appear solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement beneath the cap to be readily legible.

Identifying numbers or letters, such as code numbers, lot numbers, etc., may appear on the side (skirt) surface of the ferrule on vials containing injectable products. The appearance of such identifying data on the skirt surface of the ferrule, placed where it does not detract from, or interfere with, the cautionary statement on the top surface, should be considered to be a beneficial attribute of the in-process quality control of a product throughout the manufacturing process. Any anti-counterfeiting scheme must not detract from or interfere with the cautionary statements.

Under no circumstances will advertising such as company names, logos, or product names be permitted to appear on the top (circle) surface of any ferrule or cap overseal.▪2S (*USP29*)

(Official February 1, 2009)

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

~~Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.~~

~~Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.~~

▪The following Injections are exempt from the 1-L restriction of the foregoing requirements relating to packaging:

1. Injections packaged for extravascular use as irrigation solutions or peritoneal dialysis solutions
2. Injections packaged for intravascular use as parenteral nutrition or as replacement or substitution fluid to be administered continuously during hemofiltration

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Injections packaged for intravascular use that may be used for intermittent, continuous, or bolus replacement fluid administration during hemodialysis or other procedures, unless excepted above, must conform to the 1-L restriction.■1S (*USP30*)

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

Change to read:

PACKAGING

Containers for Injections

Containers, including the closures, for preparations for injections do not interact physically or chemically with the preparations in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use. The container is made of material that permits inspection of the contents. The type of glass preferable for each parenteral preparation is usually stated in the individual monograph. Unless otherwise specified in the individual monograph, plastic containers may be used for packaging injections (see *Containers* ⟨661⟩).

For definitions of single-dose and multiple-dose containers, see *Containers* in the *General Notices and Requirements.* Containers meet the requirements under *Containers* ⟨661⟩.

Containers are closed or sealed in such a manner as to prevent contamination or loss of contents. Validation of container integrity must demonstrate no penetration of microbial contamination or chemical or physical impurities. In addition, the solutes and the vehicle must maintain their specified total and relative quantities or concentrations when exposed to anticipated extreme conditions of manufacturing and processing, and storage, shipment, and distribution. Closures for multiple-dose containers permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle and, upon withdrawal of the needle, closes at once, protecting the container against contamination. Validation of the multiple-dose container integrity must include verification that such a package prevents microbial contamination or loss of product contents under anticipated conditions of multiple entry and use.

Piggyback containers are usually intravenous infusion containers used to administer a second infusion through a connector of some type or an injection port on the administration set of the first fluid, thereby avoiding the need for another injection site on the patient's body. Piggyback containers are also known as secondary infusion containers.

Potassium Chloride for Injection Concentrate

The use of a black closure system on a vial (e.g., a black flip-off button and a black ferrule to hold the elastomeric closure) or the use of a black band or series of bands above the constriction on an ampul is prohibited, except for *Potassium Chloride for Injection Concentrate.*

Neuromuscular Blocking and Paralyzing Agents

All injectable preparations of neuromuscular blocking agents and paralyzing agents must be packaged in vials with a cautionary statement printed on the ferrules or cap overseals. Both the container cap ferrule and the cap overseal must bear in black or white print (whichever provides the greatest color contrast with the ferrule or cap color) the words: "Warning: Paralyzing Agent" or "Paralyzing Agent" (depending on the size of the closure system). Alternatively, the overseal may be transparent and without words, allowing for visualization of the warning labeling on the closure ferrule.

Containers for Sterile Solids

Containers, including the closures, for dry solids intended for parenteral use do not interact physically or chemically with the preparation in any manner to alter the strength, quality, or purity beyond the official requirements under the ordinary or customary conditions of handling, shipment, storage, sale, and use.

A container for a sterile solid permits the addition of a suitable solvent and withdrawal of portions of the resulting solution or suspension in such manner that the sterility of the product is maintained.

Where the *Assay* in a monograph provides a procedure for the *Assay preparation,* in which the total withdrawable contents are to be withdrawn from a single-dose container with a hypodermic needle and syringe, the contents are to be withdrawn as completely as possible into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be withdrawn and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length, with care being taken to expel any air bubbles, and discharged into a container for dilution and assay.

Volume in Container

Each container of an injection is filled with sufficient excess of the labeled "size" or that volume which is to be withdrawn. See *Injections* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

DETERMINATION OF VOLUME OF INJECTION IN CONTAINERS

Select one or more containers if the volume of the container is 10 mL or more, three or more if the volume is more than 3 mL and less than 10 mL, or five or more if the volume is 3 mL or less. Individually take up the contents of each container selected into a dry hypodermic syringe of a rated capacity not exceeding three times the volume to be measured and fitted with a 21-gauge needle not less than 2.5 cm (1 inch) in length. Expel any air bubbles from the syringe and needle, and then discharge the contents of the syringe, without emptying the needle, into a standardized, dry cylinder (graduated to contain rather than to deliver the designated volumes) of such size that the volume to be measured occupies at least 40% of the cylinder's rated volume. Alternatively, the contents of the syringe may be discharged into a dry, tared beaker, the volume, in mL, being calculated as the weight, in g, of Injection taken divided by its density. •For containers with a nominal volume of 2 mL or less, the contents of a sufficient number of containers may be pooled to obtain the volume required for the measurement, provided that a separate, dry syringe assembly is used for each container.•6 The content of containers holding 10 mL or more may be determined by means of opening them and emptying the contents directly into the graduated cylinder or tared beaker.

The volume is not less than the labeled volume in the case of containers examined individually or, in the case of 1- and 2-mL containers, is not less than the sum of the labeled volumes of the containers taken collectively.

For Injections in multiple-dose containers labeled to yield a specific number of doses of a stated volume, proceed as directed in the foregoing, using the same number of separate syringes as the number of doses specified. The volume is such that each syringe delivers not less than the stated dose.

For Injections containing oil, warm the containers, if necessary, and thoroughly shake them immediately before removing the contents. •Cool to between 20° and 25°•6 before measuring the volume.

For Injections in cartridges or prefilled syringes, assemble the container with any required accessories such as a needle or plunger. Following the same procedure as above, and without emptying the needle, transfer the entire contents of each container to a dry, tared beaker by slowly and constantly depressing the plunger. Weigh, and calculate the volume as described above. The volume of each container is not less than the labeled volume.

For large-volume intravenous solutions, select 1 container, and transfer the contents into a dry measuring cylinder of such size that the volume to be measured occupies at least 40% of its rated volume. The volume is not less than the labeled volume.

In-Process Revision

~~**Printing on Ferrules and Cap Overseals**~~

▪Labeling on Ferrules and Cap Overseals▪2S (*USP29*)

~~Only cautionary statements are to be printed on the ferrules and cap overseals of vials containing an injectable drug product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements are the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", "Chemotherapy", etc.~~

~~The printing must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may be printed solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement below to be readily legible.~~

~~(Official October 1, 2005)~~

▪Only cautionary statements are to appear on the top (circle) surface of the ferrule or cap overseal of a vial containing an injectable product. A cautionary statement is one intended to prevent an imminent life-threatening situation if the injectable drug is used inappropriately. Examples of such statements include but are not limited to the following: "Warning", "Dilute Before Using", "Paralyzing Agent", "I.M. Use Only", and "Chemotherapy".

The text must be in contrasting color and conspicuous under ordinary conditions of use. The cautionary statement may appear solely on the ferrule, provided the cap overseal is constructed so as to allow the cautionary statement beneath the cap to be readily legible.

Identifying numbers or letters, such as code numbers, lot numbers, etc., may appear on the side (skirt) surface of the ferrule on vials containing injectable products. The appearance of such identifying data on the skirt surface of the ferrule, placed where it does not detract from, or interfere with, the cautionary statement on the top surface, should be considered to be a beneficial attribute of the in-process quality control of a product throughout the manufacturing process. Any anti-counterfeiting scheme must not detract from or interfere with the cautionary statements.

Under no circumstances would advertising such as company names, logos, or product names be permitted to appear on the top (circle) surface of any ferrule or cap overseal.▪2S (*USP29*)

(Official February 1, 2009)

Packaging and Storage

The volume of injection in single-dose containers provides the amount specified for parenteral administration at one time and in no case is more than sufficient to permit the withdrawal and administration of 1 L.

Preparations intended for intraspinal, intracisternal, or peridural administration are packaged only in single-dose containers.

Unless otherwise specified in the individual monograph, a multiple-dose container contains a volume of Injection sufficient to permit the withdrawal of not more than 30 mL.

~~Injections packaged for use as irrigation solutions, for hemofiltration or dialysis, or for parenteral nutrition are exempt from the 1-L restriction of the foregoing requirements relating to packaging.~~

~~Containers for Injections packaged for use as hemofiltration or irrigation solutions may be designed to empty rapidly and may contain a volume of more than 1 L.~~

▪The following injections are exempt from the 1-L restriction of the foregoing requirements relating to packaging:

1. injections packaged for extravascular use as irrigation solutions or peritoneal dialysis solutions
2. injections packaged for intravascular use as parenteral nutrition or as replacement or substitution fluid to be administered continuously during hemofiltration

Injections packaged for intravascular use that may be used for intermittent, continuous, or bolus replacement fluid administration during hemodialysis or other procedures unless excepted above must conform to the 1-L restriction.▪1S (*USP30*)

Injections labeled for veterinary use are exempt from packaging and storage requirements concerning the limitation to single-dose containers and the limitation on the volume of multiple-dose containers.

BRIEFING

〈**11**〉 **USP Reference Standards,** *USP 29* page 2458, page 1101 of *PF* 26(4) [July–Aug. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], page 1154 of *PF* 31(4) [July–Aug. 2005], page 1433 of *PF* 31(5) [Sept.–Oct. 2005], page 1680 of *PF* 31(6) [Nov.–Dec. 2005], and page 181 of *PF* 32(1) [Jan.–Feb. 2006].

The changes proposed in the structure and content of the chapter are intended to provide a more comprehensive description of the USP Reference Standards program, to reflect the changes since the last major revisions, to illustrate the complexity and diversity of the collection, to present the steps in the establishment of a Reference Standard and the rationale behind the assignment of a labeled value, and to describe the proper use of the Reference Standards.

It is also proposed to remove the directions for use, handling, and storage from the list of *USP Reference Standards Specified in USP and NF Monographs and General Chapters* in the last section of this General Chapter. These directions are lot-specific. Additional information gathered from the continuous process of evaluation of USP candidates and Reference Standards often prompts changes in the storage and/or handling of USP Reference Standards. The delay between the release of a new lot of Reference Standard (labeled with the new directions) and the publication of a new edition of the Book or of a Supplement including the revised directions creates confusion for the customers. From now on, the directions for storage, handling, and use will be provided **only** on the label of the Reference Standard and on the USP Certificates displayed on the USP website.

(HDQ) RTS—41003-2; 42805-2; 42817-2; 43513-1; 43715-1; 43952-2; 44112-1

Change to read:

~~USP Reference Standards are established and released under the authority of the USPC Board of Trustees upon recommendation of the USP Reference Standards Committee, which passes on the selection and suitability of each lot. The critical characteristics of each lot of specimen selected for the standard are usually determined independently in three or more laboratories. The USP Reference Standards Laboratory (see *Preface*) and the FDA laboratories participate in testing almost all new Standards and replacements for existing Standards. In addition, laboratories throughout the nation, both academic and industrial, participate in the testing.~~

~~Reference Standards are specifically required in many Pharmacopeial assays and tests and are provided solely for such use; suitability for other nonofficial application(s) rests with the purchaser. Originally introduced for the biological assays of *USP X*, reference standards are now required for numerous other procedures as well. This reflects the extensive use of modern chromatographic and spectrophotometric methods, which require measurements relative to a reference standard to attain accurate and reproducible results.~~

~~USP Reference Standards are substances selected for their high purity, critical characteristics, and suitability for the intended purpose. Heterogeneous substances, of natural origin, also are designated "Reference Standards" where needed. Usually these are the counterparts of international standards.~~

~~Antibiotic reference standards distributed by the USPC have been designated by the FDA as identical to FDA working standards under the FDA procedures. USPC distributes both U.S. Reference Standards and USP Reference Standards for antibiotic substances. This difference in labeling the Standards is in effect only temporarily, and eventually all vials will bear the same title. Where a USP Reference Standard is called for, the corresponding substance labeled as a "U.S. Reference Standard" may be used, and vice versa.~~

~~Reference Standards currently labeled as "NF Reference Standards" will eventually all be designated and labeled as "USP Reference Standards" pursuant to the consolidation of USP and NF within the USPC as of January 2, 1975. Meanwhile, where a USP Reference Standard is called for, the corresponding substance labeled as an "NF Reference Standard" may be used.~~

■USP Reference Standards are highly characterized specimens of drug substances, excipients, reportable impurities, degradation products, compendial reagents, and performance calibrators.

They are explicitly required in many Pharmacopeial assays and tests and are provided solely for such use. Suitability for use in nonofficial application(s) should be validated by the purchaser.■1S (*USP30*)

Delete the following:

■~~Authentic Visual Reference~~

~~Unlike chemical reference standards, Authentic Visual References (AVRs) are not used in chemical analysis. Instead, the AVRs are visual images used by analysts to compare certain test articles to ensure that they meet compendial requirements and are incorporated by reference into the monograph. Approval of AVRs for use in a monograph is the decision of the Expert Committee that approves the specific monograph.~~■1S (*USP30*)

Delete the following:

■~~Other Reference Substances~~

~~As a service, the USPC tests and distributes additional authenticated substances not currently required as USP or NF Reference Standards. These also are provided under the supervision of the USP Reference Standards Committee. These additional substances fall into three groups: (1) former USP and NF Reference Standards, not required in the current *USP* or *NF* but for which sufficient demand remains; (2) FCC Reference Standards, specified in the current edition of the Food Chemicals Codex; and (3) Authentic Substances (AS), which are highly purified samples of chemicals, including substances of abuse, that are collaboratively tested and made available as a service primarily to analytical, clinical, pharmaceutical, and research laboratories.~~

~~The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration of the Department of Justice.~~

~~As an additional service, the USPC distributes several non-commercial reagents required in certain *USP* monographs. These reagents are specially prepared for their intended use and will be distributed by USPC only until they become commercially available.~~

~~A program to provide international biological standards and chemical reference substances is maintained by the World Health Organization, an agency of the United Nations. The WHO program is concerned with reference materials for antibiotics, biologicals, and chemotherapeutic agents. As a rule, an International Standard for a material of natural origin is discontinued once the substance responsible for its characteristic activity has been isolated, identified, and prepared in such form that it can be completely characterized by chemical and physical means. The USP Reference Standards Committee collaborates closely with the WHO in order to minimize unavoidable differences in the actual units of potency, and in some cases to share in the preparation of a reference standard. Since some USP Reference Standards are standardized in terms of the corresponding International Standards, the relevant USP Units and the International Units of potency are generally identical.~~■1S (*USP30*)

Delete the following:

■~~CURRENT LOTS~~

~~It is the responsibility of each analyst to ascertain that his particular supply of USP Reference Standard is current. Only sufficient quantity for immediate use should be purchased, and long-term storage should be avoided.~~

~~To ensure ready access to the latest information, the USPC publishes the Official Catalog of Reference Standards and Authentic Substances, and the lot designations, bimonthly in *Pharmacopeial Forum*.~~[♣] ~~This system offers more positive control and flexibility in responding to revisions in Reference Standard usage than would ex-~~

[♣] ~~For nonsubscribers, the most recent Official Catalog is available from: U.S. Pharmacopeial Convention, Inc., Reference Standards Order Department, 12601 Twinbrook Parkway, Rockville, MD 20852. Telephone 1-301-881-0666. FAX 1-301-816-8148. Toll free telephone 1-800-227-USPC or access the Catalog on USP's web site www.usp.org/dsd/refstd.~~

In-Process Revision

~~piration dates. The Catalog in the most recent *Pharmacopeial Forum* identifies items that are official in the USP Reference Standards collection at the time of publication.~~

~~Two columns appear in the Catalog to identify the current official lots. One column identifies the official lot currently being shipped by USPC. In some cases, the previous lot may still be considered official. If so, it is identified in the second column. Ordinarily the previous lot is carried in official status for about one year after the current lot entered distribution unless, because of a change in monograph requirements or stability limitations, the previous lot is found to be no longer suitable.~~

~~PROPER USE OF USP REFERENCE STANDARDS~~

~~Unless a Reference Standard label states a specific potency or content, the Reference Standard is taken as being 100.0% pure for compendial purposes. The suitability of a USP Reference Standard for noncompendial application is left up to the user.~~

~~To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Generally, Reference Standards should be stored in their original stoppered containers away from heat and protected from light. Avoid humid storage areas in particular. Where special storage conditions are necessary, directions are given on the label.~~

~~Neither Reference Standards nor Authentic Substances are intended for use as drugs or as medical devices.~~

~~Many Pharmacopeial tests and assays are based on comparison of a test specimen with a USP Reference Standard. In such cases, measurements are made on preparations of both the test specimen and the Reference Standard. Where it is directed that a Standard solution or a *Standard preparation* be prepared for a quantitative determination by stepwise dilution or otherwise, it is intended that the Reference Standard substance shall be accurately weighed (see *Weights and Balances* ⟨41⟩ and *Volumetric Apparatus* ⟨31⟩). Due account should also be taken of the relatively large errors associated with weighing small masses (see also *Dilution* under *Tests and Assays* in the *General Notices and Requirements*).~~

~~Assay and test results are determined on the basis of comparisons of the specimen under test with a USP Reference Standard that has been freed from or corrected for volatile residues or water content as instructed on the label. Where special drying requirements for Reference Standards are found in specific sections of *USP* or *NF* monographs, those supersede the usual instructions (see *Procedures* under *Tests and Assays* in the *General Notices and Requirements*). Where a USP Reference Standard is required to be dried before using, transfer an amount, sufficient after drying, to a clean and dry vessel. Do not use the original container as the drying vessel, and do not dry a specimen repeatedly at temperatures above 25°. Where the titrimetric determination of water is required at the time a Reference Standard is to be used, proceed as directed for *Method I* under *Water-Determination* ⟨921⟩. Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts, about 50 mg, of the Reference Standard, titrate with a fourfold dilution of the *Reagent*.~~

~~The *USP Reference standards* section of an individual *USP* or *NF* monograph or general chapter names each USP Reference Standard required for assay and test procedures and refers to this chapter for additional information and instructions. The list that follows presents the instructions for the proper use and storage of each required USP Reference Standard. These instructions are to be the same as those appearing on the corresponding USP Reference Standard label. Where, in an isolated instance, the specific label instruction differs from the text in the following list, the instruction on the label of the item from the current lot takes precedence. A situation may be infrequently encountered where it is necessary, on scientific grounds, to effect immediately a change in the instructions. This change can be made easily on the label of the Reference Standard, whereas the formal process for revising the compendial text requires more time. Thus, it is especially important to refer to the current Supplement to *USP* and to *NF* for official revisions to the following list.~~ ■1S (*USP30*)

Add the following:

▪AUTHORITY FOR ESTABLISHMENT AND RELEASE

USP Reference Standards are established and released under the authority of the USPC Board of Trustees upon recommendation of the USP Reference Standards Expert Committee, which approves each lot as being suitable for use in its compendial applications. For some Reference Standards a preliminary review and approval is sought from other Expert Committees of the Council of Experts.

The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration of the Department of Justice.

Industry Advisory Panels and other expert groups (such as Project Teams) may be assembled to advise USP on various aspects of the Reference Standards Program. ■1S (*USP30*)

Add the following:

▪HISTORY

Future availability of the first USP Reference Standards was announced in 1926 (*USP X*) "... in order to facilitate the adoption of the biological assay standards of the Pharmacopoeia, and to provide a greater degree of uniformity in their application." The list of USP Reference Standards that in 1936 comprised 6 items has grown to almost 1650 in 2004, and the collection has tracked the progress in pharmaceutical sciences: The first vitamins (Cod Liver Oil) and the first enzyme (Pepsin) in 1936; the first sulfonamide (Sulfanilamide) and the first hormones (Insulin; Posterior Pituitary) in 1942; the first performance standards (Melting Point Standards) in 1947; the first penicillin (Penicillin G Sodium) in 1950; the first recombinant-DNA technology protein (Insulin Human) in 1985, etc.

The continuous increase in the number of USP Reference Standards (over 100 new standards are being developed yearly) reflects not only the increase in the number of monographs and General Chapters, but also the development and extensive

use of modern analytical methodology (such as chromatography, spectrophotometry, biological and biochemical assays, etc.) which require measurements relative to a reference standard.■1S (*USP30*)

Add the following:

▪NOMENCLATURE

Standards designated as USP Reference Standards (USP RS) are, with a few exceptions, required for use in compendial monographs or General Chapters. The exceptions include current lots of USP and NF Reference Standards for which uses are no longer specified in the current *USP* or *NF* but for which sufficient demand remains (upon depletion of the current lots, future lots will be designated as Authentic Substances), Reference Standards specified in the current edition of the *Food Chemicals Codex* (labeled with an additional designation "FCC"), and Fluoride Dentifrices (evaluated and distributed by agreement with the FDA and the Cosmetics, Fragrances and Toiletries Association). Occasionally, a USP Reference Standard required in a monograph or General Chapter proposed in *Pharmacopeial Forum* may be released in advance of the official date of the proposed *PF* revision.

Reference Standards currently labeled as "NF Reference Standards" will eventually all be designated and labeled as "USP Reference Standards" pursuant to the consolidation of *USP* and *NF* within the USPC as of January 2, 1975. Meanwhile, where a USP Reference Standard is called for, the corresponding substance labeled as an "NF Reference Standard" may be used.

As a service, the USPC tests and distributes additional Authentic Substances (designated by AS) not currently required as USP or NF Reference Standards. These also are provided under the supervision of the USP Reference Standards Committee. They are highly characterized samples of chemicals, including substances of abuse, which are collaboratively tested and made available as a service primarily to analytical, clinical, pharmaceutical, and research laboratories. Such materials may be used for identification, method development, evaluation of method performance, or other applications as found suitable and validated by the user.

Authentic Visual References

Unlike chemical reference standards, Authentic Visual References (AVRs) are not used in chemical analyses. Instead, the AVRs are visual images used by analysts to compare certain test articles to ensure that they meet compendial requirements and are incorporated by reference into the monograph. Approval of AVRs for use in a monograph is the decision of the Expert Committee that approves the specific monograph.■1S (*USP30*)

Add the following:

▪DIVERSITY AND IMPLICATIONS

The USP Reference Standards collection is very diverse in terms of appearance, chemical structure, composition, and uses. This diversity has significant implications for the way the materials are tested, packaged, stored, and utilized.

The USP Reference Standards may be crystalline or amorphous powders, volatile or viscous liquids, solutions or suspensions, gels or pastes, plastic sheets, etc. In chemical structure they vary from simple inorganic salts to proteins produced by recombinant DNA technology. Some are highly-purified single components, while others are complex mixtures (in most cases extracted from plant or animal sources).■1S (*USP30*)

Add the following:

▪USES OF USP REFERENCE STANDARDS

The official uses of USP Reference Standards are specified in the compendial monographs and in General Chapters and they include the following:

- quantitative uses in assays for drug substances and formulations, limit tests, or blanks and controls
- qualitative uses, such as identification tests, system suitability tests, chromatographic peak markers, etc.
- performance standards and calibrators, such as dissolution calibrators, melting point standards, the particle count set, etc.

As discussed under *Nomenclature,* USP also establishes and distributes standards without compendial applications.

The most frequent applications of USP Reference Standards (USP RS) are in chromatographic and spectroscopic methodologies. However, they are also widely used in biological and biochemical applications, such as microbial assays for antibiotics, enzymatic reactions, cell-culture tests, whole-animal tests; in thermal analysis for polymers; and in titration, etc. Some of the most frequently used USP RS are those utilized in General Chapters tests such as *Dissolution* ⟨711⟩, *Bacterial Endotoxins Test* ⟨85⟩, *Total Organic Carbon* ⟨643⟩, and *Particulate Matter in Injections* ⟨788⟩.■1S (*USP30*)

Add the following:

▪STEPS IN ESTABLISHING A USP REFERENCE STANDARD

The establishment of a new USP Reference Standard is triggered by the proposal of a new monograph or of a revision of an existing monograph by the inclusion of a test requiring a new USP RS. The need for a new lot of an existing USP Reference Standard is identified when its inventory reaches a preestablished threshold. The new lot is designated as a "replacement lot" if a new bulk material is to be procured or as a "continuation lot" if the candidate material is another portion of the bulk used for the existing official lot.

USP scientists generate a set of documents including procurement specifications and a testing protocol. A bulk material is obtained, generally from a major manufacturer of the article. The material is tested and characterized in an inter-laboratory collaborative study organized according to the protocol designed at USP Headquarters. The results are evaluated by USP Staff, additional testing or investigations are performed when necessary, and a report is compiled and presented for review and approval to the USP Reference Standards Expert Committee. After approval the material is subdivided (if not packaged prior to the collaborative study), labeled, quality checks are performed, and the standard is made available for distribution. If a candidate material is found to be unsuitable by USP scientific staff or by the Reference Standards Committee, a new bulk is procured and tested.■1S (*USP30*)

Add the following:

▪COLLABORATIVE STUDY FOR THE EVALUATION OF A USP RS CANDIDATE MATERIAL

The goals of the evaluation study are to confirm the identity and assess the purity of the material, to determine its suitability for use in the official applications, to provide the user with all the necessary information and directions for use, and to acquire time-zero information for future continued-suitability-for-use studies.

USP scientists design a detailed testing protocol that includes the following elements: types of tests, number of tests, number of collaborators, number of replicates, and references to the procedures to be used.

The following factors are considered when designing the study protocol: the compendial status of the standard, its official uses, the history of the standard, its composition and complexity, the characteristics of the methodology, and the availability of material and of competent laboratories.

The testing protocol may comprise visual and microscopic evaluation; identification tests (more elaborate for first-time standards); determination of physical–chemical constants (e.g., melting range, specific rotation, refractive index, specific gravity, etc); chromatographic and electrophoretic purity tests; inorganic contaminants determination; volatile tests (water, solvents); functional group analysis (such as titrations, UV ab-

sorptivity, elemental analysis); thermal analysis; and assays against another well-characterized standard (a previous lot, an international standard, etc). Specialized testing is implemented where appropriate, such as for dissolution calibrators and the particle count set, for standards that define an attribute (negative and positive bioreaction, ion-exchange capacity, permeability diameter), and for biological standards that define a Unit of activity (heparin, endotoxin, enzymes, complex antibiotics). Vapor sorption analysis may also be performed to assist in determining packaging and storage conditions, and directions for use. For lyophilized single-use USP RS, acceptable vial content reproducibility and stability of the lyophilized form are demonstrated.

The number of collaborators is generally not less than three (two outside of USP); but it can increase significantly, especially when the methodology is complex or does not have a high level of precision or when potential users express an interest in participating in the evaluation of the candidate. (Participation in all evaluation studies is open to all competent, interested parties.) Where appropriate, statistical control is exercised in the design of the evaluation study and in the analysis of the results. The USP Reference Standards Laboratory and the FDA laboratories participate in almost all evaluation studies. Other collaborators include Health Canada, the USP Research and Development Laboratory, and industrial and academic laboratories from the United States and from abroad.■1S (*USP30*)

Add the following:

▪BIOLOGICAL REFERENCE STANDARDS

The World Health Organization, an agency of the United Nations, manages a program providing International Standards for biological materials.

USP collaborates closely with the WHO in the harmonization of analytical methodology, in the definition of the units of potency, and in some cases to share in the preparation of a reference standard. In many cases the USP Units and the International Units of potency are identical.■1S (*USP30*)

Add the following:

▪SUITABILITY FOR USE AND PURITY ASSIGNMENT

The data collected in the collaborative evaluation study are analyzed to determine whether the material is suitable for its monograph-designated use. Characterization data and results must be considered as a whole when evaluating suitability for intended use, assignment strategy, and assigned value. For Reference Standards used in quantitative applications, this includes the determination of a calculation value to be used in the compendial utilization of the standard.

The method of choice in computing the assigned value is a mass balance analysis using independently determined components such as moisture, solvent residues, inorganic residues, chromatographic impurities, and ion content. The assay results against a previous lot or against another validated standard and the results of the functional group analysis are for confirmatory purposes only. Exceptions to the mass balance approach include many biological Reference Standards, especially those which define the Unit of activity.

The number of significant figures in the labeled calculation value is a function of the use of the standard and the number of significant figures in the acceptance range or limit. Generally, Reference Standards used in assays are labeled with three significant figures and standards used in limit tests with two significant figures. Reference Standards having multiple applications in different methodologies may require separate assay-specific assignments.

The assigned value is labeled without any associated uncertainty. However, for calibration standards, the labeled value is a range, determined by a statistical analysis of the results.

Previous approaches used a purity threshold above which the content was no longer labeled, and the analyst was directed to use a default value of 100.0%. This approach is no longer in use, but older lots of standards have not been re-labeled, and users should continue to apply the default 100.0% value for compendial quantitative applications.

For antibiotics, the designation "µg/mg" is sometimes used as a unit of biological activity, and values greater than 1000 µg/mg may be assigned to some of these standards. This can happen when the first standard is assigned a value higher than its actual purity and subsequent standards of higher purity are defined relative to the previous lot. A relatively overstated assigned value can also result when less selective separation techniques are replaced with more selective modern methodologies. As a result, the original content might have been assumed to be higher than the actual level.

No value is assigned to standards having only qualitative applications.

A report compiling the results of the evaluation study and including the proposed label text is submitted for review and approval to the USP Reference Standards Expert Committee.■1S (*USP30*)

Add the following:

▪LABEL TEXT

The label text is designed to provide the user with all the information needed for the correct storage and usage of the Reference Standard in monograph application(s). The label includes directions for use, safety warnings, required information for controlled substances, and a calculation value for standards with quantitative applications. For calibrators, acceptance ranges are provided. Where necessary, USP Reference Standards are accompanied by additional documentation, such as Technical Sheets or Typical Chromatograms. USP does not provide Certificates of Analysis, because all the information that the user needs for the official applications of the standard is provided in the label text and, where necessary, in the additional documentation provided.

Directions for use are lot-specific, and they take precedence over any other indication in the compendium.

Material Safety Data Sheets are generated for every standard that USP distributes. They are available on the USP website.■1S (*USP30*)

Add the following:

▪USP REFERENCE STANDARDS EXPERT COMMITTEE

The USP Reference Standards Expert Committee comprises professionals from industry, government agencies and academia from the United States and abroad. It is organized in groups and may be assisted in the review of the evaluation studies by an Industry Advisory Panel. The approval of the evaluation report has to be unanimous.■1S (*USP30*)

Add the following:

▪PACKAGING

The USP Reference Standard production process operates under a registered ISO 9001:2000 Quality System and appropriate cGMP principles.

USP Reference Standards are packaged in individual units designed to maintain the integrity of the contained Reference Standard material. The packaging and storage conditions for USP Reference Standards provide protection for all materials even though the material may not need such exceptional protection due to its inherent stability. The most common packaging configurations are vials for solid materials and ampuls for liquids. The packaging environment is determined by the sensitivity of the material to light, oxidation, or atmospheric humidity, and by its toxicity. Where appropriate, containers are filled in a glove box under inert gas and in conditions of controlled low residual humidity. (The need to store such standards under inert gas protection is indicated on the label.)

They may also be sealed in a foil bag as an added protective barrier. Ampuls are filled and sealed on an automated device and are typically purged with an inert gas. The most common ampul sizes are 2 mL and 5 mL. Vials may be filled by manual, semi-automated, or fully automated operations. Vials may be of different sizes depending upon the amount of material. The amount of material per individual container depends on the compendial application of the standard and is generally sufficient for several replicates. Larger amounts are provided when additional experiments are required (such as a titrimetric determination of the water content at the time of use). In general, Reference Standard containers are slightly over-filled so that the user can retrieve the labeled, nominal amount of material. Vials are closed with Teflon-lined stoppers and secured with aluminum crimps and a USP-logo tamper-evident seal. Lots using prior vial closure configurations may still be in distribution.

Various considerations may determine the need to provide the standard in single-use containers, mainly for materials with significant handling issues or for those that are available only in small amounts. Such single-use containers are generally filled by lyophilization, and their content is labeled in mass or activity Units per container. If so labeled, the content of the container is to be reconstituted in its entirety without any additional weighing. Instructions for reconstitution are given either on the label or in the monographs where the standard is being used.■1S (*USP30*)

Add the following:

▪IMPURITY REFERENCE STANDARDS

The topic of impurities is addressed in several sections of USP, such as *General Notices,* General Chapters such as *Ordinary Impurities* ⟨466⟩, *Impurities in Official Articles* ⟨1086⟩, etc. In addition, most of the monographs for drug substances and many of those for formulations include specific tests for the identification or quantitation of impurities. Such tests generally require an official Reference Standard. The development of these impurity Reference Standards is one of the reasons for the continuous accelerated growth of the USP Reference Standards.

In many cases, the materials for impurity Reference Standards are expensive and difficult to procure. Only a limited amount of material may be available—procurement might require custom synthesis—and it may be of lesser quality than the Reference Standard for the official article, requiring purification. The limited amount of material available can affect the testing protocol and the packaging. Impurity Reference Standards might be available as purified single-component materials, solutions, or solid dispersions, or mixtures of more than one impurity. Other options include samples of the official article with a labeled content of impurity(ies), the in-situ generation of the impurity from the official article by a validated specified procedure, the use of relative chromatographic mobilities and relative response factors, or of theoretical values such as UV absorptivities at selective wavelengths.

In earlier editions of the compendium, the impurities were designated by their chemical names. For ease of indexing and searching, these have been gradually replaced with the designation "X Related Compound Y RS," where X is the name of the official article and Y is a sequential alphabetical letter. Reference Standard impurity mixtures might be designated by their use, such as "X System Suitability RS". The conventional names and the chemical names are cross-referenced in the final section of this chapter and in a special section of the Official USP Reference Standards Catalog.■1S (*USP30*)

Add the following:

▪CONTINUED SUITABILITY FOR USE PROGRAM

To ensure that the Reference Standards maintain the properties determined at the initial evaluation, USP maintains a Continued Suitability for Use Program. The retesting intervals and protocols are a function of the uses and properties of the standard and of the information available about its stability. Ab-

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breviated protocols use the stability-indicating methodology employed in the initial characterization of the material to confirm the consistency of attributes such as appearance, chromatographic purity, or volatiles content.■1S (*USP30*)

Add the following:

▪PROPER USE

Neither the Reference Standards nor the Authentic Substances are intended for use as drugs or as medical devices.

USP Reference Standards do not carry an expiration date as long as they are in distribution. A lot of USP RS may be used in its official applications as long as it is listed as ''Current Lot'' in the current (most recent) Official USP Reference Standards Catalog. Upon depletion, the lot is designated in the catalog as ''Previous Lot'' and a ''Valid Use Date'' is assigned. USP publishes the Official Catalog of Reference Standards (which also includes Authentic Substances) bimonthly both as a separate brochure and in *Pharmacopeial Forum**. An updated version of the catalog can be found on the USP website at www.usp.org. It is the responsibility of the user to ascertain that a particular supply of USP Reference Standard has official status either as a ''Current Lot'' or as a ''Previous Lot'' within the valid use date.

Many Pharmacopeial tests and assays are based on comparison of a test specimen with a USP Reference Standard. In such cases, measurements are made on preparations of both the test specimen and the Reference Standard. Where it is directed that a Standard solution or a Standard preparation be prepared for a quantitative determination by stepwise dilution or otherwise, it is intended that the Reference Standard substance shall be accurately weighed (see *Weights and Balances* ⟨41⟩ and *Volumetric Apparatus* ⟨31⟩). Due account should also be taken of the relatively large errors associated with weighing small masses (see also *Dilution* under *Tests and Assays* in the *General Notices and Requirements*).

The label text provides the user with directions on the proper use of a Reference Standard. The directions include one of the following options. A Reference Standard may be used as follows:

- As-is, i.e., without any prior treatment or correction for volatiles. This is the preferred option, and it is selected whenever validated data show that the volatiles content is constant over time.
- Immediately after a prior drying under stated conditions. Drying should not be performed in the original container. A portion of the material should be transferred to a separate drying vessel.
- With a correction for the water content or the loss on drying determined on a separate portion of material. Where the titrimetric determination of water is required at the time a Reference Standard is to be used, proceed as directed for *Method I* under *Water Determination* ⟨921⟩. Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts (about 50 mg of the Reference Standard), titrate with a two- to five-fold dilution of the reagent.

Whenever the labeled directions for use require a preliminary drying or a correction for volatiles, it should be performed ''at the time'' of use. Further experimental details should be controlled by the user's Standard Operating Procedures and good laboratory practices.■1S (*USP30*)

Add the following:

▪STORAGE

To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Generally, Reference Standards should be stored in their original stoppered containers away from heat and protected from light.

* For nonsubscribers, the most recent Official Catalog is available from: U.S. Pharmacopeial Convention, Inc., Reference Standards Order Department, 12601 Twinbrook Parkway, Rockville, MD 20852. Telephone 1-301-881-0666. FAX 1-301-816-8148. Toll-free telephone 1-800-227-USPC or access the Catalog on USP's website www.usp.org/dsd/refstd.

Avoid humid storage areas in particular. Where special storage conditions are necessary, directions are given on the label.■1S (*USP30*)

Add the following:

▪RELATIONSHIPS WITH OTHER STANDARDS-SETTING ORGANIZATIONS

USP maintains continuous contact with other organizations that establish Reference Materials for compendial and other purposes, such as the European and the Japanese Pharmacopoeias (through the Pharmacopeial Discussion Group), the World Health Organization, the National Institute for Science and Technology, the Reference Materials Committee of ISO (REMCO), etc.

The specific nature of pharmacopeial reference substances has been officially recognized by ISO-REMCO in the introduction of the ISO Guide 34—General requirements for the competence of reference material producers—(Second Edition 2000): ''Pharmacopoeial standards and substances are established and distributed by pharmacopoeial authorities following the general principle of this guide. It should be noted, however, that a different approach is used by the pharmacopoeial authorities to give the user the information provided by certificate of analysis and the expiration dates. Also, the uncertainty of their assigned values is not stated since it is negligible in relation to the defined limits of the method-specific assays of the pharmacopoeias for which they are used.''

The *USP Reference standards* section of an individual *USP* or *NF* monograph or general chapter names each USP Reference Standard required for assay and test procedures and refers to this chapter for additional information and instructions. It is especially important to refer to the current Supplement to *USP* and to *NF* for official revisions listed in the following section.■1S (*USP30*)

Change to read:

USP REFERENCE STANDARDS SPECIFIED IN USP AND NF MONOGRAPHS AND GENERAL CHAPTERS

NOTE—Consult the latest Supplement or *Interim Revision Announcement* pertaining to *USP* and to *NF* for revisions, additions, or deletions.

Revisions, additions, and deletions of individual USP Reference Standards are listed cumulatively in each Supplement to *USP–NF*. As a consequence, therefore, it is necessary to consult only ~~*USP 29–NF 24*~~

▪the current edition of *USP–NF* ■1S (*USP30*) and the latest Supplement for the complete list of USP Reference Standards currently specified in *USP–NF* monographs and general chapters. The list provides up-to-date and complete names and applicable chemical information ~~, and handling instructions~~

▪■1S (*USP30*) for the USP Reference Standards that are in distribution as of the official date of that Supplement.

Revisions of this chapter are implemented continuously via the *Interim Revision Announcements* that are published in *Pharmacopeial Forum*. Those interim revisions of USP Reference Standards are cumulatively included in the next *USP–NF* Supplement.

The alphabetical list that follows constitutes an index of all revisions to this chapter. Thus, it is unnecessary to name repetitively the revised Reference Standards in the general index to the Supplement.

In the list that follows, chemical names are given for many substances (e.g., related compounds) that are not *USP* or *NF* monograph articles. Following the name of such a chemical substance RS, the empirical formula and molecular weight, separated by the ✧ symbol, may be given in parentheses if those data are available.

Change to read:

USP Acebutolol Hydrochloride RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

▪■1S (*USP30*)

Change to read:

USP Acepromazine Maleate RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

▪■1S (*USP30*)

Change to read:

USP Acesulfame Potassium RS.~~—Do not dry. Keep container tightly closed.~~

▪■1S (*USP30*)

Change to read:

USP Acetaminophen RS.~~—Dry portion over silica gel for 18 hours before using. Keep container tightly closed and protected from light.~~

▪■1S (*USP30*)

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Change to read:

USP Acetanilide Melting Point RS.~~—Dry portion over sulfuric acid for 16 hours before using. When melted by the capillary tube method, *Class Ia* in the general chapter *Melting Range or Temperature* ⟨741⟩, the observed range falls within the indicated acceptance range. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Acetazolamide RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Acetohexamide RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Acetohydroxamic Acid RS.~~—Dry portion over phosphorus pentoxide for 16 hours before using. Keep container tightly closed, and store in a desiccator in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Acetylcholine Chloride RS.~~—Dry portion at 105° for 3 hours before using. Once opened, store in a desiccator, and keep container tightly closed. This material is extremely hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Acetylcysteine RS.~~—Dry portion at a pressure of about 50 mm of mercury at 70° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Acetyltributyl Citrate RS.~~—Do not dry before using. After opening the ampul, keep the material in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Acetyltriethyl Citrate RS.~~—Do not dry before using. After opening the ampul, keep the material in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Acyclovir RS.~~—Do not dry; determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ademetionine Disulfate Tosylate RS.~~—Do not dry. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Adenine RS.~~—Dry portion at 110° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Adenosine RS.~~—Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Adipic Acid RS.~~—Dry portion at 105° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Agnuside RS.~~—This material is hygroscopic. Keep container tightly closed. Protect from light. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP L-Alanine RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Albendazole RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Albuterol RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Albuterol Sulfate RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Alclometasone Dipropionate RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Alcohol RS. ~~After opening ampul, store the unused portion in a tightly closed container. Protect from light. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Dehydrated Alcohol RS. ~~After opening ampul, store the unused portion in a tightly closed container. Protect from light. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Alcohol Determination—Acetonitrile RS. ~~Acetonitrile in water. Dispose of unused portion after opening.~~

■■1S (*USP30*)

Change to read:

USP Alcohol Determination—Alcohol RS. ~~Alcohol solution in water. Dispose of unused portion after opening.~~

■■1S (*USP30*)

Change to read:

USP Alendronate Sodium RS. ~~Do not dry. This is the trihydrate form of alendronate sodium. Keep container tightly closed. After opening, store in a desiccator at room temperature.~~

■■1S (*USP30*)

Change to read:

USP Allantoin RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Alliin RS. ~~Do not dry before using. Keep container tightly closed, and store in a refrigerator. After opening, store the container in a desiccator in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Allopurinol RS. ~~Dry portion in vacuum at 105° for 5 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Add the following:

■**USP Allopurinol Related Compound E RS** **[**ethyl 5-(formylamino)-1*H*-pyrazole-4-carboxylate**]**—[To come.]■1S (*USP30*)

Add the following:

■**USP Allopurinol Related Compound F RS** **[**ethyl 3-(2-carbethoxy-2-cyanoethenyl)amino-1*H*-pyrazole-4-carboxylate**]**—[To come.]■1S (*USP30*)

Change to read:

USP *S*-Allyl-L-Cysteine RS. ~~Do not dry before using. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Alprazolam RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Alprostadil RS. ~~Do not dry before using. Keep container tightly closed, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Altretamine RS.~~—Do not dry before using. Determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dried Aluminum Hydroxide Gel RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Amantadine Hydrochloride RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Amcinonide RS.~~—Do not dry before using. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Amifostine RS.~~—Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Amifostine Disulfide RS [1,3-propanediamine, *N,N*-(dithiodi-2,1 ethanediyl)bis, tetrahydrochloride**]** ($C_{10}H_{30}N_4S_2Cl_4$ ✧ 412.32).~~—Do not dry. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Amifostine Thiol RS [ethanethiol, 2-[(3-aminopropyl)amino]-, dihydrochloride**]** ($C_5H_{16}N_2SCl_2$ ✧ 207.17).~~—Do not dry. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Amikacin RS.~~—Do not dry before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Amiloride Hydrochloride RS.~~—Using thermogravimetric analysis (see *Thermal Analysis* ⟨891⟩), heat a 10 mg portion, accurately weighed, at 10° per minute between ambient temperature and 225° under nitrogen flowing at 40 mL per minute. From the thermogram, determine the accumulated loss in weight between ambient temperature and about 200° on the plateau. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Aminobenzoate Potassium RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Aminobenzoic Acid RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Aminobutanol RS ($C_4H_{11}NO$ ✧ 89.14).~~—This material is hygroscopic. After opening ampul, store in tightly closed container. Do not dry; determine the water content titrimetrically at the time of use.~~

■■1S (*USP30*)

Change to read:

USP Aminocaproic Acid RS.~~—Dry portion at 105° for 30 minutes before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP *N*-(Aminocarbonyl)-*N*-[([5-nitro-2-furanyl]-methylene)-amino]-glycine RS.~~—Do not dry before using.~~

■■1S (*USP30*)

Change to read:

USP 2-Amino-5-chlorobenzophenone RS ($C_{13}H_{10}ClNO$ ✧ 231.68).~~—Keep container tightly closed and protected from light. Dry portion over silica gel for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP 3-Amino-2,4,6-triiodobenzoic Acid RS ($C_7H_4I_3NO_2$ ✧ 514.83).~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP 5-Amino-2,4,6-triiodo-*N*-methylisophthalamic Acid RS ($C_9H_7I_3N_2O_3$ ✧ 571.88).~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Aminoglutethimide RS.~~—Dry portion at 105° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP *m*-Aminoglutethimide RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Aminohippuric Acid RS.~~—Do not dry before using. Keep container tightly closed and protected from light. Material will discolor if exposed to light and air.~~

■■1S (*USP30*)

Change to read:

USP 5-Aminoimidazole-4-carboxamide Hydrochloride RS ($C_4H_6N_4O \cdot HCl$ ✧ 162.58).~~—Do not dry before using. Keep container tightly closed, protected from light, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

■**USP Amino Methacrylate Copolymer RS**.~~—Dry at 110° for 3 hours. Keep container tightly closed. Store at or below room temperature.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Aminopentamide Sulfate RS.~~—Dry at 105° for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP *m*-Aminophenol RS.~~—Do not dry before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Aminosalicylic Acid RS.~~—Dry portion in vacuum at 50° for 1 hour before using. Keep container tightly closed, protected from light, and store at a temperature not exceeding 30°.~~

■■1S (*USP30*)

Change to read:

USP Amitraz RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Amitriptyline Hydrochloride RS.~~—Dry portion at a pressure not exceeding 5 mm of mercury at 60° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ammonio Methacrylate Copolymer, Type A RS.~~—Dry portion in vacuum at 80° for 5 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ammonio Methacrylate Copolymer, Type B RS.~~—Dry portion in vacuum at 80° for 5 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ammonium Chloride RS.~~—Dry over silica gel for 4 hours. This material is hygroscopic. Keep container tightly closed. Store at room temperature.~~

■■1S (*USP30*)

Change to read:

USP Amobarbital RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

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Change to read:

USP Amodiaquine Hydrochloride RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Amoxapine RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Amoxicillin RS. ~~Do not dry before using. This is a trihydrate form of amoxicillin. Keep container tightly closed. Protect from light, and store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Amphotericin B RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Ampicillin RS. ~~This is the anhydrous form of ampicillin. Before using, dry portion to constant weight in vacuum over phosphorus pentoxide at room temperature. Keep container tightly closed. Store in a cool, dry place.~~

■ ■1S (*USP30*)

Change to read:

USP Ampicillin Sodium RS. ~~Do not dry before using. Hygroscopic. Keep container tightly closed. Store in a cool, dry place.~~

■ ■1S (*USP30*)

Change to read:

USP Ampicillin Trihydrate RS. ~~Do not dry before using. Keep container tightly closed and protected from light. Store in a cold, dry place.~~

■ ■1S (*USP30*)

Change to read:

USP Amprolium RS. ~~Dry portion at a pressure not exceeding 5 mm of mercury at 100° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Anileridine Hydrochloride RS. ~~Dry portion at a pressure below 5 mm of mercury at 100° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Antazoline Phosphate RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Anthralin RS. ~~Do not dry before using. Keep container tightly closed, and store in a cool place. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Antipyrine RS. ~~Dry portion at 60° for 2 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Apigenin-7-Glucoside RS. ~~Do not dry. For quantitative USP applications use a value of 0.88 mg of apigenin-7-glucoside for each mg of this standard on the as-is basis. Keep container tightly closed, protected from light, and store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Apomorphine Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Apraclonidine Hydrochloride RS. ~~Dry portion in vacuum at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP L-Arginine RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Arginine Hydrochloride RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Arsanilic Acid RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Ascorbic Acid RS. ~~Do not dry. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Aspartame RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a desiccator.~~

■ ■1S (*USP30*)

Change to read:

USP Aspartame Acesulfame RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Aspartame Related Compound A RS [5-benzyl-3,6-dioxo-2-piperazineacetic acid] ($C_{13}H_{14}N_2O_4$ ✧ 262.27). ~~Do not dry. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Aspartic Acid RS. ~~Do not dry. Store at room temperature.~~

■ ■1S (*USP30*)

Change to read:

USP Aspirin RS. ~~Dry portion over silica gel for 5 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Astemizole RS. ~~Dry at 105° in vacuum for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Atenolol RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Atovaquone RS. ~~Do not dry before using.~~

■ ■1S (*USP30*)

Change to read:

USP Atovaquone Related Compound A RS [*cis*-2[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone]. ~~Do not dry before using.~~

■ ■1S (*USP30*)

Change to read:

USP Atracurium Besylate RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed, and store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Atropine Sulfate RS. ~~Do not dry before using. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Aurothioglucose RS. ~~Dry portion over phosphorus pentoxide for 24 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Avobenzone RS. ~~Dry portion in vacuum at 70° for 4 hours before using. For quantitative applications use a value of 0.994 mg of avobenzone per mg on the dried basis. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Azaerythromycin A RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

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Change to read:

USP Azaperone RS.~~—Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Azatadine Maleate RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Azathioprine RS.~~—Dry portion in vacuum at 105° for 5 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Azithromycin RS.~~—Do not dry before using. Keep container tightly closed, and store in a freezer.~~

■■1S (*USP30*)

Add the following:

■**USP Azithromycin Identity RS** **[**A mixture of azithromycin, 3′-(*N*-*N*-dimethyl-3′-*N*-formyl-azithromycin, 3′-*N*-demethyl-3′-*N*-formylazithromycin (Rotamer 1), 3′-*N*-demethyl-3′-*N*-formylazithromycin (Rotamer 2), 3′-de(dimethylamino)-3′-oxoazithromycin, 2-desethyl-2-propylazithromycin, 3-deoxyazithromycin and 3′-*N*-demethyl-3′-*N*-[(4-methylphenyl)sulfonyl]azithromycin**]**.■1S (*USP30*)

Add the following:

■**USP Azithromycin *N*-Oxide RS.**—[To come.]■1S (*USP30*)

Change to read:

USP Azo-aminoglutethimide RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Aztreonam RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Aztreonam *E*-Isomer RS.~~—Do not dry before using. Keep container tightly closed, protected from light, air, and moisture, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Open Ring Aztreonam RS ($C_{18}H_{19}N_5O_9S_2$ ✧ 453.46).~~—Do not dry before using. Keep container tightly closed, protected from light, and store in a freezer. This material is extremely hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Bacampicillin Hydrochloride RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Bacitracin Zinc RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Baclofen RS.~~—Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Baclofen Related Compound A RS **[**4-(4-chlorophenyl)-2-pyrrolidinone**]** ($C_{10}H_{10}ClNO$ ✧ 195.65).~~—Do not dry before using. Keep container tightly closed, protect from light, and store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Beclomethasone Dipropionate RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

■**USP Benazepril Hydrochloride RS.**~~—Dry portion at 105° for 3 hours before using.~~

■■1S (*USP30*)
■2S (*USP29*)

In-Process Revision

Change to read:

■**USP Benazepril Related Compound A RS** ~~[3-(1-ethoxycarbonyl-3-phenyl-(1*R*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*R*)-benazepine)-1-acetic acid]~~**[** (3*R*) 3-[[(1*R*) 1-(ethoxycarbonyl)-3-phenylpropyl] amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, monohydrochloride**]** ($C_{24}H_{28}N_2O_5 \cdot HCl$ ✧ ~~460.96~~ 460.95).~~— Do not dry. Store in a refrigerator. Protect from light.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Benazepril Related Compound B RS** ~~[3-(1-ethoxycarbonyl-3-phenyl-(1*R*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benazepine)-1-acetic acid]~~**[**(3*S*) 3-[[(1*R*) 1-(ethoxycarbonyl)-3-phenylpropyl] amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, monohydrochloride**]** ($C_{24}H_{28}N_2O_5 \cdot HCl$ ✧ ~~460.96~~ 460.95).~~— Do not dry. Store in a refrigerator. Protect from light.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

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

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Bendroflumethiazide RS.~~— Do not dry. Keep container tightly closed. Store in a refrigerator. Protect from moisture.~~

■■1S (*USP30*)

Change to read:

USP Benoxinate Hydrochloride RS.~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Benzalkonium Chloride RS.~~— After opening ampul, store in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Benzocaine RS.~~— Dry portion over phosphorus pentoxide for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Benzoic Acid RS.~~— Dry portion over silica gel for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Benzonatate RS.~~— Do not dry. After opening ampul, store in a tightly closed, light resistant container.~~

■■1S (*USP30*)

Change to read:

USP 1,4-Benzoquinone RS.~~— Do not dry before using. Keep container tightly closed and store in a refrigerator, protected from light. Sonication may be necessary to dissolve the material.~~

■■1S (*USP30*)

Change to read:

USP Benzothiadiazine Related Compound A RS **[**4-amino-6-chloro-1,3-benzenedisulfonamide**]** ($C_6H_8ClN_3O_4S_2$ ✧ 285.73).~~— Keep container tightly closed and protected from light. Dry portion over silica gel for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Benztropine Mesylate RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Benzyl Alcohol RS.~~— Do not dry before using. Store under an inert gas (nitrogen or argon) atmosphere, between 2° and 8°. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Benzyl Benzoate RS.~~—Do not dry. After opening the ampul, store in a tightly closed container, protected from light.~~

■■1S (*USP30*)

Change to read:

USP 1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride RS ($C_{11}H_{13}N_3 \cdot HCl$ ✧ 223.71.~~—Keep container tightly closed and protected from light. Dry portion over silica gel for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Betahistine Hydrochloride RS.~~—Dry portion at 100° to 105° for 4 hours before using. Keep container tightly closed. Very hygroscopic. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Betaine Hydrochloride RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Betamethasone RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Betamethasone Acetate RS.~~—Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Betamethasone Benzoate RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Betamethasone Dipropionate RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Betamethasone Valerate RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Betaxolol Hydrochloride RS.~~—Dry portion in vacuum at 65° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Bethanechol Chloride RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed. The dried material is hygroscopic. After drying, immediately transfer the material to a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Bile Salts RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed. *[Caution—Avoid inhaling airborne particles.]*~~

■■1S (*USP30*)

Change to read:

USP Positive Bioreaction RS.~~—Exercise care in handling. Prepare samples as directed in the respective USP General Test Chapters.~~

■■1S (*USP30*)

Change to read:

USP Biotin RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Biperiden RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Biperiden Hydrochloride RS.~~—Dry portion at 105° for 3 hours. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Bisacodyl RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Bis(2-ethylhexyl) Maleate RS ($C_{20}H_{36}O_4$ ✧ 340.51).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP 4,4′-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone RS ($C_{34}H_{34}N_6O_3$ ✧ 574.69.~~—Keep container tightly closed and protected from light. Dry portion in vacuum at 70° for 4 hours before using. Unstable material.~~

■■1S (*USP30*)

Change to read:

USP Bismuth Citrate RS.~~—Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Bismuth Subsalicylate RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Add the following:

■**USP Bisoctrizole RS**—[To come.]■1S (*USP30*)

Add the following:

■**USP Bisoctrizole Related Compound A RS**—[To come.]■1S (*USP30*)

Add the following:

■**USP Bisoctrizole Resolution Mixture RS**—[To come.]■1S (*USP30*)

Change to read:

USP Bisoprolol Fumarate RS.~~—Dry portion at 60° for 3 hours before using. Protect from light. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Bleomycin Sulfate RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at room temperature for 3 hours in a desiccator containing phosphorous pentoxide before using. Store in a freezer, protected from light, and allow to attain room temperature before opening. This material is very hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Bretylium Tosylate RS.~~—Dry portion in vacuum at 75° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Brinzolamide RS.~~—Do not dry. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Brinzolamide Related Compound A RS **[**brinzolamide *(S)*-isomer**]** ($C_{12}H_{21}N_3O_5S_3$ ✧ 383.52).~~—Do not dry. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Brinzolamide Related Compound B RS **[**(*R*-4-amino)-2,3-dihydro-2-(3-methoxypropyl)-4*H*-thieno[3,2,-*e*]-thiazine-6-sulfonamide-1,1-dioxide ethandioate 1 : 1**]** ($C_{10}H_{17}N_3O_5S_3 \cdot C_2H_2O_4$ ✧ 445.49).~~—Do not dry. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Bromocriptine Mesylate RS.~~—This material is hygroscopic. Determine the volatiles content by TGA, heating a separate 5–10 mg portion from 25° to 160° at 10° per minute under nitrogen flowing at about 45 mL per minute. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Bromodiphenhydramine Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP 8-Bromotheophylline RS [8-bromo-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione] ($C_7H_7N_4O_2Br$ ✧ 259.06). ~~Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Brompheniramine Maleate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Bumetanide RS. ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Bumetanide Related Compound A RS [3-amino-4-phenoxy-5-sulfamoylbenzoic acid] ($C_{13}H_{12}N_2O_5S$ ✧ 308.31). ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Bumetanide Related Compound B RS [3-nitro-4-phenoxy-5-sulfamoylbenzoic acid] ($C_{13}H_{10}N_2O_7S$ ✧ 338.29). ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Bupivacaine Hydrochloride RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Buprenorphine Hydrochloride RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Buprenorphine Related Compound A RS [21-[3-(1-propenyl)]-7α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-*endo*-ethano-6,7,8,14-tetrahydrooripavine] ($C_{29}H_{41}NO_4$ ✧ 467.65). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Bupropion Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Bupropion Hydrochloride Related Compound A RS [2-(*tert*-butylamino)-4′-chloropropiophenone hydrochloride] ($C_{13}H_{18}ClNO \cdot HCl$ ✧ 276.21). ~~Do not dry. ★Keep container tightly closed. Protect from light. Store in a freezer.★~~*USP29*

■■1S (*USP30*)

Change to read:

USP Bupropion Hydrochloride Related Compound B RS [2-(*tert*-butylamino)-3′-bromopropiophenone hydrochloride] ($C_{13}H_{18}BrNO \cdot HCl$ ✧ 320.66). ~~Do not dry. ★Keep container tightly closed. Protect from light. Store in a refrigerator.★~~*USP29*

■■1S (*USP30*)

Change to read:

USP Bupropion Hydrochloride Related Compound C RS [1-(3-chlorophenyl)-2-hydroxy-1-propanone] ($C_9H_9O_2Cl$ ✧ 184.62). ~~Do not dry. ★Protect from light. Store in a freezer. After opening ampul, store in a tightly closed container.★~~*USP29*

■■1S (*USP30*)

Change to read:

USP Bupropion Hydrochloride Related Compound F RS [1-(3-chlorophenyl)-1-hydroxy-2-propanone] ($C_9H_9O_2$ ✧ 184.62). ~~Do not dry. ★Protect from light. Store in a freezer. After opening ampul, store in a tightly closed container.★~~*USP29*

■■1S (*USP30*)

Change to read:

USP Buspirone Hydrochloride RS. ~~Do not dry. After opening, store in a desiccator. Keep container tightly closed and protected from light. Store in a refrigerator.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Butabarbital RS. ~~Keep container tightly closed. Dry portion at 105° for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Butalbital RS. ~~Dry portion in vacuum at room temperature to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Butamben RS. ~~Dry portion over phosphorus pentoxide for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Butoconazole Nitrate RS. ~~Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Butorphanol Tartrate RS. ~~Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP 2-*tert*-Butyl-4-hydroxyanisole RS ($C_{11}H_{16}O_2$ ✧ 180.25). ~~Do not dry before using. Keep container tightly closed. Store in a cool place. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP 3-*tert*-Butyl-4-hydroxyanisole RS ($C_{11}H_{16}O_2$ ✧ 180.25). ~~Do not dry before using. Keep container tightly closed. Store in a cool place. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate RS ($C_{21}H_{28}N_2O_5S$ ✧ 420.53). ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Butylparaben RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Caffeine RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Caffeine Melting Point RS. ~~Dry portion over silica gel for 16 hours before using. When melted by the USP capillary tube method, *Class Ia* in the general chapter *Melting Range or Temperature* ⟨741⟩, the observed range falls within the indicated acceptance range. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Calcifediol RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

■**USP Calcitonin Salmon RS**. ~~Preserve in a freezer at −20° to −10°; and after opening the vial, store in a tight container. Do not dry before use for tests and assays.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Calcitonin Salmon Related Compound A RS** .[*N*-acetyl-cys[1]-calcitonin] ($C_{146}H_{243}N_{44}O_{49}S_2$ ✧ 3463). ~~Preserve in a freezer at −20° to −10°; and after opening the vial, store in a tight container. Do not dry before use for tests and assays.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Calcitrol RS**. ~~Store in a refrigerator. Protect from light.~~

■■1S (*USP30*)
■2S (*USP29*)

In-Process Revision

Change to read:

■**USP Calcitrol Solution RS**.~~— Store in a refrigerator. Protect from light.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Calcium Ascorbate RS.~~— Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Calcium Gluceptate RS.~~— This is the alpha form of Calcium Gluceptate. Dry portion in vacuum at 60° for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Calcium Lactobionate RS.~~— Dry portion at 105° for 8 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Calcium Pantothenate RS.~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Calcium Saccharate RS.~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Candelilla Wax RS.~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Capreomycin Sulfate RS.~~— Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 100° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Caprylocaproyl Polyoxylglycerides RS.~~— Do not dry. After opening the ampul, store the material in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Capsaicin RS.~~— Dry portion at 40° in vacuum over phosphorus pentoxide for 5 hours before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Captopril RS.~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Captopril Disulfide RS.~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Carbachol RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Carbamazepine RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Carbenicillin Indanyl Sodium RS.~~— Do not dry. For quantitative applications determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Carbenicillin Monosodium Monohydrate RS.~~— Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Carbidopa RS.~~—Do not dry before using. On a separate portion determine the *Loss on drying* at a pressure not exceeding 5 mm of mercury at 100° to constant weight, and apply correction for quantitative use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Carbidopa Related Compound A RS [3-*O*-methylcarbidopa] ($C_{11}H_{16}N_2O_4$ ✧ 240.26).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Carbinoxamine Maleate RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Urea C 13 RS.~~—Dry portion in vacuum at 40° for 3 hours before using. Preserve in tight, light-resistant containers.~~

■■1S (*USP30*)

Change to read:

USP Carboplatin RS.~~—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Carisoprodol RS.~~—Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Carteolol Hydrochloride RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Casticin RS.~~—Do not dry. Keep container tightly closed. Store in a refrigerator. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cathinone Hydrochloride RS [α-aminopropiophenone hydrochloride] ($C_9H_{11}NO \cdot HCl$ ✧ 185.65).~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Cefaclor RS.~~—Do not dry. For quantitative applications determine the water content in percentage (*W*) titrimetrically at the time of use. Where calculation formulas require a correction factor use $F = 1000 - 10W$. Keep container tightly closed, protected from light, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Cefaclor Delta-3 Isomer RS.~~—Do not dry before using. Keep container tightly closed, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Cefadroxil RS.~~—Do not dry before using. This is the monohydrate form of cefadroxil. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cefamandole Lithium RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cefamandole Nafate RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cefazolin RS.~~—Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Cefepime Hydrochloride RS.—~~Do not dry before using. Store in a cold place. Protect from light. For quantitative applications, determine the water titrimetrically at the time of use.~~

■■1S (*USP30*)

Change to read:

USP Cefepime Hydrochloride System Suitability RS—This is a mixture of cefepime hydrochloride related compound A ([6*R*-[6α,7β(*E*)]]-1-[[7-[[(2-amino-4-thiazolyl) (methoxyimino)acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]-methyl]-1-methylpyrrolidinium chloride, monohydrochloride, monohydrate; ($C_{19}H_{25}ClN_6O_5S_2 \cdot HCl \cdot H_2O$ ✧ 571.50); cefepime related compound B ([6*R-trans*]-7-[[[2-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-4-thiazolyl](methoxyimino)acetyl]amino]-3-(1-methylpyrrolidinium-1-yl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid, inner salt; ($C_{25}H_{29}N_9O_7S_3$ ✧ 663.75); and cefepime hydrochloride.~~Do not dry before using. Keep container tightly closed. Store in the dark, in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cefixime RS.—~~This is the trihydrate form of cefixime. Do not dry. For quantitative applications determine the water content titrimetrically at the time of use, and use a value of 986 µg of cefixime per mg on the anhydrous basis. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cefmenoxime Hydrochloride RS.—~~Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed, protected from light and moisture, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Cefmetazole RS.—~~Do not dry before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cefonicid Sodium RS.—~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed, and store in a cold, dry place, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Cefoperazone Dihydrate RS.—~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Ceforanide RS.—~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cefotaxime Sodium RS.—~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Cefotetan RS.—~~Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed, protected from light, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Cefotiam Hydrochloride RS.—~~Do not dry before using. For quantitative applications, determine the water content titrimetrically prior to use. Keep container tightly closed, protected from light and moisture, and store at a temperature not exceeding 5°. Prepare solutions immediately prior to use.~~

■■1S (*USP30*)

Change to read:

USP Cefoxitin RS.—~~★This is the monohydrate form. Do not dry. For quantitative applications, determine the water content titrimetrically. Keep container tightly closed. Protect from light. Store in a freezer.~~★*USP29*

■■1S (*USP30*)

Change to read:

USP Cefpiramide RS.—~~Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Cefpodoxime Proxetil RS.—~~Do not dry; determine the water content titrimetrically on a separate portion prior to use. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Cefprozil (*E*)-Isomer RS.~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cefprozil (*Z*)-Isomer RS.~~— Do not dry. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Ceftazidime Delta-3-Isomer RS.~~— Do not dry before using. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Ceftazidime Pentahydrate RS.~~— Do not dry before using. Keep container tightly closed. Protect from light, air, and moisture. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Ceftizoxime RS.~~— Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold, dry place.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Ceftriaxone Sodium *E*-Isomer RS.~~— Do not dry before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cefuroxime Axetil RS.~~— Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed, store in a refrigerator, and protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cefuroxime Axetil Delta-3 Isomers RS.~~— Do not dry. Keep container tightly closed, protected from light, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Cefuroxime Sodium RS.~~— Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold, dry place.~~

■■1S (*USP30*)

Change to read:

USP Cellaburate RS.~~— Dry a portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cellacefate RS.~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP F_1 Cells for Cell Proliferation Test RS (ATCC cell line FDCP-F1 shipped with approval from USP).~~— Store in a tight container in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Cellulose Acetate RS.~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cephaeline Hydrobromide RS.~~— Dry a portion at 105° to constant weight before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cephalexin RS.~~— Do not dry before using. This is the monohydrate form of cephalexin. Keep container tightly closed. For quantitative applications, determine the water content titrimetrically at the time of use.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Cephalothin Sodium RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Cephapirin Benzathine RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cephapirin Sodium RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold, dry place.~~

■■1S (*USP30*)

Change to read:

USP Cephradine RS. ~~Do not dry before using. This is the Dihydrate form of cephadrine. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Add the following:

■**USP Cetirizine Hydrochloride RS.**■1S (*USP30*)

Add the following:

■**USP Cetirizine Related Compound A RS [**(*RS*)-2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl] ethoxy]acetic acid, ethyl ester**]**—[To come.]■1S (*USP30*)

Change to read:

USP Cetyl Alcohol RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cetyl Palmitate RS. ~~Do not dry before using. Store at room temperature not exceeding 30°. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cetylpyridinium Chloride RS. ~~Do not dry before using. For quantitative applications determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chlorambucil RS. ~~*[Caution—Avoid contact.]* Dry portion over silica gel for 24 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Chloramphenicol RS. ~~Do not dry before using. Keep container tightly closed. Store in a cold dry place.~~

■■1S (*USP30*)

Change to read:

USP Chloramphenicol Palmitate RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Chloramphenicol Palmitate Nonpolymorph A RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Chloramphenicol Palmitate Polymorph A RS. ~~Do not dry before using. Keep container tightly closed and store in a cold, dry place.~~

■■1S (*USP30*)

Change to read:

USP Chlordiazepoxide RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Chlordiazepoxide Related Compound A RS [7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide**]** ($C_{15}H_{11}ClN_2O^2$ ✧ 286.72). ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Chlordiazepoxide Hydrochloride RS.~~—Dry portion in vacuum over phosphorus pentoxide at 60° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Chlorhexidine RS.~~—Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Chlorhexidine Acetate RS.~~—Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Chlorhexidine Related Compounds RS.~~—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Chlorobutanol RS.~~—Do not dry before using. This is the hydrous form of chlorobutanol. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP 2-Chloro-3,5-dimethylphenol RS (C_8H_9ClO ✧ 156.61).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP β-Chlorogenin RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Chloroprocaine Hydrochloride RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chloroquine Phosphate RS.~~—Dry portion at 105° for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chlorothiazide RS.~~—Dry portion at 105° for 1 hour before using. Keep container tightly closed. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Chloroxylenol RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chloroxylenol Related Compound A RS [2-chloro-3,5-dimethylphenol**]**.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chlorpheniramine Extended-Release Tablets RS (Drug Release Calibrator, Single Unit).~~—Use in conjunction with the test for *Drug Release* ⟨724⟩. The label states the nominal weight of chlorpheniramine maleate in each tablet. Use only whole tablets. Remove any surface dust with a soft brush before using. Keep container tightly closed and avoid exposure to excessive humidity.~~

■■1S (*USP30*)

Change to read:

USP Chlorpheniramine Maleate RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Chlorpromazine Hydrochloride RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Chlorpropamide RS.~~—Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP (*E*)-Chlorprothixene RS.~~— Keep container tightly closed and protected from light. Dry portion over silica gel to constant weight before using.~~

■■1S (*USP30*)

Change to read:

USP Chlortetracycline Hydrochloride RS.~~— Do not dry before using. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Chlorthalidone RS.~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chlorthalidone Related Compound A RS [4′-chloro-3′-sulfamoyl-2-benzophenone carboxylic acid**]**.~~— Do not dry. Keep container tightly closed. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Chlorzoxazone RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chlorzoxazone Related Compound A RS [2-amino-4-chlorophenol**]** (C_6H_6ClNO ✧ 143.57).~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed, protected from light, and store in a cold, dry place.~~

■■1S (*USP30*)

Change to read:

USP Cholecalciferol RS.~~— Store in a cold place, protected from light. Allow it to attain room temperature before opening ampul. Use the material promptly and discard the unused portion.~~

■■1S (*USP30*)

Change to read:

USP $\Delta^{4,6}$-Cholestadienol RS [cholesta-4,6-dien-3β-ol**]** ($C_{27}H_{44}O$ ✧ 384.64).~~— Do not dry. Transfer unused contents to a tightly closed container, and store under nitrogen, in the dark, in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Cholesteryl Caprylate RS ($C_{35}H_{60}O_2$ ✧ 512.86).~~— Dry portion in vacuum over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Cholestyramine Resin RS.~~— Dry portion in a suitable vacuum drying tube over phosphorus pentoxide at a pressure not exceeding 50 mm of mercury at 70° for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Choline Bitartrate RS.~~— Dry at 65° in vacuum for 4 hours before using. Keep container tightly closed. Store in a desiccator. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Choline Chloride RS.~~— Dry at 65° in vacuum for 4 hours before using. Keep container tightly closed. Store in a desiccator. This material is extremely hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Chondroitin Sulfate Sodium RS.~~— Dry a portion at 105° for 4 hours just before use. [NOTE— This material is extremely hygroscopic once dried. Weigh promptly, avoiding moisture from the environment.] Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chorionic Gonadotropin RS.~~— Store in a refrigerator and do not dry before using. Use a fresh ampul for each group of assays and discard any unused portion.~~

■■1S (*USP30*)

Change to read:

USP Chromium Picolinate RS.~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Chymotrypsin RS.~~—Keep container tightly closed, and store in a refrigerator. Allow contents to reach room temperature before opening, and do not dry before using. Protect from light. Determine loss on drying on a separate portion in a vacuum oven at 60° for 4 hours.~~

■■1S (*USP30*)

Change to read:

USP Ciclopirox RS.~~—Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Ciclopirox Related Compound A RS **[**3-cyclohexyl-4,5-dihydro-5-methyl-5-isoxazolyl acetic acid**]**.~~—Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Ciclopirox Related Compound B RS **[**6-cyclohexyl-4-methyl-2-pyrone**]**.~~—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Ciclopirox Olamine RS.~~—Dry a portion in vacuum to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cilastatin Ammonium Salt RS.~~—Do not dry before using. Keep container tightly closed, and store in a freezer under nitrogen.~~

■■1S (*USP30*)

Change to read:

USP Cimetidine RS.~~—Do not dry. Keep container tightly closed. Protect from light. Store at room temperature.~~

■■1S (*USP30*)

Change to read:

USP Cimetidine Hydrochloride RS.~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cinoxacin RS.~~—Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ciprofloxacin RS.~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Ciprofloxacin Ethylenediamine Analog RS **[**1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[(2-aminoethyl)amino]-3-quinolinecarboxylic acid hydrochloride**]** ($C_{15}H_{16}FN_3O_3 \cdot HCl$ ✧ 341.77).~~—Do not dry before using. Keep container tightly closed. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ciprofloxacin Hydrochloride RS.~~—This is the monohydrate form of ciprofloxacin hydrochloride. Do not dry; determine the water content titrimetrically when used for quantitative analysis. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cisplatin RS.~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Citric Acid RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed. This material is the anhydrous form of citric acid.~~

■■1S (*USP30*)

Change to read:

USP Clarithromycin RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Clarithromycin Related Compound A RS **[**6,11-di-*O*-methylerythromycin A**]** ($C_{39}H_{71}NO_{13}$ ✧ 762.00).~~—Do not dry before using. Keep container tightly closed, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Clavam-2-Carboxylate Potassium RS.~~—Each vial contains 3 µg of clavam-2-carboxylate potassium dispersed in poly(vinylpyrrolidone). For quantitative applications, reconstitute the entire contents with a suitable volume of water. Do not dry. Keep container tightly closed. Protect from light. Store in a freezer. *Standard solutions* may be stored in a refrigerator for 1 week.~~

■■1S (*USP30*)

Change to read:

USP Clavulanate Lithium RS.~~—Do not dry before using. Keep container tightly closed and protected from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Clemastine Fumarate RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clidinium Bromide RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clidinium Bromide Related Compound A RS [3-hydroxy-1-methylquinuclidinium bromide] ($C_8H_{16}BrNO$ ✧ 222.13).~~—Dry portion over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Clindamycin Hydrochloride RS.~~—Do not dry before using. This is the monohydrate form. Keep container tightly closed. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Clindamycin Palmitate Hydrochloride RS.~~—★Do not dry. Keep container tightly closed. Store in a freezer.★*USP29*~~

■■1S (*USP30*)

Change to read:

USP Clindamycin Phosphate RS.~~—Do not dry. Keep container tightly closed. Protect from light. Store in a cool, dry place.~~

■■1S (*USP30*)

Change to read:

USP Clioquinol RS.~~—Dry portion over phosphorus pentoxide for 5 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clobetasol Propionate RS.~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Clobetasol Propionate Related Compound A RS [9α-fluoro-11*β*-hydroxy-16*β*-methyl 3-oxo-androsta-1,4-diene-17(*R*)-spiro-2′-[4′-chloro-5′-ethylfuran-3′(2′*H*)-one]**]** ($C_{25}H_{30}ClFO_4$ ✧ 448.96).~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Clocortolone Pivalate RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clofazimine RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed, protect from light, and store at room temperature.~~

■■1S (*USP30*)

Change to read:

USP Clofibrate RS.~~—After opening ampul, store in a tight, light-resistant container. Do not dry before using.~~

■■1S (*USP30*)

Change to read:

USP Clomiphene Citrate RS.~~—Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Clomiphene Related Compound A RS [(*E*,*Z*)-2-[4-(1,2-diphenylethenyl)phenoxy]-*N*,*N*-diethylethanamine hydrochloride**]** ($C_{26}H_{29}NO \cdot HCl$ ✧ 407.98).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Clomipramine Hydrochloride RS. ~~Do not dry. This material is hygroscopic. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Clonazepam RS. —~~*Do not dry.~~ ▲*USP30*~~ Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clonazepam Related Compound A RS [3-amino-4-(2-chlorophenyl)-6-nitrocarbostyril] ($C_{15}H_{10}ClN_3O_3$ ✧ 315.72). ~~Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Clonazepam Related Compound B RS [2-amino-2′-chloro-5-nitrobenzophenone] ($C_{13}H_9ClN_2O_3$ ✧ 276.68). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Clonazepam Related Compound C RS [2-bromo-2′-(2-chlorobenzoyl)-4′-nitroacetanilide]. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Clonidine RS. ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clonidine Hydrochloride RS. ~~Dry portion at 105° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Clonidine Related Compound B RS [2-[(*E*)-2,6-dichlorophenylimino]-1-(1-{2-[(*E*)-2,6-dichlorophenylimino]-imidazolidin-1-yl}-ethyl)-imidazolidine] ~~($C_{24}H_{24}Cl_4N_8$ ✧ 485.24)~~

▲($C_{20}H_{20}Cl_4N_6$ ✧ 486.23).▲*USP30*
~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clorazepate Dipotassium RS. ~~Do not dry. Store under nitrogen. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clorsulon RS. ~~Dry portion in vacuum at 100° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clotrimazole RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Clotrimazole Related Compound A RS [(*o*-chlorophenyl)diphenylmethanol] ($C_{19}H_{15}ClO$ ✧ 294.78. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Powdered Red Clover Extract RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Cloxacillin Benzathine RS. ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cloxacillin Sodium RS. ~~Do not dry before using. This is the monohydrate form of cloxacillin sodium. Keep container tightly closed, protected from light, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Clozapine RS. ~~Dry at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Cocaine Hydrochloride RS.~~—Dry portion over silica gel for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Codeine *N*-Oxide RS ($C_{18}H_{21}NO_4$ ✧ 315.37).~~—Store in a tightly closed container, protected from light. Do not dry before using.~~

■■1S (*USP30*)

Change to read:

USP Codeine Phosphate RS.~~—This is the hemihydrate form of codeine phosphate. Dry portion at 105° for 18 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Codeine Sulfate RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Powdered Black Cohosh Extract RS.~~—Do not dry. Keep container tightly closed. Store in a refrigerator. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Colchicine RS.~~—Do not dry. For quantative use, determine the water content titrimetrically and correct for labeled solvent content at time of use. Keep container tightly closed. Protect from light. Store in a cold, dry place.~~

■■1S (*USP30*)

Change to read:

USP Colestipol Hydrochloride RS.~~—Do not dry before using. Keep container tightly closed, and store over a desiccant.~~

■■1S (*USP30*)

Change to read:

USP Colistimethate Sodium RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Colistin Sulfate RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Copovidone RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Corticotropin RS.~~—Do not dry before using. Store at a temperature of 0° or below.~~

■■1S (*USP30*)

Change to read:

USP Cortisone Acetate RS.~~—Dry portion at 105° for 30 minutes before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Creatinine RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cromolyn Sodium RS.~~—Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Crospovidone RS.~~—Dry portion in vacuum at 105° for 1 hour before using. Keep container tightly closed. Store in a desiccator once removed from hermetic bag. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Crotamiton RS.~~—Do not dry before using. After opening the ampul, store in a tightly closed container, protected from light in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Cyclandelate RS.— ~~Dry portion over silica gel for 24 hours before using. Keep container tightly closed. Store in a refrigerator. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cyanocobalamin RS.— ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Cyclizine Hydrochloride RS.— ~~Dry portion at 120° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cyclobenzaprine Hydrochloride RS.— ~~Dry portion at 105° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Alpha Cyclodextrin RS.— ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Beta Cyclodextrin RS.— ~~Do not dry before using. Determine the water content titrimetrically when used for quantitative analyses. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cyclomethicone 4 RS.— ~~After opening, store in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Cyclomethicone 5 RS.— ~~Do not dry. After opening ampul, store the material in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Cyclomethicone 6 RS.— ~~After opening, store in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Cyclopentolate Hydrochloride RS.— ~~Dry portion at 105° for 4 hours before using. Use solutions immediately after preparation. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Cyclophosphamide RS.— ~~Do not dry; determine the water content titrimetrically when used for quantitative analyses. Keep container tightly closed, and store between 2° and 8°.~~

■■1S (*USP30*)

Change to read:

USP 2-Cyclopropylmethylamino-5-chlorobenzophenone RS.— ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Cycloserine RS.— ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cyclosporine RS.— ~~Dry portion before use in a capillary-stoppered bottle in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours. Keep container tightly closed, protected from light, and store in a cold place. Where calculations require a purity factor, use $P = 1000$.~~

■■1S (*USP30*)

Change to read:

USP Cyclosporine Resolution Mixture RS [This material is a 100 : 1 mixture of cyclosporine and cyclosporine U**]**. — ~~Do not dry before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Cyproheptadine Hydrochloride RS.~~—Do not dry; determine the water content titrimetrically when used for quantitative analyses. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP L-Cysteine Hydrochloride RS.~~—This is the monohydrate form of L-cysteine hydrochloride. Dry portion at a pressure not exceeding 5 mm of mercury for 24 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Cytarabine RS.~~—Dry portion at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Dacarbazine RS.~~—Keep container tightly closed and protected from light, and store in a refrigerator. Dry portion in vacuum over phosphorus pentoxide at 60° for 2 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Dacarbazine Related Compound A RS **[**5-aminoimidazole-4-carboxamide hydrochloride**]**.~~—Do not dry before using. Keep container tightly closed and protected from light, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Dacarbazine Related Compound B RS **[**2-azahypoxanthine**]** ($C_4H_3N_5O$ ✧ 137.10).~~—This is the monohydrate form of 2-azahypoxanthine. Do not dry before using. Keep container tightly closed and protected from light, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Dactinomycin RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Danazol RS.~~—Dry portion at a pressure not exceeding 5 mm of mercury at 60° to constant weight before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Add the following:

■**USP Dantrolene Sodium RS.**■1S (*USP30*)

Add the following:

■**USP Dantrolene RS.**■1S (*USP30*)

Add the following:

■**USP Dantrolene Related Compound A RS** **[**5-(4-nitrophenyl)furaldehyde azine**]** ($C_{22}H_{14}N_4O_6$)—[To come.]■1S (*USP30*)

Add the following:

■**USP Dantrolene Related Compound B RS** **[**5-(4-nitrophenyl)-2-furaldehyde-2-carboxymethyl semicarbazone**]** ($C_{14}H_{12}N_4O_6$)—[To come.]■1S (*USP30*)

Add the following:

■**USP Dantrolene Related Compound C RS** **[**5-(4-nitrophenyl)-1-furancarboxyaldehyde**]**($C_{11}H_7NO_4$)—[To come.]■1S (*USP30*)

Change to read:

USP Danthron RS.~~—Dry portion over silica gel for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dapsone RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Daunorubicin Hydrochloride RS.~~—Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a freezer. Allow to equilibrate to room temperature before opening.~~

■■1S (*USP30*)

Change to read:

USP Deferoxamine Mesylate RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dehydrocarteolol Hydrochloride RS **[**5-(3-*tert*-butylamino-2-hydroxy)-propoxycarbostyril hydrochloride**]** ($C_{16}H_{22}N_2O_3 \cdot HCl$ ✧ 326.82). ~~Do not dry. Use as is. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Dehydrocholic Acid RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Demecarium Bromide RS. ~~Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Demeclocycline Hydrochloride RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Denatonium Benzoate RS. ~~This material is the anhydrous form of denatonium benzoate. Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Desacetyl Diltiazem Hydrochloride RS ($C_{20}H_{24}N_2O_3S \cdot HCl$ ✧ 408.95). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Desflurane RS. ~~Do not dry. After opening ampul, store in a tightly closed container. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Desipramine Hydrochloride RS. ~~Dry portion in vacuum at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Deslanoside RS. ~~Dry portion in vacuum over phosphorus pentoxide to constant weight before using. Keep container tightly closed. Protect from light. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

■**USP Desogestrel RS.** ~~Dry portion in vacuum at room temperature to constant weight.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Desogestrel Related Compound A RS** **[**13-ethyl-11-methylene-18, 19-dinor-5α, 17α-pregn-3-en-20-yn-17-ol, desogestrel Δ^3-isomer**]** ($C_{22}H_{30}O$ ✧ 310.48). ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Desogestrel Related Compound B RS** **[**3-hydroxy-desogestrel**]** ($C_{22}H_{30}O_2$ ✧ 326.48). ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Desogestrel Related Compound C RS **[**3-keto-desogestrel**]** ($C_{22}H_{28}O_2$ ✧ 324.46). ~~Do not dry.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Desoaminylazithromycin RS. ~~Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Desoximetasone RS. ~~Dry portion at 105° to constant weight before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Desoxycorticosterone Acetate RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Desoxycorticosterone Pivalate RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Dexamethasone RS. ~~Keep container tightly closed. Dry portion at 105° for 3 hours before using.~~

■ ■1S (*USP30*)

Change to read:

USP Dexamethasone Acetate RS. ~~Dry portion in vacuum at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dexamethasone Phosphate RS. ~~This material is Dexamethasone Phosphate Acid. Dry portion at a pressure of 5 mm of mercury at 40° to constant weight before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dexbrompheniramine Maleate RS. ~~Dry portion at 65° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Dexchlorpheniramine Maleate RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Dexpanthenol RS. ~~Do not dry; determine the water content titrimetrically before using for quantitative analyses. Keep container tightly closed and protected from moisture.~~

■ ■1S (*USP30*)

Change to read:

USP Dextran 1 RS. ~~Dry portion at 105° for 5 hours before using. Keep container tightly closed. Store in a desiccator.~~

■ ■1S (*USP30*)

Change to read:

USP Dextran 4 Calibration RS. ~~Do not dry. Store at room temperature. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dextran 10 Calibration RS. ~~Do not dry. Store at room temperature. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dextran 40 Calibration RS. ~~Do not dry. Store at room temperature. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dextran 70 Calibration RS. ~~Do not dry. Store at room temperature. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dextran 250 Calibration RS. ~~Do not dry. Store at room temperature. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dextran T-10 RS.~~—Dry at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dextroamphetamine Sulfate RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dextromethorphan RS.~~—Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dextromethorphan Hydrobromide RS.~~—Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dextrose RS.~~—This is the anhydrous form of dextrose. Dry portion at 105° for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Diacetylated Monoglycerides RS.~~—Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Diacetylfluorescein RS ($C_{24}H_{16}O_7$ ✧ 416.39).~~—Keep container tightly closed. Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Diatrizoic Acid RS.~~—This material is the hydrous form of diatrizoic acid. Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Diatrizoic Acid Related Compound A RS **[**5-acetamido-3-amino-2,4,6-triiodobenzoic acid**]** ($C_9H_7I_3N_2O_3$ ✧ 571.88).~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Diazepam RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Diazepam Related Compound A RS **[**2-methylamino-5-chlorobenzophenone**]** ($C_{14}H_{12}ClNO$ ✧ 245.71).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Diazepam Related Compound B RS **[**3-amino-6-chloro-1-methyl-4-phenylcarbostyril**]** ($C_{16}H_{13}ClN_2O$ ✧ 284.74).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Diazoxide RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dibucaine Hydrochloride RS.~~—Dry portion at 80° for 5 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Dibutyl Phthalate RS.~~—Do not dry. After opening ampul, store the materials in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Dichlorphenamide RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Diclofenac Sodium RS.~~Dry portion at 105° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Diclofenac Related Compound A RS [*N*-(2,6-dichlorophenyl)indolin-2-one**]** ($C_{14}H_9Cl_2NO$ ✧ 278.14).~~Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Dicloxacillin Sodium RS.~~Do not dry before using. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Dicyclomine Hydrochloride RS.~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dienestrol RS.~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

■**USP Diethanolamine RS.**~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Diethylcarbamazine Citrate RS.~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Diethyl Phthalate RS.~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Diethylpropion Hydrochloride RS.~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed. Protect from light. Use within 2 years of purchase.~~

■■1S (*USP30*)

Change to read:

USP Diethylstilbestrol RS.~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Diethyltoluamide RS.~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Diflorasone Diacetate RS.~~Dry portion in vacuum at 60° and at a pressure not exceeding 5 mm of mercury for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Diflunisal RS.~~Dry portion in vacuum at 60° and at a pressure not exceeding 5 mm of mercury for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Digitalis RS.~~Do not dry before using. Keep container tightly closed, and store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Digitoxin RS.~~Dry portion in vacuum at 105° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Digoxin RS.~~Dry portion in vacuum at 105° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dihydrocapsaicin RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Dihydrocodeine Bitartrate RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP 17α-Dihydroequilin RS ($C_{18}H_{22}O_2$ ✧ 270.37). ~~Do not dry before using. Store in a cold place, protected from light. Store the contents of the opened ampul in a tightly closed container, under nitrogen, protected from light, in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Dihydroergotamine Mesylate RS. ~~Dry portion in vacuum at 100° to constant weight before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Dihydrostreptomycin Sulfate RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 100° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Dihydrotachysterol RS. ~~Do not dry. Store in a cold place, protected from light. Allow to reach room temperature before opening ampuls, and use the material promptly.~~

■ ■1S (*USP30*)

Change to read:

USP Dihydroxyacetone RS. ~~Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Diloxanide Furoate RS. ~~Dry portion at 105° to constant weight before using.~~

■ ■1S (*USP30*)

Change to read:

USP Diltiazem Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Dimenhydrinate RS. ~~Dry portion in vacuum over phosphorus pentoxide for 24 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Dimethyl Sulfoxide RS. ~~Do not dry. After opening, store in a tightly closed, light-resistant container. This material is extremely hygroscopic.~~

■ ■1S (*USP30*)

Change to read:

USP Dinoprost Tromethamine RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dioxybenzone RS. ~~Dry portion at 40° and 5 mm of mercury for 2 hours before using. Store tightly closed, protected from light, in a cool place.~~

■ ■1S (*USP30*)

Change to read:

USP Diphenhydramine Citrate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Diphenhydramine Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Diphenoxylate Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Dipivefrin Hydrochloride RS.~~— Dry portion in a suitable vacuum drying tube over phosphorus pentoxide at 60° for 6 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dipyridamole RS.~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Disopyramide Phosphate RS.~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP 2,4-Disulfamyl-5-trifluoromethylaniline RS ($C_7H_8F_3N_3O_4S_2$ ✧ 319.29).~~— Keep container tightly closed and protected from light. Dry portion in vacuum over silica gel for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Disulfiram RS.~~— Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Dobutamine Hydrochloride RS.~~— Determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Docusate Calcium RS.~~— Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Docusate Potassium RS.~~— Do not dry; determine the water content at the time of use. Keep container tightly closed. Store in dry place. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Docusate Sodium RS.~~Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Dolasetron Mesylate RS~~— This is the monohydrate form of dolasetron mesylate. Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dolasetron Mesylate Related Compound A RS [hexahydro-8-hydroxy-2,6-methano-2*H*-quinolizin-3 (4*H*)-one, hydrochloride**].**~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dopamine Hydrochloride RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dorzolamide Hydrochloride RS.~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dorzolamide Hydrochloride Related Compound A RS [(4*R*,6*R*)-4-(ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide, monohydrochloride**]** ($C_{10}H_{16}N_2O_4S_3 \cdot HCl$ ✧ 360.91).~~— Do not dry. Keep container tightly closed. Store in a cool room.~~

■■1S (*USP30*)

Change to read:

■USP Doxazosin Mesylate RS.~~— Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Doxepin Hydrochloride RS.~~— Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Add the following:

■**USP Doxepin Related Compound A RS**—[To come.]■1S (*USP30*)

Add the following:

■**USP Doxepin Related Compound B RS**—[To come.]■1S (*USP30*)

Add the following:

■**USP Doxepin Related Compound C RS**—[To come.]■1S (*USP30*)

Change to read:

USP Doxorubicin Hydrochloride RS. ~~Do not dry before using. Store in a cold place. Protect from light, and allow to attain room temperature before opening.~~

■■1S (*USP30*)

Change to read:

USP Doxycycline Hyclate RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Doxylamine Succinate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Droperidol RS. ~~Dry portion in vacuum at 70° for 4 hours before using. Store under nitrogen. Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Dyclonine Hydrochloride RS. ~~Dry portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Dydrogesterone RS. ~~Dry portion in vacuum at 50° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Dyphylline RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Powdered *Echinacea angustifolia* Extract RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Powdered *Echinacea purpurea* Extract RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Econazole Nitrate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Edetate Calcium Disodium RS. ~~Do not dry before using. This material is hygroscopic. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Edetate Disodium RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Edetic Acid RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Edrophonium Chloride RS. ~~Dry portion in vacuum over phosphorus pentoxide for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Powdered Eleuthero Extract RS. ~~Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Store in a refrigerator. This material is hygroscopic.~~

■ ■1S (*USP30*)

Change to read:

USP Emedastine Difumarate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Emetine Hydrochloride RS. ~~Do not dry before quantitative use. Determine volatiles content by heating a separate portion at 105° to constant weight to determine correction factor for quantitative use. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Enalapril Maleate RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Enalaprilat RS. ~~Do not dry; determine the water content titrimetrically at time of use for quantitative analyses. Sonicate as necessary to effect solution. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Endotoxin RS. ~~*[Caution—Contents are pyrogenic. Handle vials and their contents with extreme care to avoid contamination.]* Reconstitute entire contents; use solution within 14 days. Store unopened vial and solution in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Enflurane RS. ~~Do not dry. After opening ampul, store in a tightly closed, light-resistant container. Avoid exposure to excessive heat.~~

■ ■1S (*USP30*)

Change to read:

USP Ephedrine Sulfate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP 4-Epianhydrotetracycline Hydrochloride RS. ~~Dry portion in vacuum at 60° for 3 hours before using. The dried material is extremely hygroscopic. Keep container tightly closed. Protect from light. Store in a cold, dry place.~~

■ ■1S (*USP30*)

Change to read:

USP Epilactose RS. ~~Dry portion at 70° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Epinephrine Bitartrate RS. ~~Dry portion in vacuum over silica gel for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Equilin RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Ergocalciferol RS. ~~Store in a cold place, protected from light. Allow it to attain room temperature before opening ampul. Use the material promptly, and discard the unused portion.~~

■ ■1S (*USP30*)

Change to read:

USP Ergoloid Mesylates RS. ~~Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Ergonovine Maleate RS. ~~Dry portion in vacuum at 80° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Ergosterol RS ($C_{28}H_{44}O$ ✧ 396.66). ~~Do not dry before using. Keep container tightly closed, keep protected from light and air, and store in a refrigerator. Allow to equilibrate to room temperature before opening container.~~

■ ■1S (*USP30*)

Change to read:

USP Ergotamine Tartrate RS. ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Ergotaminine RS. ~~Do not dry; use as is. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin RS. ~~Do not dry before using, unless otherwise specified. Allow to equilibrate to ambient temperature before opening ampul. Hygroscopic. After opening, weigh portions immediately, avoiding excessive humidity, and discard material remaining. Store unopened material in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin B RS. ~~Do not dry before using. Keep container tightly closed and protected from light, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin C RS. ~~Do not dry before using. Keep container tightly closed and protected from light, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin Related Compound N RS **[***N*-demethylerythromycin A**]** ($C_{36}H_{65}NO_{13}$ ✧ 719.91). ~~Do not dry before using. Keep container tightly closed, protected from light, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin Estolate RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin Ethylsuccinate RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin Gluceptate RS. ~~Do not dry before using. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin Lactobionate RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Erythromycin Stearate RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Estradiol RS. ~~Do not dry; this is the hemihydrate form of estradiol. Determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Estradiol Cypionate RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Estradiol Valerate RS. ~~Do not dry; use as is. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Estriol RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Estrone RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Estropipate RS. ~~Dry portion at 105° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ethacrynic Acid RS. ~~Dry portion at a pressure not exceeding 5 mm of mercury at 60° for 2 hours before using. Keep container tightly closed. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Ethambutol Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ethinyl Estradiol RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

■**USP Ethinyl Estradiol Related Compound A RS [**6-keto-ethinyl estradiol**]** ($C_{20}H_{23}O_3$ ✧ 311.39). ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Ethionamide RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ethopabate RS. ~~Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed, and store in a cool, dry place.~~

■■1S (*USP30*)

Change to read:

USP Ethopabate Related Compound A RS [methyl-4-acetamido-2-hydroxybenzoate**]** ($C_{10}H_{11}NO_4$ ✧ 209.20). ~~Do not dry before using. Keep container tightly closed, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Ethosuximide RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ethotoin RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

■**USP Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion RS.** ~~Dry at 105° for 1.5 hours before use.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Ethylcellulose RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ethylparaben RS. ~~Dry portion over silica gel for 5 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ethyl Vanillin RS. ~~Dry portion over phosphorus pentoxide for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Ethynodiol Diacetate RS. ~~Do not dry; use as is. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Etidronate Disodium RS. ~~Do not dry before using. Keep container tightly closed, and store in a cool, dry place.~~

■■1S (*USP30*)

Change to read:

USP Etidronate Disodium Related Compound A RS [sodium phosphite dibasic pentahydrate] ($Na_2HPO_3 \cdot 5H_2O$ ✧ 216.04 ✧ CAS-13708-85-5). ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Etidronic Acid Monohydrate RS ($C_2H_8O_7P_2 \cdot H_2O$ ✧ 224.04). ~~Do not dry before using. Keep container tightly closed, and store in a cool, dry place.~~

■■1S (*USP30*)

Change to read:

USP Etodolac RS. ~~Do not dry before using; determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Etodolac Related Compound A RS [(±)-8-ethyl-1-methyl-1,3,4,9-tetrahydropyrano [3,4-*b*]-indole-1-acetic acid] ($C_{16}H_{19}NO_3$ ✧ 273.33). ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Etoposide RS. ~~Do not dry before using. Determine the water content titrimetrically at the time of use. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Etoposide Resolution Mixture RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Eucatropine Hydrochloride RS. ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Famotidine RS. ~~Dry portion at a pressure between 1 and 5 mm of mercury at 80° for 5 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Felodipine RS. ~~Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Felodipine Related Compound A RS [ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate] ($C_{18}H_{17}Cl_2NO_4$ ✧ 382.24). ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Fenbendazole RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fenbendazole Related Compound A RS [methyl (1*H*-benzimidazole-2-yl)carbamate] ($C_9H_9N_3O_2$ ✧ 191.19). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fenbendazole Related Compound B RS [methyl [5(6)-chlorobenzimidazole-2-yl]carbamate] ($C_9H_8ClN_3O_2$ ✧ 225.63). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fenoldopam Mesylate RS. ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Fenoldopam Related Compound A RS [1-methyl-3-benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt)] ($C_{17}H_{18}ClNO_3 \cdot CH_4SO_3$ ✧ 415.89). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Fenoldopam Related Compound B RS [1*H*-3-benzazepine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt)] ($C_{16}H_{16}NO_3 \cdot CH_4SO_3$ ✧ 366.42). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a desiccator.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Fenoprofen Calcium RS. ~~This is the dihydrate form of fenoprofen calcium. Do not dry before using; determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Fenoprofen Sodium RS. ~~This is the dihydrate form of fenoprofen sodium. Do not dry before using; determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Fentanyl Citrate RS. ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Fexofenadine Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Fexofenadine Related Compound A RS **[**benzeneacetic acid, 4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl**]** ($C_{32}H_{37}NO_4$ ✧ 499.65). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Fexofenadine Related Compound B RS **[**3-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-α,α-dimethyl benzeneacetic acid hydrochloride**]** ($C_{32}H_{39}NO_4 \cdot HCl$ ✧ 538.12). ~~Do not dry. Keep container tightly closed. Protect from light. This is the monohydrate form.~~

■ ■1S (*USP30*)

Change to read:

USP Finasteride RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Flecainide Acetate RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 2 hours before using. Keep container tightly closed, and store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Floxuridine RS. ~~Dry portion in vacuum over silica gel at 60° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Fluconazole RS. ~~Do not dry. Keep container tightly closed, and avoid exposure to > 70% relative humidity. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

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

■ ■1S (*USP30*)

Change to read:

USP Flucytosine RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Fludarabine Phosphate RS. ~~Keep container tightly closed, protect from light, and store in a desiccator in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Fludeoxyglucose RS.★ ~~Do not dry. Keep container tightly closed. Protect from light.~~ ▲*USP30*

■ ■1S (*USP30*)

Change to read:

USP Fludeoxyglucose Related Compound A RS **[**4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8.]hexacosane**]** ($C_{18}H_{36}N_2O_6$ ✧ 376.49). ~~Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Fludeoxyglucose Related Compound B RS ($C_6H_{11}ClO_5$ ✧ 198.60).~~—Keep container tightly closed. Store in a freezer at −20°, in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Fludrocortisone Acetate RS.~~—Dry portion in vacuum at 100° for 2 hours over magnesium perchlorate before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Flumazenil RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Flumethasone Pivalate RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Flunisolide RS.~~—Dry portion in vacuum at 60° for 3 hours before using. This dried standard is the hemihydrate of flunisolide. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Flunixin Meglumine RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Fluocinolone Acetonide RS.~~—The label indicates the hydrous or the anhydrous form of fluocinolone acetonide. Dry portion in vacuum at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Fluocinonide RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Fluorescein RS.~~—Dry portion over silica gel for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Fluorometholone RS.~~—Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fluorometholone Acetate RS.~~—Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Fluoroquinolonic Acid RS.~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fluorouracil RS.~~—Dry portion in vacuum over phosphorus pentoxide at 80° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fluoxetine Hydrochloride RS.~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Fluoxetine Related Compound A RS [*N*-methyl-3-phenyl-3-[(α,α,α-(trifluoro-*m*-tolyl)oxy]propylamine hydrochloride**]** ($C_{17}H_{18}F_3NO \cdot HCl$ ✧ 345.79).~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Fluoxetine Related Compound B RS [*N*-methyl-3-phenylpropylamine**]** ($C_{10}H_{15}N$ ✧ 149.24).~~—This is a solution containing approximately 2 mg of fluoxetine related compound B in diluted hydrochloric acid (approximately 0.01 N). Store in a refrigerator. After opening the ampul, store it in a tightly closed container.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Fluoxetine Related Compound C RS [*N*-methyl-*N*-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid] ($C_{21}H_{22}F_3NO_4$ ✧ 409.40).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fluoxymesterone RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fluphenazine Decanoate Dihydrochloride RS.~~—Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Fluphenazine Enanthate Dihydrochloride RS ($C_{29}H_{38}F_3N_3O_2S \cdot 2HCl$ ✧ 622.63).~~—Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Fluphenazine Hydrochloride RS.~~—Dry portion at 65° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Flurandrenolide RS.~~—Dry portion in vacuum at 105° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Flurazepam Hydrochloride RS.~~—Do not dry. Keep container tightly closed. Protect from light. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Flurazepam Related Compound C RS [5-chloro-2-(2-diethylaminoethyl(amino)-2′-fluorobenzophenone hydrochloride] ($C_{19}H_{22}ClFN_2O \cdot HCl$ ✧ 385.31).~~—▲Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.▲*USP29*~~

■■1S (*USP30*)

Change to read:

USP Flurazepam Related Compound F RS [7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one] ($C_{15}H_{10}Cl\ FN_2O$ ✧ 288.71).~~—Keep container tightly closed and protected from light. Dry portion in vacuum over silica gel at 60° for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Flurbiprofen RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Flurbiprofen Related Compound A RS [2-(4-biphenylyl)propionic acid] ($C_{15}H_{14}O_2$ ✧ 226.28).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Flurbiprofen Sodium RS.~~—Dry portion in vacuum at a pressure not exceeding 1 mm of mercury over phosphorus pentoxide in a suitable drying tube at 60° for 18 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Flutamide RS.~~—Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP *o*-Flutamide RS [2-methyl-*N*-[6-nitro-3-(trifluoromethyl)phenyl]propanamide] ($C_{11}H_{11}F_3N_2O_3$ ✧ 276.22).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fluticasone Propionate Resolution Mixture RS.~~—It is a mixture of fluticasone propionate and fluticasone propionate related compound D.~~

■■1S (*USP30*)

Change to read:

USP Fluvoxamine Maleate RS.~~—▲Dry portion at 80° for 2 hours before using. Keep container tightly closed. Protect from light.▲*USP29*~~

■■1S (*USP30*)

Change to read:

USP Folic Acid RS. ~~Do not dry; determine the water content at time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Folic Acid Related Compound A RS [calcium formyltetrahydrofolate**].** ~~Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Formononetin RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP 10-Formylfolic Acid RS. ~~Do not dry. Keep container tightly closed, protected from light, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Fosphenytoin Sodium RS. ~~Do not dry. For quantitative application, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fructose RS. ~~Dry portion in vacuum at 70° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Fumaric Acid RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Furazolidone RS. ~~Dry portion at 100° for 1 hour before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Furosemide RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Furosemide Related Compound A RS [2-chloro-4-*N*-furfurylamino-5-sulfamoylbenzoic acid**]** ($C_{12}H_{11}ClN_2O_5S$ ✧ 330.74). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Furosemide Related Compound B RS [4-chloro-5-sulfamoylanthranilic acid**]** ($C_7H_7ClN_2O_4S$ ✧ 250.66). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Gabapentin RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

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

■**[**2-aza-spiro[4.5]decan-3-one**]**■1S (*USP29*)
($C_9H_{15}NO$ ✧ 153.22). ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Gadodiamide RS. ~~Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use, and use a value of 0.989 mg gadodiamide per mg on the anhydrous basis. Keep container tightly closed. Protect from light. Store in a desiccator in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Gadodiamide Related Compound A RS [gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide**]** ($C_{15}H_{22}GdN_4NaO_9$ ✧ 582.60). ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Gadodiamide Related Compound B RS [gadolinium disodium diethylenetriamine pentaacetic acid**]** ($C_{14}H_{18}GdN_3Na_2O_{10}$ ✧ 591.54).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Gadoversetamide RS.~~—Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. This material is hygroscopic. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Gadoversetamide Related Compound A RS [hydrogen [8,11,14-tris(carboxymethyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(4-)]gadolinium**].**~~—Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. This material is hygroscopic. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Galactose RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Gallamine Triethiodide RS.~~—Dry portion at 100° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Ganciclovir RS.~~—Dry portion in vacuum at 80° for 3 hours before using. Keep container tightly closed and protected from light. Store in a refrigerator. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Ganciclovir Related Compound A RS [(RS)-2-amino-9-(2,3-dihydroxy-propoxymethyl)-1,9-dihydro-purin-6-one**].**~~—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Gemcitabine Hydrochloride RS.~~—Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Gemfibrozil RS.~~—Dry portion over silica gel for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Gentian Violet RS.~~—Do not dry; determine the water content at the time of use. Keep container tightly closed. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Powdered Ginger RS.~~—Do not dry before using. Keep container tightly closed, protected from light and moisture.~~

■■1S (*USP30*)

Change to read:

USP Powdered Asian Ginseng Extract RS.~~—Do not dry; determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Gitoxin RS ($C_{41}H_{64}O_{14}$ ✧ 780.96).~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Glipizide RS. ~~— Do not dry before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Glipizide Related Compound A RS [*N*-{2-[(4-aminosulfonyl)phenyl]ethyl}-5-methyl-pyrazinecarboxamide**]** ($C_{14}H_{16}N_4O_3S$ ✧ 320.37). ~~— Do not dry before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Glucagon RS. ~~— See outer hermetic bag for potency. Do not dry. Store at −20° before opening, allow to attain room temperature, and protect from air and humidity after opening.~~

■ ■1S (*USP30*)

Change to read:

USP Glucosamine Hydrochloride RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Glutamic Acid RS. ~~— Do not dry. Keep container tightly closed. Store at room temperature.~~

■ ■1S (*USP30*)

Change to read:

USP Glutamine RS. ~~— Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP γ-Glutamyl-(*S*)-Allyl-L-Cysteine RS. ~~— Dry portion in vacuum at 80° over phosphorus pentoxide for 2 hours before using. Keep container tightly closed and protected from light. Store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Glyburide RS. ~~— Dry portion at 105° for 6 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Glycerin RS. ~~— Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Glyceryl Behenate RS. ~~— Do not dry before using. Keep container tightly closed. Store at a temperature not higher than 35°.~~

■ ■1S (*USP30*)

Change to read:

USP Glycine RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Glycopyrrolate RS. ~~— Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Glycyrrhizic Acid RS. ~~— Dry portion at 50° for 12 hours before using. Keep container tightly closed. Protect from light. Store in a cool place.~~

■ ■1S (*USP30*)

Change to read:

USP Chorionic Gonadotropin RS. ~~— Store in a refrigerator, and do not dry before using. Use a fresh ampul for each group of assays, and discard any unused portion.~~

■ ■1S (*USP30*)

Change to read:

USP Gramicidin RS. ~~— Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Griseofulvin RS. ~~— Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Griseofulvin Permeability Diameter RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Guaiacol RS. ~~Do not dry. After opening ampul, store in a tightly closed container. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Guaifenesin RS. ~~Dry portion in vacuum at a pressure not below 10 mm of mercury at 60° to constant weight before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Guanabenz Acetate RS. ~~Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Guanadrel Sulfate RS. ~~Dry portion at room temperature at a pressure not exceeding 5 mm of mercury for 16 hours at time of use for quantitative analyses. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Guanethidine Monosulfate RS. ~~Dry portion at 105° to constant weight before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Guanfacine Hydrochloride RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Halcinonide RS. ~~Dry portion in vacuum at 100° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Haloperidol RS. ~~Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Haloperidol Related Compound A RS **[**4,4′-bis[4-*p*-chlorophenyl)-4-hydroxypiperidino]butyrophenone**]** ($C_{32}H_{36}Cl_2N_2O_3$ ✧ 567.56). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Halothane RS. ~~Do not dry. Material is highly volatile. After opening ampul, store in a tightly closed, light-resistant container. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Heparin Sodium RS. ~~Store in a cool place and do not freeze.~~

■ ■1S (*USP30*)

Change to read:

USP Hetacillin RS. ~~Do not dry before using. Keep container tightly closed. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Hexachlorophene RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cool, dry place.~~

■ ■1S (*USP30*)

Change to read:

USP 2*E*,4*E*-Hexadienoic Acid Isobutylamide RS. ~~Do not dry. Keep container tightly closed. Store in a refrigerator. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hexylene Glycol RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hexylresorcinol RS. ~~— Dry over silica gel for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Histamine Dihydrochloride RS. ~~— Dry portion over silica gel for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP L-Histidine RS. ~~— Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Homatropine Hydrobromide RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Homatropine Methylbromide RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Homopolymer Polypropylene RS. ~~— Exercise care in handling and storage to avoid scratching surface of strips. Prepare samples as directed in the respective USP General Test Chapter.~~

■ ■1S (*USP30*)

Change to read:

USP Homosalate RS. ~~— Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hyaluronidase RS. ~~— This is a mixture of hyaluronidase and lactose. Do not dry before using. Keep container tightly closed, and store in a cool, dry place, preferably under refrigeration in a desiccator.~~

■ ■1S (*USP30*)

Change to read:

USP Hydralazine Hydrochloride RS. ~~— Dry it at 110° for 15 hours before using. Keep container tightly closed. Store in a dry place.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrochlorothiazide RS. ~~— Dry portion at 105° for 1 hour before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocodone Bitartrate RS. ~~— Dry portion in vacuum at 105° for 2 hours before using. [NOTE— Hydrocodone Bitartrate, after drying, is extremely hygroscopic. After drying, immediately transfer the material to a desiccator containing phosphorus pentoxide.] Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocodone Bitartrate Related Compound A RS. ~~— Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocortisone RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocortisone Acetate RS. ~~— Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocortisone Butyrate RS. ~~— Dry portion in vacuum at 78° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocortisone Hemisuccinate RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocortisone Phosphate Triethylamine RS ($C_{21}H_{31}O_8P \cdot C_6H_{15}N$ ✧ 543.64). ~~— Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydrocortisone Valerate RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroflumethiazide RS. ~~— Dry portion over silica gel for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydromorphone Hydrochloride RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroquinone RS. ~~— Do not dry; determine the water content by the titrimetric method before using for quantitative analyses. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxyamphetamine Hydrobromide RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxychloroquine Sulfate RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxyprogesterone Caproate RS. ~~— Dry portion in vacuum over silica gel for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxypropyl Cellulose RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxyurea RS. ~~— *[Caution—Hygroscopic; decomposes in the presence of moisture.]* Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed. Store in a desiccator at 0° or less.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxyzine Hydrochloride RS. ~~— *[Caution—The dried material is hygroscopic.]* Dry portion in vacuum at 75° for 3 hours before using. Keep container tightly closed. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxyzine Related Compound A RS [*p*-chlorobenzhydrylpiperazine**].** ~~— Do not dry; use as is. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hydroxyzine Pamoate RS. ~~— Do not dry before using. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Hyoscyamine Sulfate RS. ~~— Dry portion in vacuum at 105° for 16 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Hypromellose RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. This material is hygroscopic.~~

■ ■1S (*USP30*)

Change to read:

USP Hypromellose Phthalate RS. ~~— Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Ibuprofen RS. ~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Idarubicin Hydrochloride RS. ~~— Do not dry before using. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Idoxuridine RS. ~~— Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Ifosfamide RS. ~~— Do not dry; determine the water content titrimetrically when used for quantitative analysis. Keep container tightly closed. Store at a temperature not exceeding 25°.~~

■■1S (*USP30*)

Change to read:

USP Imidazole RS. ~~— Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Imidurea RS. ~~— Dry portion in vacuum over phosphorus pentoxide for 48 hours before using. Keep container tightly closed. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Iminodibenzyl RS ($C_{14}H_{13}N$ ✧ 195.28). ~~— Dry portion over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Imipenem Monohydrate RS. ~~— Do not dry before using. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Imipramine Hydrochloride RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Inamrinone RS. ~~— Do not dry before using; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Inamrinone Related Compound A RS [5-carboxamide[3,4′-bipyridin]-6(1*H*)-one**]** ($C_{11}H_9N_3O_2$ ✧ 215.21). ~~— Do not dry; use as is. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Inamrinone Related Compound B RS [*N*-(1,6-dihydro-6-oxo-(3,4′-bipyridine)-5-yl)-2-hydroxypropanamide**]** ($C_{13}H_{13}N_3O_3$ ✧ 259.3). ~~— Do not dry; use as is.~~

■■1S (*USP30*)

Change to read:

USP Inamrinone Related Compound C RS [1,6-dihydro-6-oxo-(3,4′-bipyridine)-5-carbonitrile**]** ($C_{11}H_7N_3O$ ✧ 197.20). ~~— Do not dry; use as is.~~

■■1S (*USP30*)

Change to read:

USP Indapamide RS. ~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Indigotindisulfonate Sodium RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Indinavir RS. ~~— Do not dry. This is the monohydrate form of indinavir. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Indinavir ▲*USP29* System Suitability RS.— ~~Do not dry. Keep container tightly closed.~~ *USP29*

■1S (*USP30*)

Change to read:

USP Indocyanine Green RS.— ~~Dry portion in vacuum at 50° for 3 hours before using. Keep container tightly closed.~~

■1S (*USP30*)

Change to read:

USP Indomethacin RS.— ~~Dry portion at a pressure below 5 mm of mercury at 100° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■1S (*USP30*)

Change to read:

USP Insulin RS.— ~~Preserve at a temperature not exceeding −15°. After opening the vial, without delay, transfer the entire contents of the vial in accurately weighed portions to clean, dry volumetric flasks. Keep the flasks tightly closed, and store in a freezer. Do not dry before use for tests and assays.~~

■1S (*USP30*)

Change to read:

USP Insulin (Beef) RS.— ~~Do not dry. Store in a freezer at −20° to −18°; after opening, store in a tight container protected from air and humidity.~~

■1S (*USP30*)

Change to read:

USP Insulin Human RS.— ~~Preserve in a freezer at −20° to −18°, and, after opening the vial, store in a tight container. After opening the vial, without delay, transfer accurately weighed portions to clean, dry volumetric flasks. Keep the flasks tightly closed, and store in a freezer. Do not dry before use for tests and assays.~~

■1S (*USP30*)

Change to read:

USP Insulin (Pork) RS.— ~~Do not dry. Store in a freezer at −20° to −18°; after opening, store in a tight container protected from air and humidity.~~

■1S (*USP30*)

Change to read:

USP Iodipamide RS.— ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■1S (*USP30*)

Change to read:

USP Iodixanol RS.— ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed, protected from light, and store in a dry place, preferably in a desiccator.~~

■1S (*USP30*)

Change to read:

USP *o*-Iodohippuric Acid RS ($C_9H_8INO_3$ ✧ 305.07).— ~~Do not dry before using. Keep container tightly closed, and store in a desiccator. Protect from light.~~

■1S (*USP30*)

Change to read:

USP Iodoquinol RS.— ~~Do not dry. Keep container tightly closed.~~

■1S (*USP30*)

Change to read:

USP Iohexol RS.— ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■1S (*USP30*)

Change to read:

USP Iohexol Related Compound A RS **[**5-(acetylamino)-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide**]**.— ~~Do not dry. Keep container tightly closed. Protect from light.~~

■1S (*USP30*)

Change to read:

USP Iohexol Related Compound B RS **[**5-amino-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide**]**.— ~~Do not dry. Keep container tightly closed and protected from light.~~

■1S (*USP30*)

Change to read:

USP Iohexol Related Compound C RS **[***N*,*N*′-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide**]**.— ~~Do not dry. Keep container tightly closed and protected from light.~~

■1S (*USP30*)

In-Process Revision

Change to read:

USP Iopamidol RS. ~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Iopamidol Related Compound A RS **[***N*,*N*′-bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide**]** ($C_{14}H_{18}I_3N_3O_6$ ✧ 705.03). ~~— Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Iopamidol Related Compound B RS **[**5-glycolamido-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide**]** ($C_{16}H_{20}I_3N_3O_7$ ✧ 747.07). ~~— Do not dry. Keep container tightly closed, protected from light, at room temperature.~~

■■1S (*USP30*)

Change to read:

USP Iopromide RS. ~~— Do not dry. For quantitative applications, use a value of 0.979 mg iopromide per mg on as-is basis. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Iopromide Related Compound A RS. ~~— Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Iopromide Related Compound B RS **[**5-(acetylamino)-*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-*N*-methyl-1,3-benzenedicarboxamide**]**. ~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Iothalamic Acid RS. ~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ioversol Related Compound A RS. ~~— Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Ioversol Related Compound B RS. ~~— Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Ioxilan RS. ~~— Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Ioxilan Related Compound A RS **[**5-amino-2,4,6-triiodo-3 *N*-(2-hydroxyethyl)carbamoyl benzoic acid**]** ($C_{10}H_9I_3N_2O_4$ ✧ 601.90). ~~— Dry at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Ipodate Sodium RS. ~~— Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Irbesartan RS. ~~— Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Isoetharine Hydrochloride RS. ~~— Dry portion at 100° for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Isoflupredone Acetate RS. ~~— Dry a portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Isoflurane RS. ~~— Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Isoflurane Related Compound B RS **[**2,2,2-trifluoroethyldifluoromethyl ether**]** ($C_3H_3F_5O$ ✧ 150.05).~~—Do not dry before using. Keep container tightly closed. Protect from light. *[Caution—Extremely volatile liquid. Cool contents before opening ampul.]*~~

■■1S (*USP30*)

Change to read:

USP L-Isoleucine RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Isomalathion RS ($C_{10}H_{19}O_6PS_2$ ✧ 330.37).~~—Do not dry. Keep container tightly closed, and store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Isoniazid RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Isopropamide Iodide RS.~~—Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Isopropyl Myristate RS.~~—Do not dry before using. After opening ampul, transfer contents to a tightly closed container, and protect from light.~~

■■1S (*USP30*)

Change to read:

USP Isopropyl Palmitate RS.~~—Do not dry before using. After opening ampul, transfer contents to a tightly closed container. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Isoproterenol Hydrochloride RS.~~—Dry portion in vacuum over phosphorus pentoxide for 4 hours before using. Keep the container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Isosorbide RS.~~—For quantitative applications, determine the water content titrimetrically. After opening the ampul, store in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Diluted Isosorbide Dinitrate RS.~~—*[Caution—Undiluted material is explosive by percussion or excessive heat.]* This is a mixture containing 25% of isosorbide dinitrate in mannitol. Do not dry before using. Keep container tightly closed. Prevent exposure to excessive heat.~~

■■1S (*USP30*)

Change to read:

USP Isotretinoin RS~~—Do not dry. Store vials at a temperature below 0°; allow to reach room temperature before opening, and use the contents promptly after opening vials. Protect from air and light once vial has been opened.~~

■■1S (*USP30*)

Change to read:

USP Isoxsuprine Hydrochloride RS.~~—Dry portion at 105° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Isradipine RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Ivermectin RS.~~—Do not dry. Protect from light. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Kanamycin Sulfate RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Ketamine Hydrochloride RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ketamine Related Compound A RS **[**1-[(2-chlorophenyl)-(methylimino)methyl]cyclopentanol**]** ($C_{13}H_{16}NOCl$ ✧ 237.73). ~~Do not dry. Keep container tightly closed. Protect from light. *[Caution—Protect solution from light and use immediately after preparation.]*~~

■■1S (*USP30*)

Change to read:

USP Ketoconazole RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ketoprofen RS. ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ketorolac Tromethamine RS. ~~Dry portion at 60° in vacuum for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Labetalol Hydrochloride RS. ~~Dry portion in vacuum at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Lactase RS. ~~Do not dry before using. Keep container tightly closed. Store in a refrigerator. Before opening, allow to attain room temperature. Protect from air and humidity after opening.~~

■■1S (*USP30*)

Change to read:

USP Anhydrous Lactose RS. ~~Dry portion at 80° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Lactose Monohydrate RS. ~~For identification test, dry a portion at 80° for 2 hours. For quantitative use, determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Lactulose RS. ~~Dry portion at 70° for 4 hours before using. Keep container tightly closed. Store between 2° and 30°.~~

■■1S (*USP30*)

Change to read:

USP Lamivudine RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Lamivudine Resolution Mixture A RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Lamivudine Resolution Mixture B RS. ~~Do not dry. Keep container tightly closed. Protect from light, and store at controlled room temperature.~~

■■1S (*USP30*)

Change to read:

USP Lanolin RS. ~~Keep container tightly closed, and store at controlled room temperature.~~

■■1S (*USP30*)

Change to read:

USP Lanolin Alcohols RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Lansoprazole RS ($C_{16}H_{14}F_3N_3O_2S$ ✧ 369.36). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Lansoprazole Related Compound A RS [2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole] ($C_{16}H_{14}F_3N_3O_3S$ ✧ 385.36). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Lauroyl Polyoxylglycerides RS. ~~Store in original container and prevent exposure to air, heat, and moisture.~~

■■1S (*USP30*)

Change to read:

USP Letrozole RS. ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Letrozole Related Compound A RS [4,4′-(1*H*-1,3,4-triazol-1-ylmethylene)dibenzonitrile] ($C_{17}H_{11}N_5$ ✧ 285.31). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP L-Leucine RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Leucovorin Calcium RS. ~~[NOTE—This material is extremely hygroscopic.] Do not dry; determine the water content titrimetrically at time of use for quantitative analyses. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Levamisole Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Levmetamfetamine RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Levobunolol Hydrochloride RS. ~~Dry portion in vacuum over phosphorus pentoxide in a suitable drying tube at 110° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Levocarnitine RS. ~~For quantitative use, determine the water content titrimetrically at the time of use. For IR identification use, dry portion at 50° in vacuum for 5 hours. Keep container tightly closed. This material is extremely hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Levocarnitine Related Compound A RS [2-propen-1-aminium, 3-carboxy-*N*,*N*,*N*-trimethyl-, chloride] ($C_7H_{14}ClNO_2$ ✧ 179.65). ~~Do not dry. Keep container tightly closed. Store in a dry place.~~

■■1S (*USP30*)

Change to read:

USP Levodopa RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a dry place and prevent exposure to excessive heat.~~

■■1S (*USP30*)

Change to read:

USP Levodopa Related Compound A RS [3-(3,4,6-trihydroxyphenyl)alanine] ($C_9H_{11}NO_5$ ✧ 213.19). ~~Do not dry. Keep container tightly closed and protected from light. Store in a cool, dry place.~~

■■1S (*USP30*)

Change to read:

USP Levodopa Related Compound B RS [3-methoxytyrosine] ($C_{10}H_{13}NO_4$ ✧ 211.22). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cool, dry place.~~

■■1S (*USP30*)

Add the following:

■**USP Levofloxacin RS.**■1S (*USP30*)

Add the following:

■**USP Levofloxacin Related Compound A RS**—[To come.]■1S (*USP30*)

In-Process Revision

Add the following:

■**USP Levofloxacin Related Compound B RS**—[To come.]■1S (*USP30*)

Change to read:

USP Levonordefrin RS. ~~— Dry portion in vacuum at 60° for 15 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Levorphanol Tartrate RS. ~~— This is the dihydrate form. Do not dry; determine the water content titrimetically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Levothyroxine RS. ~~— Use without drying; correct for moisture, determined by drying a separate portion in vacuum at 60° for 4 hours. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Lidocaine RS. ~~— Dry portion in vacuum over silica gel for 24 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Lincomycin Hydrochloride RS. ~~— Do not dry. This is the monohydrate form of lincomycin hydrochloride. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Lindane RS. ~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Linoleoyl Polyoxylglycerides RS. ~~— Store in original container, and prevent exposure to air, heat, and moisture.~~

■■1S (*USP30*)

Change to read:

USP Liothyronine RS. ~~— Do not dry before using.~~ ★~~Correct for moisture, determined by drying a separate portion in vacuum at 60° for 3 hours.~~▲*USP30*~~ Keep container tightly closed. Protect from light.~~ ★~~Store in a refrigerator.~~▲*USP30*

■■1S (*USP30*)

Change to read:

USP Lisinopril RS. ~~— This material is the dihydrate form of Lisinopril. Do not dry; determine the water content titrimetrically at time of use for quantitative analyses. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Lithium Carbonate RS. ~~— Dry portion at 200° for 4 hours before using. Keep container tightly closed. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Loperamide Hydrochloride RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Loracarbef RS. ~~— Do not dry before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Loracarbef L-Isomer RS. ~~— Do not dry before using. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Loratadine RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Loratadine Related Compound A RS [8-chloro-6,11-dihydro-11(4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*] pyridine] ($C_{19}H_{19}ClN_2$ ✧ 310.83). ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Loratadine Related Compound B RS [8-chloro-6,11-dihydro-11(*N*-methyl-4-piperinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine] ($C_{20}H_{21}ClN_2$ ✧ 324.88).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Lorazepam RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Lorazepam Related Compound A RS [7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-acetoxy-2*H*-1,4-benzodiazepin-2-one] ($C_{17}H_{12}Cl_2N_2O_3$ ✧ 363.20).~~—Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Lorazepam Related Compound B RS [2-amino-2′,5-dichlorobenzophenone] ($C_{13}H_9ClNO$ ✧ 266.13).~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Lorazepam Related Compound C RS [6-chloro-4-(*o*-chlorophenyl)-2-quinazolinecarboxaldehyde] ($C_{15}H_8Cl_2N_2O$ ✧ 303.15).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Lorazepam Related Compound D RS [6-chloro-4-(*o*-chlorophenyl)-2-quinazolinecarboxylic acid] ($C_{15}H_8Cl_2N_2O_2$ ✧ 319.15).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Lorazepam Related Compound E RS [6-chloro-4-(*o*-chlorophenyl)-2-quinazoline methanol] ($C_{15}H_{10}Cl_2N_2O$ ✧ 305.16).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Lovastatin RS.~~—Do not dry; use as is. Keep container tightly closed, and store in a freezer under nitrogen.~~

■■1S (*USP30*)

Change to read:

USP Lovastatin Related Compound A RS [dihydro-lovastatin] [butanoic acid, 2-methyl-, 1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-[2(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α(*R**),3α,7β,8β(2*S**,4*S**),-8$\alpha\beta$]]-] ($C_{24}H_{38}O_5$ ✧ 406.56).~~—Do not dry. This material is hygroscopic. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Loxapine Succinate RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Lutein RS.~~—Do not dry. Keep container tightly closed, and store under nitrogen in a cool place. Protect from light.~~

■■1S (*USP30*)

Change to read:

■**USP Lynestrenol RS** [(17α)-19-Norpregn-4-en-20-yn-17-ol] ($C_{20}H_{28}O$ ✧ 284.42).~~—Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP L-Lysine Acetate RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP L-Lysine Hydrochloride RS.~~—Dry portion at 105° for 3 hours before using. This is the monohydrochloride form. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Mafenide Acetate RS.~~—Determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Mafenide Related Compound A RS [4-formylbenzenesulfonamide**]** ($C_7H_7NO_3S$ ✧ 185.20).~~— Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Magaldrate RS.~~— Do not dry before using. Keep container tightly closed, and store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Magnesium Salicylate RS.~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Malathion RS.~~— Do not dry. After opening ampul, transfer contents to a suitable container. Keep container tightly closed and protected from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Maleic Acid RS.~~— Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Malic Acid RS.~~— Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Maltitol RS.~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Maltose RS.~~— Do not dry; determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Maltose Monohydrate RS.★~~Do not dry. Keep container tightly closed.~~★*USP29*

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Mannitol RS.~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Maprotiline Hydrochloride RS.~~— Dry portion in vacuum at 80° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Maritime Pine Extract RS.~~— Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Mazindol RS. ~~Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed. Store at a temperature not exceeding 25°.~~

■ ■1S (*USP30*)

Change to read:

USP Mebendazole RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Mebrofenin RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Mecamylamine Hydrochloride RS. ~~Dry portion at a pressure not exceeding 5 mm of mercury at 105° for 1 hour before using. Keep container tightly closed. Store in a cool, dry place.~~

■ ■1S (*USP30*)

Change to read:

USP Mechlorethamine Hydrochloride RS. ~~Do not dry before using. This material is hygroscopic. Keep container tightly closed, protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Meclizine Hydrochloride RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Meclocycline Sulfosalicylate RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Meclofenamate Sodium RS. ~~Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Medroxyprogesterone Acetate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Medroxyprogesterone Acetate Related Compound A RS [4,5β-dihydromedroxyprogesterone acetate**]** ($C_{24}H_{36}O_4$ ✧ 388.54). ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Mefenamic Acid RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Megestrol Acetate RS. ~~Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Melengestrol Acetate Related Compound A RS [16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-acetate**].** ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Melengestrol Acetate Related Compound B RS [17α-hydroxy-6,16-dimethyleneprogna-4-ene-3,20-dione 17-acetate**].** ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Melphalan Hydrochloride RS. ~~Do not dry before using. Keep container tightly closed and protected from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Menadione RS. ~~*[Caution—Avoid contact; avoid exposure to light.]* Dry portion over silica gel for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Menthol RS.—~~Do not dry. This is the L-form of menthol. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Meperidine Hydrochloride RS.—~~Dry portion in vacuum at a pressure between 20 and 40 mm of mercury at 80° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Mephobarbital RS.—~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Mepivacaine Hydrochloride RS.—~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Meprednisone RS.—~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Meprobamate RS.—~~Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP 3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt RS ($C_4H_7O_2S \cdot C_{14}H_{16}N$ ✧ 317.45).—~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Mercaptopurine RS.—~~Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Meropenem RS.—~~Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Mesalamine RS.—~~Dry portion in vacuum at 105° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Mesoridazine Besylate RS.—~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Mestranol RS.—~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metaproterenol Sulfate RS.—~~Dry portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metaraminol Bitartrate RS.—~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Metformin Hydrochloride RS.—~~Do not dry. Keep container tightly closed. Store in a refrigerator. Keep away from alkali.~~

■■1S (*USP30*)

Change to read:

USP Metformin Related Compound A RS [1-cyanoguanidine**].**—~~Do not dry. Keep container tightly closed. Store in a refrigerator. Keep away from alkali.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Methacrylic Acid Copolymer, Type A RS. ~~Dry portion at 110° for 6 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methacrylic Acid Copolymer, Type B RS. ~~Dry portion at 110° for 6 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methacrylic Acid Copolymer, Type C RS. ~~Dry portion at 110° for 6 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methacycline Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Methadone Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Methamphetamine Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Methazolamide RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Methdilazine Hydrochloride RS. ~~Dry portion in vacuum at 65° for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methenamine RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methenamine Hippurate RS. ~~Dry portion in vacuum at 60° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methenamine Mandelate RS. ~~Dry portion over silica gel for 18 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methicillin Sodium RS. ~~Do not dry. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Methimazole RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP L-Methionine RS. ★~~Do not dry.~~★*USP24* ~~Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methocarbamol RS. ~~Dry portion at 60° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methohexital RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methotrexate RS. ~~This material is hygroscopic. Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Methotrimeprazine RS. ~~Dry portion at 100° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Methoxsalen RS. ~~Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Methoxyflurane RS. ~~Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Methscopolamine Bromide RS. ~~Dry portion at 105° for 3 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Methsuximide RS. ~~Dry portion over phosphorus pentoxide for 16 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methyclothiazide RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Methyclothiazide Related Compound A RS [4-amino-6-chloro-N^3-methyl-*m*-benzenedisulfonamide] ($C_7H_{10}ClN_3O_4S_2$ ✧ 299.76). ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Methyl Caprate RS. ~~Do not dry before using. After opening ampul, store in a tightly closed container, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Methyl Caproate RS. ~~Do not dry before using. After opening ampul, store in a tightly closed container, protected from light.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Methyl Laurate RS. ~~Do not dry before using. After opening ampul, store in a tightly closed container, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Methyl Linoleate RS. ~~Store in a freezer. Do not dry before using. After opening ampul, discard the unused portion.~~

■■1S (*USP30*)

Change to read:

USP Methyl Linolenate RS. ~~Store in a freezer. Do not dry before using. After opening ampul, discard the unused portion.~~

■■1S (*USP30*)

Change to read:

USP Methyl 5-Methyl-3-isoxazolecarboxylate RS. ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Methyl Myristate RS. ~~Do not dry before using. After opening ampul, store in a tightly sealed container, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Methyl Oleate RS. ~~— Store in a freezer. Do not dry before using. After opening ampul, store it in a tightly closed container under an inert gas, protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Methyl Palmitate RS. ~~— Do not dry before using. Keep container tightly closed. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Methyl Palmitoleate RS. ~~— Store in a freezer. Do not dry before using. After opening ampul, store it in a tightly closed container under an inert gas, protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Methyl Stearate RS. ~~— Do not dry before using. Keep container tightly closed. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Methyldopa RS. ~~— Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Delete the following:

■ ~~**USP Methyldopa-Glucose Reaction Product RS.**~~ ■1S (*USP30*)

Change to read:

USP Methyldopate Hydrochloride RS. ~~— Dry portion at a pressure not exceeding 5 mm of mercury at 100° for 2 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Methylene Blue RS. ~~— Dry portion at a pressure not exceeding 5 mm of mercury at 75° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Methylergonovine Maleate RS. ~~— Dry portion in vacuum at 80° to constant weight before using. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP 3-*O*-Methylmethyldopa RS ($C_{11}H_{15}NO_4$ ✧ 225.25). ~~— Do not dry. This is the monohydrate form of 3-*O*-methylmethyldopa. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Methylparaben RS. ~~— Dry portion over silica gel for 5 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Methylphenidate Hydrochloride RS. ~~— Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Methylphenidate Hydrochloride Erythro Isomer Solution RS.—This solution contains ~~0.5 mL~~

■0.5 mg■1S (*USP30*)
of methylphenidate hydrochloride erythro isomer per mL in methanol. ~~Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Methylphenidate Related Compound A RS [α-phenyl-2-piperidineacetic acid hydrochloride**]** ($C_{13}H_{17}NO_2 \cdot HCl$ ✧ 255.75). ~~— Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Methylprednisolone RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Methylprednisolone Acetate RS. ~~— Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■ ■1S (*USP30*)

In-Process Revision

Change to read:

USP Methylprednisolone Hemisuccinate RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Methyltestosterone RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Methysergide Maleate RS. ~~Dry portion in vacuum at 120° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metoclopramide Hydrochloride RS. ~~Do not dry; determine the water content titrimetrically at time of use for quantitative analyses. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metolazone RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metoprolol Fumarate RS. ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Metoprolol Related Compound A RS [(±)1-ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol**]** ($C_{14}H_{23}NO_3$ ✧ 253.34). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Metoprolol Related Compound B RS [(±)1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane**]** ($C_{12}H_{17}ClO_3$ ✧ 244.71). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Metoprolol Related Compound C RS [(±)4-[2-hydroxy-3-(1-methylethyl)aminopropoxy]benzaldehyde**]** ($C_{13}H_{19}NO_3$ ✧ 237.29). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Metoprolol Related Compound D RS [(±) *N,N*-bis[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine**]** ($C_{27}H_{41}NO_6$ ✧ 475.62). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Metoprolol Succinate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metoprolol Tartrate RS. ~~Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metrifonate RS [trichlorfon**].** ~~Do not dry. Keep container tightly closed, protected from light, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Metronidazole RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Metronidazole Benzoate RS. ~~Dry at 80° for 3 hours.~~

■■1S (*USP30*)

Change to read:

USP Metyrapone RS. ~~Dry portion in vacuum at room temperature for 6 hours before using. Keep container tightly closed. Protect from light. Store in a cool, dry place.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Metyrosine RS. ~~Dry portion at a pressure not exceeding 5 mm of mercury at 100° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Mexiletine Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Mezlocillin Sodium RS. ~~Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed, and store in a cool, dry place. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Miconazole RS. ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Miconazole Nitrate RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Powdered Milk Thistle Extract RS. ~~Dry portion at 105° for 2 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Milrinone RS. ~~Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. This material is hygroscopic. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Milrinone Related Compound A RS [1,6-dihydro-2-methyl-6-oxo-(3,4′-bipyridine)-5-carboxamide**]** ($C_{12}H_{11}N_3O_2$ ✧ 229.23). ~~Do not dry. This material is hygroscopic. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Minocycline Hydrochloride RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Minoxidil RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Mirtazapine RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Mitomycin RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold dry place.~~

■■1S (*USP30*)

Change to read:

USP Mitotane RS. ~~Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Mitoxantrone Hydrochloride RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Mitoxantrone System Suitability Mixture RS [9, 10-anthracenedione, 8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-, hydrochloride**]** ($C_{18}H_{19}N_3O_5 \cdot HCl$ ✧ 393.83). ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Molindone Hydrochloride RS. ~~Dry portion at 105° to constant weight before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Mometasone Furoate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Monobenzone RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light. Avoid exposure to temperatures above 30°.~~

■■1S (*USP30*)

Change to read:

■**USP Monoethanolamine RS.** ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Monoglycerides RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Monostearyl Maleate RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Morantel Tartrate RS. ~~Do not dry. Keep container tightly closed. Protect from light. After opening, store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Moricizine Hydrochloride RS. ~~Do not dry. For quantitative applications, determine the water content titrimetrically. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Morphine Sulfate RS. ~~This is the pentahydrate form. Do not dry before using, except as instructed for compliance with official standards. Determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Add the following:

■**USP Multi-Metal Elements RS**—[To come.]■1S (*USP30*)

Change to read:

USP Mupirocin RS. ~~Do not dry before using. Keep container tightly closed, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Mupirocin Lithium RS. ~~Do not dry before using. Keep container tightly closed, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Nabumetone RS. ~~Do not dry. Keep container tightly closed. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Nabumetone Related Compound A RS [1-(6-methoxy-2-naphthyl)-but-1-en-3-one] ($C_{15}H_{14}O_2$ ✧ 226.27). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Nadolol RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Nafcillin Sodium RS. ~~Do not dry before using. Keep container tightly closed. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Naftifine Hydrochloride RS. ~~Dry over phosphorous pentoxide at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Nalidixic Acid RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Nalorphine Hydrochloride RS. ~~Dry portion in vacuum at 100° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Naloxone RS. ~~Dry portion at 105° to constant weight before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Naltrexone RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Naltrexone Related Compound A RS [*N*-(3-butenyl)-noroxymorphone hydrochloride**]** ($C_{20}H_{23}NO_4 \cdot HCl$ ✧ 377.87). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Nandrolone RS. ~~Do not dry before using. Keep container tightly closed and protected from light, and store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

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

■ ■1S (*USP30*)

Change to read:

USP Nandrolone Phenpropionate RS. ~~Dry portion in a suitable vacuum drying tube, using phosphorus pentoxide as the desiccant, at 80° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Naphazoline Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Naproxen RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Naproxen Sodium RS. ~~Dry portion in vacuum at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Naratriptan Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Naratriptan Related Compound A RS [3-(1-methylpiperidin-4-yl)-1*H*-indole hydrochloride**]** ($C_{14}H_{18}N_2 \cdot HCl$ ✧ 250.8). ~~Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Naratriptan Related Compound B RS [2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]ethanesulfonic acid methylamide oxalate**]** ($C_{17}H_{23}N_3O_2S \cdot C_2H_2O_4$ ✧ 423.5). ~~Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Natamycin RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Neomycin Sulfate RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Neostigmine Bromide RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Neostigmine Methylsulfate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Netilmicin Sulfate RS. ~~Do not dry before using; determine the volatiles content by heating a separate 100-mg portion at 110° at a pressure of 5 mm of mercury or less for 3 hours. Keep container tightly closed. Protect from light. Store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Nevirapine Anhydrous RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Nevirapine Hemihydrate RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Nevirapine Related Compound A RS **[**5,11-dihydro-6*H*-11-ethyl-4-methyl-dipyrido[3,2-*b*: 2′,3′-*e*][1,4]diazepin-6-one**]** ($C_{14}H_{14}N_4O$ ✧ 254.29). ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Nevirapine Related Compound B RS **[**5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*: 2′,3′-*e*][1,4]diazepin-6-one**]** ($C_{12}H_{10}N_4O$ ✧ 226.23). ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Niacin RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Niacinamide RS. ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Nicotine Bitartrate Dihydrate RS. ~~Do not dry; determine the water content titrimetrically at time of use for quantitative analyses. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Nifedipine RS. ~~Do not dry. Keep container tightly closed. Avoid exposure to light. Handle with care.~~

■ ■1S (*USP30*)

Change to read:

USP Nifedipine Nitrophenylpyridine Analog RS **[**dimethyl 4-(2-nitrophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate**]** ($C_{17}H_{16}N_2O_6$ ✧ 344.33). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Nifedipine Nitrosophenylpyridine Analog RS **[**dimethyl 4-(2-nitrosophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate**]** ($C_{17}H_{16}N_2O_5$ ✧ 328.33). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Nitrofurantoin RS. ~~Dry portion at 140° for 30 minutes before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Nitrofurantoin Related Compound A RS **[***N*-(aminocarbonyl)-*N*-[([5-nitro-2-furanyl]methylene)amino]glycine**]**. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Nitrofurazone RS. ~~Dry portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light. Avoid exposure to direct sunlight, to strong fluorescent lighting, to excessive heat, and to alkaline materials.~~

■ ■1S (*USP30*)

Change to read:

USP Nitrofurazone Related Compound A RS [5-nitro-2-fufuraldazine**]** ($C_{10}H_6N_4O_6$ ✧ 278.18).~~—Dry portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Nitrofurfural Diacetate RS ($C_9H_9NO_7$ ✧ 243.17).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Diluted Nitroglycerin RS.~~—*[Caution—Handle with care; may be exploded by percussion or excessive heat.]* Do not dry; each ampul contains approximately 200 mg of a 1.00% solution (w/w) of nitroglycerin in propylene glycol. Store unopened ampuls at 4°; allow to equilibrate to room temperature before opening ampul. Once opened, protect from moisture and light, and use promptly. Discard any unused portion.~~

■■1S (*USP30*)

Change to read:

USP Nizatidine RS.~~—Dry portion at 100° for 1 hour before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Nonoxynol 9 RS.~~—Do not dry. Once opened, take precautions against contact with air. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Nordazepam RS [7-chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one**]** ($C_{15}H_{11}ClN_2O$ ✧ 270.72).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Norepinephrine Bitartrate RS.~~—Do not dry. This is the monohydrate form of norepinephrine bitartrate. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Norethindrone RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Norethindrone Acetate RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Norethynodrel RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Norfloxacin RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 100° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Norgestimate RS.~~—Dry a portion at 105° for 3 hours. Keep containers tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Norgestrel RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Noroxymorphone Hydrochloride RS.~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Nortriptyline Hydrochloride RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Noscapine RS.~~—Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Novobiocin RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 100° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Nystatin RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 40° for 2 hours before using. Keep container tightly closed. Protect from light. Store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Octinoxate RS [octyl methoxycinnamate**].** ~~Do not dry. Keep container tightly closed. Store in a cool place. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Octisalate RS [octyl salicylate**].** ~~★Do not dry. Keep container tightly closed.★*USP29*~~

■ ■1S (*USP30*)

Change to read:

USP Octocrylene RS. ~~Do not dry. After opening ampul, store in a tightly closed container.~~

■ ■1S (*USP30*)

Change to read:

USP Octoxynol 9 RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Octyldodecanol RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Ofloxacin RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Oleoyl Polyoxylglycerides RS. ~~Do not dry. After opening the ampul, store the material in a tightly closed container.~~

■ ■1S (*USP30*)

Change to read:

USP Omeprazole RS. ~~Do not dry before using. Keep container tightly closed, and store in a cold place, protected from moisture.~~

■ ■1S (*USP30*)

Change to read:

USP Ondansetron Hydrochloride RS. ~~This is the dihydrate form. Do not dry. For quantitative applications, determine the water content titrimetrically. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Ondansetron Related Compound A RS [3[(dimethylamino)-methyl]-1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one**].** ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Ondansetron Related Compound C RS [1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one**].** ~~Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Ondansetron Related Compound D RS [1,2,3,9-tetrahydro-9-methyl-3-methylene-4*H*-carbazol-4-one**].** ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Ondansetron Resolution Mixture RS—Ondansetron hydrochloride having approximately 0.4% w/w of both ondansetron related compound A and 6,6′-methylene bis-[(1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)-methyl]-4*H*-carbazol-4-one)]. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Orphenadrine Citrate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

In-Process Revision

Change to read:

USP Oxacillin Sodium RS. ~~Do not dry before using. Keep container tightly closed. Store at a controlled room temperature.~~

■■1S (*USP30*)

Change to read:

USP Oxandrolone RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Oxaprozin RS. ~~Dry portion over silica gel at room temperature for 24 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Oxazepam RS. ~~Dry portion at a pressure below 5 mm of mercury at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Oxfendazole RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Oxprenolol Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Oxtriphylline RS. ~~Dry portion at 80° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Oxybenzone RS. ~~Dry portion in vacuum at 40° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Oxybutynin Chloride RS. ~~Dry portion in vacuum at 60° for 24 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Oxybutynin Related Compound A RS [phenylcyclohexylglycolic acid**]** ($C_{14}H_{18}O_3$ ✧ 234.30). ~~Dry portion at 105° for 2 hours. Keep container tightly closed. Store in a dry place.~~

■■1S (*USP30*)

Change to read:

USP Oxybutynin Related Compound B RS [methyl ester of phenylcyclohexylglycolic acid, or CHMME (cyclohexyl mandelic acid methyl ester)**].** ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Oxybutynin Related Compound C RS [methylethyl analog of oxybutynin chloride, or (4-(ethylmethylamino) but-2-ynyl (±) 2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride)**].** ~~Do not dry. Store in a tightly closed container blanketed under inert gas. Protect from light. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Oxycodone RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Oxymetazoline Hydrochloride RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Oxymetholone RS. ~~Dry portion in vacuum over phosphorus pentoxide for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Oxymorphone RS. ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Oxyquinoline Sulfate RS. ~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Oxytetracycline RS. ~~— Do not dry. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Oxytocin RS. ~~— Store at or below 0°. Reconstitute the entire content of one vial in water, quantitatively transfer with water to a 5-mL volumetric flask, dilute with water to volume, and mix. For the *System suitability* test spike a portion of the final solution with chlorobutanol.~~

■■1S (*USP30*)

Change to read:

USP Paclitaxel RS. ~~— Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Paclitaxel Related Compound A RS [cephalomannine**].** ~~— Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Paclitaxel Related Compound B RS [10-deacetyl-7-epipaclitaxel**].** ~~— Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Add the following:

■**USP Paclitaxel Impurity Mixture RS**—[To come.]■1S (*USP30*)

Change to read:

USP Padimate O RS. ~~— Do not dry; determine the water content titrimetrically, for quantitative application, at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Palmitic Acid RS. ~~— Do not dry. Store in a refrigerator. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pamoic Acid RS ($C_{23}H_{16}O_6$ ✧ 388.38). ~~— Dry portion in vacuum at 100° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pancreatin Amylase and Protease RS. ~~— Keep container tightly closed, and store in a refrigerator. Do not open while cold, and do not dry before using.~~

■■1S (*USP30*)

Change to read:

USP Pancreatin Lipase RS. ~~— Keep container tightly closed, and store in a refrigerator. Do not open while cold, and do not dry before using.~~

■■1S (*USP30*)

Change to read:

USP Racemic Panthenol RS. ~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pantolactone RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Papain RS. ~~— Do not dry before using. Keep container tightly closed, protected from light, and store in a refrigerator. Do not open while cold.~~

■■1S (*USP30*)

Change to read:

USP Papaverine Hydrochloride RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Paramethasone Acetate RS. ~~Dry portion in vacuum at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Parbendazole RS. ~~Do not dry before using. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Paromomycin Sulfate RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Paroxetine Hydrochloride RS. ~~Do not dry. This is the hemihydrate form of Paroxetine Hydrochloride. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Paroxetine Related Compound C RS **[**(+)-*trans*-paroxetine hydrochloride**]**. ~~Do not dry before use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Paroxetine Related Compound E Mixture RS (paroxetine hydrochloride spiked with 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Paroxetine Related Compound F RS **[***trans*(–)-1-methyl-3-[1,3-benzodioxol-5-yloxy)methyl]-4-(fluorophenyl)piperidine**]** ($C_{20}H_{22}FNO_3$ ✧ 343.39). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Paroxetine Related Compound G RS **[**(±)*trans*-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4″-fluorophenyl-4′-phenyl)piperidine hydrochloride**]** ($C_{25}H_{24}FNO_3$ ✧ 405.46). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

▲~~**USP Paroxetine Hydrochloride for System Suitability RS**~~

■**USP Paroxetine System Suitability Mixture A RS**■1S (*USP30*)—Mixture of 1% paroxetine related compound A **[**piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)-, hydrochloride (3 *S-trans*); and 1% of paroxetine related compound B [piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenyl)-, hydrochloride (3 *S-trans*)]**]** in a matrix of paroxetine hydrochloride.▲*USP29*

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Particle Count RS (2 blanks and 2 suspensions). ~~The set consists of 2 vials containing a suspension of 15-µm polystyrene spheres and 2 vials containing the aqueous phase without particles (the blank). Particles must be resuspended before use. Do not open until ready to begin the test as set forth in chapter *Particulate Matter in Injections* ⟨788⟩. Store in a cool place. **PROTECT FROM FREEZING.**~~

■■1S (*USP30*)

Change to read:

USP Penbutolol Sulfate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Penicillamine RS. ~~Do not dry. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Penicillamine Disulfide RS ($C_{10}H_{20}N_2O_4S_2$).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Penicillin G Benzathine RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Penicillin G Potassium RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Penicillin G Procaine RS.~~—Do not dry. This is the monohydrate form of Penicillin G Procaine. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Penicillin G Sodium RS.~~—Dry portion in vacuum at 60° for 3 hours. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Penicillin V RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Penicillin V Potassium RS.~~—Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Pentazocine RS.~~—Dry portion at 60° and at a pressure not exceeding 5 mm of mercury to constant weight before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pentetic Acid RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pentobarbital RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pentoxifylline RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Perflubron RS.~~—Do not dry. After opening ampul, store in a tightly closed container. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pergolide Mesylate RS.~~—Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Pergolide Sulfoxide RS [(8β)-8-[(methylsulfinyl)methyl]-6-propyl-D-ergoline**].**~~—Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Perphenazine RS.~~—Dry portion in vacuum at 65° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Perphenazine Sulfoxide RS.~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Phenacetin Melting Point RS. ~~Dry portion over silica gel for 16 hours before using. When melted by the USP capillary tube method, *Class Ia* in the general chapter *Melting Range or Temperature* ⟨741⟩, the observed range falls within the indicated acceptance range. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenazopyridine Hydrochloride RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phendimetrazine Tartrate RS. ~~Dry portion at 105° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenelzine Sulfate RS. ~~Dry portion at a pressure not exceeding 5 mm of mercury over silica gel at 80° for 2 hours before using. Keep container tightly closed. Protect from light and heat.~~

■■1S (*USP30*)

Change to read:

USP Pheniramine Maleate RS. ~~Dry portion in vacuum at 65° for 6 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenmetrazine Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenobarbital RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenoxybenzamine Hydrochloride RS. ~~Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenoxyethanol RS [2-phenoxyethanol]**.** ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phensuximide RS. ~~Dry portion in vacuum at 50° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phentermine Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phentolamine Mesylate RS. ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP L-Phenylalanine RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

■**USP Phenylbenzimidazole Sulfonic Acid RS.** ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Phenylbutazone RS. ~~Dry portion in vacuum at a pressure of 30 ± 10 mm of mercury at 80° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenylephrine Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phenylethyl Alcohol RS

■($C_8H_{10}O$ ✧ 122.17).■1S (*USP30*)
~~— Do not dry. After opening ampul, store in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP 5-Phenylhydantoin RS. ~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenylpropanediol RS [1-phenyl-1,2-propanediol] ($C_9H_{12}O_2$ ✧ 152.19). ~~— Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Phenylpropanolamine Bitartrate RS. ~~— Dry portion at 65° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Phenylpropanolamine Hydrochloride RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phenyltoloxamine Citrate RS. ~~— Dry it in vacuum at 80° for 3 hours. Keep the container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phenyltoloxamine Related Compound A RS [2-(2-benzylphenoxy)ethylmethylamine hydrochloride] ($C_{16}H_{19}NO \cdot HCl$ ✧ 277.79). ~~— Do not dry. Keep the container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phenytoin RS.★ ~~— Do not dry.~~▲*USP29*~~ Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phenytoin Related Compound A RS [diphenylglycine] ($C_{14}H_{15}NO_2$ ✧ 227.26). ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phenytoin Related Compound B RS [diphenylhydantoic acid] ($C_{15}H_{14}N_2O_3$ ✧ 270.29). ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phenytoin Sodium RS. ~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Phosphated Riboflavin RS. ~~— Dry portion at 105° for 2 hours. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Physostigmine Salicylate RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Phytonadione RS. ~~— This material decomposes on exposure to sunlight. Do not dry before using. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Pilocarpine RS. ~~— Do not dry. Allow ampul to equilibrate to room temperature before opening.~~

■■1S (*USP30*)

Change to read:

USP Pilocarpine Hydrochloride RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Pilocarpine Nitrate RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Pimozide RS. ~~Dry portion in vacuum at 80° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Pindolol RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Piperacillin RS. ~~Do not dry. For quantitative applications determine the water content at the time of use. Keep container tightly closed, and store in a cold, dry place, protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Piroxicam RS. ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Plicamycin RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 25° for 4 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Polacrilex Resin RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Polacrilin Potassium RS. ~~Dry portion at 105° for 6 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Poloxalene RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.~~

■ ■1S (*USP30*)

Change to read:

USP Polydimethylsiloxane RS. ~~Do not dry before using. After opening ampul, store in a tightly closed container.~~

■ ■1S (*USP30*)

Change to read:

USP High-Density Polyethylene RS. ~~[NOTE—Exercise care in handling and storage to avoid scratching the smooth surfaces of the strips.] Prepare samples as directed in the respective USP General Tests Chapters. Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Polyethylene Oxide RS. ~~Dry portion in vacuum at room temperature to constant weight before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Low-Density Polyethylene RS. ~~[NOTE—Exercise care in handling and storage to avoid scratching smooth surfaces of strips.] Cut segments to dimensions necessary for mounting in holders used for reflectance spectrum determinations. Prepare samples for thermal analysis from remaining portions of strips. Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Polyethylene Terephthalate RS. ~~[NOTE—Exercise care in handling and storage to avoid scratching smooth surfaces of strips.] Cut segments to dimensions necessary for mounting in holders used for reflectance spectrum determinations. Prepare samples for thermal analysis from remaining portions of strips. Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Polyethylene Terephthalate G RS. ~~[NOTE—Exercise care in handling and storage to avoid scratching smooth surfaces of strips.] Cut segments to dimensions necessary for mounting in holders used for reflectance spectrum determinations. Prepare samples for thermal analysis from remaining portions of strips. Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Polymyxin B Sulfate RS. ~~— Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Polyoxyl 35 Castor Oil RS.—

~~★Do not dry. After opening, store in a tightly closed container. Protect from light.★*USP30*~~

■■1S (*USP30*)

Change to read:

USP Polyoxyl 40 Stearate RS. ~~— Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Add the following:

■**USP Polyvinyl Acetate RS.**■1S (*USP30*)

Change to read:

USP Posterior Pituitary RS. ~~— Do not dry before using. Store at a temperature of 0° or below. Each mg represents 2.4 USP Posterior Pituitary Units of oxytocic activity and 2.1 USP Posterior Pituitary Units of vasopressor activity. Do not freeze.~~

■■1S (*USP30*)

Change to read:

USP Potassium Gluconate RS. ~~— Dry portion in vacuum at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Potassium Guaiacolsulfonate RS. ~~— Do not dry. Determine the water content titrimetrically before use for quantitative analyses. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Potassium Sucrose Octasulfate RS [NOTE—Sucrosofate Potassium is USAN] **[**α-D-glucopyranoside, 1,3,4,6-tetra-*O*-sulfo-β-D-fructofuranosyl, tetrakis (hydrogen sulfate), octapotassium salt, heptahydrate**]** ($C_{12}H_{14}K_8O_{35}S_8 \cdot 7H_2O$ ✧ 1413.64 ✧ CAS-76578-81-9). (anhydrous $C_{12}H_{14}K_8O_{35}S_8$ ✧ 1287.53 ✧ CAS-73264-44-5). ~~— Do not dry; determine the water content titrimetrically when used for quantitative analyses. Keep container tightly closed, and store in a freezer. Allow to equilibrate to ambient temperature before opening.~~

■■1S (*USP30*)

Change to read:

USP Potassium Trichloroammineplatinate RS (Cl_3H_3KNPt ✧ 357.58). ~~— Dry portion in vacuum at room temperature over phosphorus pentoxide in a desiccator for 20 hours before use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pralidoxime Chloride RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pramoxine Hydrochloride RS. ~~— Dry portion at 105° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Praziquantel RS. ~~— Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 50° over phosphorus pentoxide for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Praziquantel Related Compound A RS **[**2-benzoyl-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino [2,1-*a*]isoquinolin-4-one**]** ($C_{19}H_{18}N_2O_2$ ✧ 306.37). ~~— Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 50° over phosphorus pentoxide for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Praziquantel Related Compound B RS **[**2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4*H*-pyrazino [2,1-*a*]isoquinolin-4-one**]** ($C_{19}H_{22}N_2O_2$ ✧ 310.40). ~~— Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 50° over phosphorus pentoxide for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Praziquantel Related Compound C RS **[**2-(*N*-formylhexahydrohippuroyl-1,2,3,4-tetrahydroisoquinolin-1-one**]** ($C_{19}H_{22}N_2O_4$ ✧ 342.39).~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 50° over phosphorus pentoxide for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Prazosin Hydrochloride RS.~~—Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

■**USP Prednicarbate RS.**~~—Keep container tightly closed, protect from light, and store at controlled room temperature.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Prednicarbate Related Compound A RS** **[**1,2-dihydroprednicarbate**].**~~—Keep container tightly closed, protect from light, and store at controlled room temperature.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Prednisolone Acetate RS.~~—Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Prednisolone Hemisuccinate RS.~~—Dry portion in vacuum at 65° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Prednisolone Tebutate RS.~~—Dry portion in vacuum at a pressure of not more than 5 mm of mercury at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating).~~—The label states the nominal weight of prednisone in each tablet. Use only whole tablets. Remove any surface dust with a soft brush before using. Keep container tightly closed. Store in a desiccator or in a dry place at room temperature.~~

■■1S (*USP30*)

Change to read:

USP Prilocaine Hydrochloride RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Prilocaine Related Compound A RS **[***o*-toluidine hydrochloride**]** ($CH_3C_6H_4NH_2HCl$ ✧ 143.62 ✧CAS-636-21-5).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Prilocaine Related Compound B RS **[**(*RS*)-*N*-(4-methylphenyl)-2-(propylamino)propanamide**]** ($C_{13}H_{20}N_2O$ ✧ 220.31).~~—Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Primaquine Phosphate RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Primidone RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Probenecid RS. ~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Probucol RS. ~~— Dry portion in a vacuum at 80° for 1 hour before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Probucol Related Compound A RS **[**2,2′,6,6′-tetra-*tert*-butyldiphenoquinone**]** ($C_{28}H_{40}O_2$ ✧ 408.63). ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Probucol Related Compound B RS **[**4,4′-(dithio)bis(2,6-di-*tert*-butylphenol)**]** ($C_{28}H_{42}O_2$ ✧ 474.78). ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Probucol Related Compound C RS **[**4-[(3,5-di-*tert*-butyl-2-hydroxyphenylthio)isopropylidenethio]-2,6-di-*tert*-butylphenol**]** ($C_{31}H_{48}O_2S_2$ ✧ 516.86). ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Procainamide Hydrochloride RS. ~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed. Material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Procaine Hydrochloride RS. ~~— Dry portion over silica gel for 18 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Procarbazine Hydrochloride RS. ~~— Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Prochlorperazine Maleate RS. ~~— Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Procyclidine Hydrochloride RS. ~~— Dry portion in vacuum at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Progesterone RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP L-Proline RS. ~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Promazine Hydrochloride RS. ~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Promethazine Hydrochloride RS. ~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Add the following:

■**USP Promethazine Related Compound A RS**—[To come.]■1S (*USP30*)

Change to read:

USP Propafenone Hydrochloride RS. ~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Propantheline Bromide RS. ~~Dry portion at 105° for 4 hours before using. Store under inert gas, and keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Propantheline Bromide Related Compound A RS [9-hydroxypropantheline bromide**]** ($C_{23}H_{30}BrNO_4$ ✧ 464.39). ~~Do not dry. Keep container tightly closed. Avoid contact. Store in a desiccator. Protect from light. Store under inert atmosphere.~~

■ ■1S (*USP30*)

Change to read:

USP Proparacaine Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Propofol RS. ★ ~~Do not dry. After opening, keep in tight, light-resistant containers under inert gas.~~ ▲*USP29*

■ ■1S (*USP30*)

Change to read:

USP Propofol Related Compound A RS [3,3′-5,5′-tetraisopropyldiphenol**].** ~~★ Do not dry. Store in a refrigerator. Protect from light.~~ ▲*USP29*

■ ■1S (*USP30*)

Change to read:

USP Propofol Related Compound B RS [2,6-diisopropylbenzoquinone**].** ~~★ Do not dry. Keep in tight, light-resistant containers under inert gas. Store in a refrigerator.~~ ▲*USP29*

■ ■1S (*USP30*)

Change to read:

USP Propofol Related Compound C RS [2,6-diisopropylphenylisopropyl ether**]** ($C_{14}H_{22}O$ ✧ 206.32). ~~Do not dry. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Propoxycaine Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Propoxyphene Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Propoxyphene Napsylate RS. ~~This is the monohydrate form. Do not dry; determine the water content titrimetrically at time of use for quantitative analyses. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Propoxyphene Related Compound A RS [*a-d*-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol hydrochloride**]** ($C_{19}H_{25}NO \cdot HCl$ ✧ 319.87). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Propoxyphene Related Compound B RS [α-*d*-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane**]** ($C_{21}H_{27}NO_2$ ✧ 325.45). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Propranolol Hydrochloride RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Propylene Carbonate RS. ~~Do not dry before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Propylene Glycol RS. ~~Do not dry before using. After opening ampul, transfer to a tightly closed container.~~

■ ■1S (*USP30*)

Change to read:

USP Propyl Gallate RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light, and avoid contact with metals.~~

■ ■1S (*USP30*)

Change to read:

USP Propylparaben RS. ~~Do not dry.~~ ~~*USP29*~~ ~~Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Propylthiouracil RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Prostaglandin A_1 RS. ~~Do not dry before using. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Prostaglandin B_1 RS ($C_{20}H_{32}O_4$ ✧ 336.47). ~~Do not dry before using. Keep container tightly closed, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Protriptyline Hydrochloride RS. ~~Dry portion at a pressure below 5 mm of mercury at 60° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pseudoephedrine Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pseudoephedrine Sulfate RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pyrantel Pamoate RS. ~~Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pyrazinamide RS. ~~Dry portion over silica gel for 18 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Pyridostigmine Bromide RS. ~~Dry portion in a suitable vacuum drying tube, using phosphorus pentoxide as the desiccant, at 100° for 4 hours before using. Keep container tightly closed, and store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Pyridoxine Hydrochloride RS. ~~Dry portion in vacuum over silica gel for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pyrilamine Maleate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pyrimethamine RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Pyrvinium Pamoate RS. ~~Do not dry; determine the water content titimetrically at time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Quazepam RS. ~~*[WARNING! Reproductive Hazard.]* Dry portion at 105° for 4 hours. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Quazepam Related Compound A RS [7-chloro-1-(2,2,2 trifluoroethyl)-5-(2-Fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one**].** ~~*[WARNING! Reproductive Hazard.]* Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Quercetin RS.—★~~Do not dry. This is the dihydrate form. Keep container tightly closed. Protect from light. Store in a freezer.~~▲*USP29*

■ ■1S (*USP30*)

Change to read:

USP Quinapril Hydrochloride RS.—~~Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Quinapril Related Compound A RS **[**ethyl [3*S*-[2*R**), 3a, 11ab]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-a-(2-phenylethyl)-2*H*-pyrazino[1,2-b]isoquinoline-2-acetate**]** ($C_{25}H_{27}N_2O_4$ ✧ 419.49).—~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Quinapril Related Compound B RS **[**3-isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3*S*-[2[*R**(*R**)],3*R**]]**]** ($C_{23}H_{26}N_2O_5$ ✧ 410.47).—~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

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

■ ■1S (*USP30*)

Change to read:

USP Quinidine Gluconate RS.—~~Dry portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Quinidine Sulfate RS.—~~Do not dry. This is the dihydrate form of quinidine sulfate. Determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Quinine Sulfate RS.—~~Do not dry. This is the dihydrate form of quinine sulfate. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Quininone RS ($C_{20}H_{22}N_2O_2$ ✧ 322.40).—~~Do not dry. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP 3-Quinuclidinyl Benzilate RS ($C_{21}H_{23}NO_3$ ✧ 337.42).—~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Ramipril RS.—~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Ramipril Related Compound A RS **[**(2*S*,3a*S*,6a*S*)-1-[(*S*)2-[[(*S*)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid**]** ($C_{22}H_{30}N_2O_5$ ✧ 402.48).—~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■ ■1S (*USP30*)

Change to read:

USP Ramipril Related Compound B RS **[**(2*S*,3a*S*,6a*S*)-1-[(*S*)2-[[(*S*)1-(methylethoxy)carbonyl-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid**]** ($C_{24}H_{34}N_2O_5$ ✧ 430.54).—~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Ramipril Related Compound C RS **[**(2*S*,3a*S*,6a*S*)-1-[(*S*)2-[[(*S*)1-ethoxycarbonyl-3-cyclohexyl propyl]amino]-1-oxopropyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid**]** ($C_{23}H_{38}N_2O_5$ ✧ 422.56).—~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Ramipril Related Compound D RS **[**ethyl (2*S*)2-[(3*S*,5a*S*,8a*S*, 9*aS*)-3-methyl-1,4-dioxodecahydro-1*H*-cyclopenta[*e*]-pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenyl-butanoate**]** ▲**Ramipril Diketopiperazine**▲*USP29* ($C_{23}H_{30}N_2O_4$ ✧ 398.50).—~~Do not dry. Keep container tightly closed.~~ ★~~Protect from light. Store in a refrigerator.~~▲*USP29*

■ ■1S (*USP30*)

In-Process Revision

Change to read:

USP Ranitidine Hydrochloride RS. ~~Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Ranitidine Related Compound A RS **[**5-[[(2-aminoethyl)thio]methyl]-*N*,*N*-dimethyl-2-furanmethanamine, hemifumarate salt**]**. ~~Keep container tightly closed and protected from light. Do not dry before using.~~

■ ■1S (*USP30*)

Change to read:

USP Ranitidine Related Compound B RS **[***N*,*N*′-bis[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-2-nitro-1,1-ethenediamine**]**. ~~Keep container tightly closed and protected from light. Do not dry before using.~~

■ ■1S (*USP30*)

Change to read:

USP Ranitidine Related Compound C RS **[***N*-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]sulfinyl]ethyl]-*N*-methyl-2-nitro-1,1-ethenediamine**]**. ~~Do not dry before using. Keep container tightly closed and protected from light. Store in a cool place.~~

■ ■1S (*USP30*)

Change to read:

USP Rauwolfia Serpentina RS. ~~Do not dry before using. Keep container tightly closed, and store at a controlled room temperature in a dry place.~~

■ ■1S (*USP30*)

Change to read:

USP Repaglinide RS. ~~Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Repaglinide Related Compound A RS **[**(*S*)-3-methyl-1-[2-(1-piperidinyl)phenyl]butylamine, *N*-acetyl-L-glutamate salt**]** ($C_{16}H_{26}N_2 \cdot C_7H_{11}NO_5$ ✧ 435.6). ~~Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Repaglinide Related Compound B RS **[**3-ethoxy-4-ethoxycarbonylphenylacetic acid**]** ($C_{13}H_{16}O_5$ ✧ 252.27). ~~Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Repaglinide Related Compound C RS **[**(*S*)-2-ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl]benzoic acid**]** ($C_{30}H_{34}N_2O_4$ ✧ 486.61). ~~Do not dry.~~

■ ■1S (*USP30*)

Change to read:

USP Reserpine RS. ~~Dry portion at 60° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Resorcinol RS. ~~Do not dry. Keep container tightly closed. Protect from light. Avoid contact with metals.~~

■ ■1S (*USP30*)

Change to read:

USP Ribavirin RS. ~~Do not dry. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Riboflavin RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Rifabutin RS. ~~Do not dry before using. Keep container tightly closed. Store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Rifampin RS. ~~Do not dry; determine the loss on drying of a separate portion at the time of use. Avoid exposure to oxygen. Keep container tightly closed. Protect from light. Store in a cold place.~~

■ ■1S (*USP30*)

Change to read:

USP Rifampin Quinone RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold, dry place.~~

■ ■1S (*USP30*)

In-Process Revision

Change to read:

USP Rimexolone RS. ~~Dry portion in vacuum at 105° for 3 hours before using. Protect from light. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

▲**USP Risperidone RS** **[**3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one**]** (410.48 ✧ CAS-106266-06-2).— ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)
▲*USP30*

Change to read:

▲**USP Risperidone System Suitability Mixture RS** ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Contains risperidone and about 0.2% of each of the following:

Z-oxime-3-[2-[4-[(*Z*)-(2,4-difluorophenyl)(hydroxyimino)-methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

9-hydroxyrisperidone-(6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one;

6-methylrisperidone-(6*RS*)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one.▲*USP30*

Change to read:

USP Ritodrine Hydrochloride RS. ~~Dry portion at 105° for 1 hour before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Roxarsone RS. ~~Dry portion at 100° for 6 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Rutin RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Saccharin RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Saccharin Calcium RS. ~~Dry portion at 105° for 2 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Saccharin Sodium RS. ~~Dry portion at 105° for 2 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Salicylamide RS. ~~Dry portion over silica gel for 18 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Salicylic Acid RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Salicylic Acid Tablets RS (Dissolution Calibrator, Non-disintegrating). ~~The label states the nominal weight of each tablet. Use only whole tablets—extra tablets are provided. Remove any surface dust with a soft brush before using. Keep container tightly closed. Store in a desiccator or in a dry place at room temperature.~~

■■1S (*USP30*)

Change to read:

USP Salsalate RS. ~~Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Scopolamine Hydrobromide RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Scopoletin RS. ~~Do not dry. Keep container tightly closed. Store in a refrigerator. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Secobarbital RS. ~~Dry portion over silica gel for 18 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Selegiline Hydrochloride RS. ~~Dry portion in vacuum at 60° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Sennosides RS. ~~Do not dry before using. Dry a separate portion in vacuum at 100° to constant weight to obtain loss on drying for quantitative analyses. Keep container tightly closed. Material is extremely hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP L-Serine RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sevoflurane RS. ~~Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sevoflurane Related Compound A RS [1,1,1,3,3-pentafluoroisopropenyl fluoromethyl ether] ($C_4H_2F_6O$ ✧ 179.97). ~~Do not dry. After opening ampul, store in a tightly closed container. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sevoflurane Related Compound B RS [1,1,1,3,3,3-hexafluoro-2-methoxy-propane]. ~~Do not dry. After opening the ampul, store the material in a tightly closed container. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sevoflurane Related Compound C RS [1,1,1,3,3,3-hexafluoro-2-propanol]. ~~Do not dry. After opening the ampul, store the material in a tightly closed container. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sevomethyl Ether RS [1,1,1,3,3,3-hexafluoro-2-methoxy-propane]. ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Silver Sulfadiazine RS. ~~Dry portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Silydianin RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in freezer.~~

■■1S (*USP30*)

Change to read:

USP Simethicone RS. ~~Mix well before using. Keep container tightly closed. After opening, store under inert gas.~~

■■1S (*USP30*)

Change to read:

USP Simvastatin RS. ~~Do not dry before using. Keep container tightly closed, protected from light, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Sisomicin Sulfate RS. ~~Do not dry.~~ *[~~Caution: Hygroscopic.~~]* ~~Correct for volatiles content as determined by heating a separate 100-mg portion at 110° at a pressure of 5 mm of mercury or less for 3 hours. Keep container tightly closed, protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP β-Sitosterol RS. ~~Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Sodium Ascorbate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sodium Butyrate RS. ~~Do not dry before using. Keep container tightly closed. This material is hygroscopic.~~

■■1S (*USP30*)

Change to read:

USP Sodium Fluoride RS. ~~Do not dry.~~ *USP24* ~~Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sodium Lactate RS. ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sodium Nitroprusside RS. ~~This is the dihydrate form. Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sodium Propionate RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

■**USP Sodium Starch Glycolate Type A RS.** ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)
■1S (*USP29*)

Change to read:

■**USP Sodium Starch Glycolate Type B RS.** ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)
■1S (*USP29*)

Change to read:

USP Sodium Stearyl Fumarate RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Somatropin RS. ~~Store in a tight container in a freezer. When reconstituted, store in a cold place, and use within 24 hours.~~

■■1S (*USP30*)

Change to read:

USP 1,4-Sorbitan RS ($C_6H_{12}O_5$ ✧ 164.16). ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sorbitol RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sotalol Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sotalol Hydrochloride Related Compound A RS [*N***-[4-[[(1-methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride]** ($C_{12}H_{18}N_2O_3S \cdot HCl$ ✧ 306.81). ~~Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sotalol Hydrochloride Related Compound B RS [*N***-(4-formylphenyl)methanesulfonamide]** ($C_8H_9NO_3S$ ✧ 199.23). ~~Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Sotalol Hydrochloride Related Compound C RS **[***N*-[4-[2-[(1-methylethyl)amino]ethyl]phenyl]methanesulfonamide monohydrochloride**]** ($C_{12}H_{20}N_2O_2S \cdot HCl$ ✧ 292.83).~~—Do not dry. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Spectinomycin Hydrochloride RS.~~—This is the pentahydrate form of Spectinomycin Hydrochloride. Do not dry before using. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Spironolactone RS.~~—Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Squalane RS.~~—Do not dry before using. After opening ampul, transfer the contents to a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Stanozolol RS.~~—Dry portion at a pressure not exceeding 5 mm of mercury at 100° to constant weight before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Stavudine RS.~~—★Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.▲*USP29*~~

■■1S (*USP30*)

Change to read:

USP Stavudine System Suitability Mixture RS.—It is a mixture of stavudine and the following related compounds: thymidine, thymine, alpha-stavudine, and *xylo*-thymidine. ~~★Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.▲*USP29*~~

■■1S (*USP30*)

Change to read:

USP Stearic Acid RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Stearyl Alcohol RS.~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Stearoyl Polyoxylglycerides RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Streptomycin Sulfate RS.~~—Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Succinylcholine Chloride RS.~~—Do not dry; determine the water content potentiometrically at time of use for quantitative analyses. Keep container tightly closed. Store in a desiccator.~~

■■1S (*USP30*)

Change to read:

USP Succinylmonocholine Chloride RS.~~—Dry portion in vacuum at 55° for 16 hours. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sucralose RS.~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sucrose RS.~~—Do not dry before use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sufentanil Citrate RS.~~—Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Sulbactam RS. ~~Do not dry before using. Keep container tightly closed, and store in a freezer.~~

■ ■1S (*USP30*)

Change to read:

USP Sulconazole Nitrate RS. ~~Dry portion in vacuum at 80° for 3 hours before using. Keep container tightly closed.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfabenzamide RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfacetamide RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfacetamide Sodium RS. ~~Determine the water content titrimetrically at time of use. This material is very hygroscopic. Store over silica gel. Keep container tightly closed. Protect from light. Store in a cool place.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfachlorpyridazine RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfadiazine RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfadimethoxine RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfadoxine RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfamerazine RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfamethazine RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfamethizole RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfamethoxazole RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfamethoxazole N_4-Glucoside RS. ~~Do not dry; use as is. Keep container tightly closed. Protect from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfanilamide RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfanilamide Melting Point RS. ~~Dry portion over silica gel for 16 hours before using. The melting range is the temperature range within which the substance coalesces and is completely melted when tested by the USP capillary tube method. Keep container tightly closed and protected from light.~~

■ ■1S (*USP30*)

Change to read:

USP Sulfanilic Acid RS ($C_6H_7NO_3S$ ✧ 173.19).~~— Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sulfapyridine RS.~~— Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sulfapyridine Melting Point RS.~~— Dry portion over silica gel for 16 hours before using. When melted by the USP capillary tube method, *Class Ia* in the general chapter *Melting Range or Temperature* ⟨741⟩, the observed range falls within the indicated acceptance range. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sulfaquinoxaline Related Compound A RS [*N*^{1}-*N*^{2}-diquinoxalin-2-ylsulfanilamide**]** ($C_{22}H_{16}N_6SO_2$ ✧ 428.50).~~—★Do not dry. Keep container tightly closed. Protect from light.★*USP30*~~

■■1S (*USP30*)

Change to read:

USP Sulfasalazine RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sulfathiazole RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sulfinpyrazone RS.~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sulfisoxazole RS.~~— Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sulfisoxazole Acetyl RS.~~— Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Sulindac RS.~~— Dry portion in vacuum at 100° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Sumatriptan RS.~~— Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sumatriptan Succinate RS [1*H*-indole-5-methanesulfonamide, 3-[2-(dimethylamino)ethyl]-*N*-methyl-, butanedioate (1 : 1)**]** ($C_{14}H_{21}N_3O_2S \cdot C_4H_6O_4$ ✧ 413.49).~~— Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sumatriptan Succinate Related Compound A RS [[3-[2-(dimethylamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl]-methyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide succinate salt**]** ($C_{27}H_{37}N_5O_2S \cdot C_4H_6O_4$✧ 613.77).~~— Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Sumatriptan Succinate Related Impurities RS [Mixture of sumatriptan succinate, [3-[2-(methylamino)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide maleate salt, sumatriptan succinate related compound C, [3-[2-(dimethylamino-*N*-oxide)ethyl]-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide, and [3-[2-(aminoethyl)-1*H*-indol-5-yl]-*N*-methylmethanesulfonamide**]**~~—★Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.★*USP30*~~

■■1S (*USP30*)

Change to read:

USP Suprofen RS.~~— Dry portion in vacuum at 70° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Tacrine Hydrochloride RS. ~~Do not dry. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Store at room temperature. Protect from light.~~

■■1S (*USP30*)

Change to read:

■**USP Tagatose RS.** ~~Dry at 102° for 2 hours before using.~~

■■1S (*USP30*)
■1S (*USP29*)

Change to read:

USP Tamoxifen Citrate RS. ~~Do not dry. Store in a refrigerator. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Taurine RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Temazepam RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Terazosin Hydrochloride RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Terazosin Related Compound A RS **[**1-(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride**]** ($C_{14}H_{19}N_5O_2 \cdot 2HCl$ ✧ 362.25). ~~Do not dry. Keep container tightly closed. Protect from light. Store with desiccant in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Terazosin Related Compound B RS **[**1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl))-4-[(tetrahydro-2-furanyl)carbonyl]piperazine**]** ($C_{19}H_{24}N_4O_5$ ✧ 388.42). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Terazosin Related Compound C RS **[**1,4-bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine, dihydrochloride**]** ($C_{24}H_{28}N_8O_4 \cdot 2HCl$ ✧ 565.45). ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Terbutaline Sulfate RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light, and store at controlled room temperature.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Terconazole RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Terpin Hydrate RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Testolactone RS. ~~Dry portion in vacuum at 100° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Testosterone RS. ~~Dry portion in vacuum over phosphorus pentoxide for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Testosterone Cypionate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Testosterone Enanthate RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place. Allow to equilibrate to room temperature before opening vial.~~

■■1S (*USP30*)

Change to read:

USP Testosterone Propionate RS. ~~Dry portion in vacuum over silica gel for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tetracaine Hydrochloride RS. ~~Dry portion in vacuum over phosphorus pentoxide for 18 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tetracycline Hydrochloride RS. ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Δ^8-Tetrahydrocannabinol RS. ~~Store in a refrigerator, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Δ^9-Tetrahydrocannabinol RS. ~~Store in a refrigerator, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Tetrahydrozoline Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Thalidomide RS. ~~Dry portion in vacuum at 60° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Theophylline RS. ~~This material is the anhydrous form of theophylline. Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Thiabendazole RS. ~~Dry portion in vacuum at 100° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Thiamine Hydrochloride RS. ~~Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Thiethylperazine Maleate RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Thimerosal RS. ~~Dry portion in vacuum over phosphorus pentoxide to constant weight before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Thioguanine RS. ~~Dry in vacuum at 105° for 5 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Thiopental RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Thioridazine RS. ~~Dry portion in vacuum at 50° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Thioridazine Hydrochloride RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Thiostrepton RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Thiotepa RS. ~~Dry over silica gel for 24 hours before using. Keep container tightly closed. Protect from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Thiothixene RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP (*E*)-Thiothixene RS. ~~Dry portion in vacuum at 100° for 3 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP L-Threonine RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tiagabine Hydrochloride RS. ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Tiagabine Related Compound A RS **[**(*R*)-ethyl 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate**]** ($C_{22}H_{29}NO_2S_2 \cdot HCl$ ✧ 440.0). ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Racemic Tiagabine Hydrochloride Mixture RS **[**(*S*)-(+), (*R*)-(–)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid, hydrochloride**]** ($C_{20}H_{25}NO_2S_2 \cdot HCl$ ✧ 412.0). ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Tiamulin Fumarate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tiamulin Related Compound A RS **[**tosyl pleuromutilin**]**. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Ticarcillin Monosodium Monohydrate RS ($C_{15}H_{15}N_2NaO_6S_2 \cdot H_2O$ ✧ 424.43). ~~Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Tiletamine Hydrochloride RS. ~~Dry at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tilmicosin RS. ~~★Allow vial to reach room temperature before opening. Open and allow to equilibrate for 30 minutes with ambient humidity before weighing for analysis. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light. Store in a refrigerator.★*USP29*~~

■■1S (*USP30*)

Change to read:

USP Timolol Maleate RS. ~~Dry portion in vacuum at 100° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Add the following:

■**USP Tin RS**—[To come.]■1S (*USP30*)

In-Process Revision

Change to read:

USP Tinidazole RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Tinidazole Related Compound A RS [(2-methyl-5-nitroimidazole**]** ($C_4H_5N_3O_2$ ✧ 127.10). ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Tinidazole Related Compound B RS [1-(2-ethyl-sulfonyl-ethyl)-2-methyl-4-nitroimidazole] ($C_8H_{13}N_3O_4S$ ✧ 247.28). ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Tioconazole RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tioconazole Related Compound A RS [1-[2,4-dichloro-β-[(3-thenyl)-oxy]phenethyl]imidazole hydrochloride**]** ($C_{16}H_{14}Cl_2N_2OS \cdot HCl$ ✧ 389.73). ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tioconazole Related Compound B RS [1-[2,4-dichloro-β-[(2,5-dichloro-3-thenyl)oxy]phenethyl]imidazole hydrochloride**]** ($C_{16}H_{12}Cl_4N_2OS \cdot HCl$ ✧ 458.62). ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tioconazole Related Compound C RS [1-[2,4-dichloro-β-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole hydrochloride**]** ($C_{16}H_{13}BrCl_2N_2OS \cdot HCl$ ✧ 468.63). ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tobramycin RS. ~~★Do not dry. Store in a refrigerator. The material is hygroscopic.★*USP29*~~

■■1S (*USP30*)

Change to read:

USP Tocainide Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Alpha Tocopherol RS. ~~Do not dry before using. Keep container tightly closed and protected from light. After opening ampul, without delay withdraw specimen, and store ampul with remaining portion under an inert gas atmosphere in a tightly closed container and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Alpha Tocopheryl Acetate RS. ~~Do not dry before using. Keep container tightly closed and protected from light. After opening ampul, without delay withdraw specimen, and store ampul with remaining portion under a nitrogen atmosphere.~~

■■1S (*USP30*)

Change to read:

USP Alpha Tocopheryl Acid Succinate RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tolazamide RS. ~~Dry portion at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tolazoline Hydrochloride RS. ~~Dry portion in vacuum over silica gel for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tolbutamide RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tolcapone RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Tolcapone Related Compound A RS [4*N*-methyl-3,4-dihydroxybenzophenone] ($C_{14}H_{12}O_3$ ✧ 228.24).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tolcapone Related Compound B RS [4-hydroxy-3-methoxy-4′-methyl-5-nitrobenzophenone] ($C_{15}H_{13}NO_5$ ✧ 287.27).~~—Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tolmetin Sodium RS.~~—Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tolnaftate RS.~~—Dry portion in vacuum at 65° for 3 hours before using. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP *o*-Toluenesulfonamide RS ($C_7H_9NO_2S$ ✧ 171.22).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP *p*-Toluenesulfonamide RS ($C_7H_9NO_2S$ ✧ 171.22).~~—Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

■**USP Topiramate RS.**~~—Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Topiramate Related Compound A RS** [2,3 : 4,5-bis-*O*-(1-methylethylidene)-*β*-D-fructopyranose] ($C_{12}H_{20}O_6$ ✧ 260.28).~~—Preserve in tight, light resistant containers between 2° and 8°.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Torsemide RS (Form 1).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Torsemide Related Compound A RS [4-[(3-methylphenyl)amino]-3-pyridinesulfonamide] ($C_{12}H_{13}N_3O_2S$ ✧ 263.32).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Torsemide Related Compound B RS [*N*-[(*n*-butylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide] ($C_{17}H_{22}N_4O_3S$ ✧ 362.45).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Torsemide Related Compound C RS [*N*-[(ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide] ($C_{15}H_{18}N_4O_3S$ ✧ 334.39).~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Transplatin RS.~~—Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Trazodone Hydrochloride RS.~~—Dry portion at a pressure of about 50 mm of mercury at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Trenbolone RS.— ★~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~ ▲~~*USP29*~~

■■1S (*USP30*)

Change to read:

USP Trenbolone Acetate RS.— ★~~Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.~~ ▲~~*USP29*~~

■■1S (*USP30*)

Change to read:

USP Tretinoin RS.— ~~Do not dry before using. Store in a freezer, protected from light, allow to reach room temperature before opening, and use the contents promptly after opening.~~

■■1S (*USP30*)

Change to read:

USP Triacetin RS.— ~~Do not dry before using. After opening ampul, store in a tightly closed container. Avoid contact with metal.~~

■■1S (*USP30*)

Change to read:

USP Triamcinolone RS.— ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed. This material is hygroscopic. Protect accordingly.~~

■■1S (*USP30*)

Change to read:

USP Triamcinolone Acetonide RS.— ~~Do not dry. For quantitative applications, determine the water content titrimetrically. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Triamcinolone Diacetate RS.— ~~Dry portion in vacuum at 60° for 4 hours before using. [NOTE— Dried material is hygroscopic.] Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Triamcinolone Hexacetonide RS.— ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Triamterene RS.— ~~Dry portion in vacuum at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Triazolam RS.— ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tributyl Citrate RS.— ~~Do not dry before using. After opening the ampul, keep the material in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Trichlormethiazide RS.— ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Triclosan RS.— ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Trientine Hydrochloride RS.— ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 40° for 4 hours before using. Keep container tightly closed. Protect from light, and store under an inert gas in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Triethyl Citrate RS.— ~~Do not dry before using. After opening the ampul, keep the material in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Trifluoperazine Hydrochloride RS.— ~~Dry portion in vacuum at 60° for 4 hours before using.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Triflupromazine Hydrochloride RS. ~~Dry portion at 100° for 2 hours before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Trifluridine RS. ~~Dry portion in vacuum at 105° for 4 hours before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Trifluridine Related Compound A RS [5-carboxy-2′-deoxyuridine] ($C_{10}H_{12}N_2O_7$ ✧ 272.22). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Trihexyphenidyl Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Trimeprazine Tartrate RS. ~~Dry portion in vacuum at 60° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Trimethobenzamide Hydrochloride RS. ~~Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Trimethoprim RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Trioxsalen RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Tripelennamine Hydrochloride RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Triprolidine Hydrochloride RS. ~~Do not dry; determine the water content titrimetrically at the time of use for quantitative analyses. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Triprolidine Hydrochloride Z-isomer RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Trisalicylic Acid RS ($C_{21}H_{14}O_7$ ✧ 378.34). ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

■**USP Trolamine RS.** ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Troleandomycin RS. ~~Dry portion in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours before using. Keep container tightly closed, protected from light, and store in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Tromethamine RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tropicamide RS. ~~Dry portion in vacuum over phosphorus pentoxide at 80° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

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Change to read:

USP Trypsin Crystallized RS. ~~Allow container to reach room temperature before opening, and do not dry before using. Determine the loss on drying on a separate portion in vacuum at 60° for 4 hours. Keep container tightly closed, protected from light and heat, and store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP L-Tryptophan RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Tubocurarine Chloride RS. ~~Do not dry. Keep container tightly closed. Use as directed on the label.~~

■■1S (*USP30*)

Change to read:

■**USP Tylosin Tartrate RS.** ~~Dry portion in vacuum at 60° for 3 hours before using.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Tyloxapol RS. ~~Do not dry before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP L-Tyrosine RS. ~~Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Ubidecarenone RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Ubidecarenone for System Suitability RS. ~~Do not dry. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Undecylenic Acid RS. ~~Do not dry. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Uracil Arabinoside RS. ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Urea RS. ~~Do not dry.~~

■■1S (*USP30*)

Change to read:

USP Ursodiol RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Valerenic Acid RS. ~~Do not dry before using. Keep container tightly closed. Store in a freezer.~~

■■1S (*USP30*)

Add the following:

■**USP Valganciclovir Hydrochloride RS.**■1S (*USP30*)

Change to read:

USP L-Valine RS. ~~Dry portion at 105° for 3 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Valproic Acid RS. ~~Do not dry. After opening ampul, store in a tightly closed container.~~

■■1S (*USP30*)

Change to read:

USP Valproic Acid Related Compound A RS [diallylacetic acid**]** ($C_8H_{12}O_2$ ✧ 140.18). ~~*[WARNING! Reproductive Hazard, Causes Irritation.]* Do not dry. After opening, store in a tightly closed container. Avoid contact. Store in a refrigerator.~~

■■1S (*USP30*)

In-Process Revision

Change to read:

USP Valrubicin RS. ~~Dry in vacuum over phosphorus pentoxide at 80° for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

USP Valrubicin Related Compound A RS **[***N*-trifluoroacetyl-14-bromodaunorubicin-13,13-dimethylketal**].** ~~Dry in vacuum over phosphorus pentoxide at 80° for 4 hours before using.~~

■■1S (*USP30*)

Change to read:

■**USP Valsartan RS.** ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Valsartan Related Compound A RS** ~~**[**(*R*) *N*-([2′-1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl)valine**]**~~**[**(*R*-*N*-valeryl-*N*-([2′-(1*H*-tetrazole-5-yl)biphen-4-yl]methyl)valine**]** ($C_{24}H_{29}N_5O_3$ ✧ ~~435.53~~ 435.52). ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Valsartan Related Compound B RS** **[**(*S*-*N*-butyryl-*N*-([2′-(1*H*-tetrazole-5-yl)biphen-4-yl]methyl)-valine**]** ($C_{23}H_{27}N_5O_{>3}$ ✧ ~~421.50~~ 421.49). ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

■**USP Valsartan Related Compound C RS** **[**(*S*-*N*-valeryl-*N*-([2′-(1*H*-tetrazole-5-yl)biphen-4-yl]methyl)-valine benzyl ester**]** ($C_{31}H_{35}N_5O_3$ ✧ ~~526.65~~ 525.64). ~~Do not dry.~~

■■1S (*USP30*)
■2S (*USP29*)

Change to read:

USP Vancomycin Hydrochloride RS. ~~Do not dry. Constitute the entire contents, without weighing, and rinsing as necessary, for assay. Keep unopened containers tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Vanillin RS. ~~Dry portion over silica gel for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Vanillin Melting Point RS. ~~Do not dry. When melted by the USP capillary tube method, *Class Ia* in the general chapter *Melting Range or Temperature* ⟨741⟩, the observed range falls within the indicated acceptance range. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Vecuronium Bromide RS. ~~Dry portion in vacuum over phosphorus pentoxide for 3 hours before using. The material is very hygroscopic. Weigh under controlled humidity conditions less than 10% relative humidity. Keep container tightly closed. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Verapamil Hydrochloride RS. ~~Dry portion at 105° for 2 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Verapamil Related Compound A RS **[**3,4-dimethoxy-α-[3-(methylamino)propyl]-α-(1-methylethyl)-benzeneacetonitrile monohydrochloride**]** ($C_{17}H_{26}N_2O_2 \cdot HCl$ ✧ 326.87). ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Verapamil Related Compound B RS **[**benzeneacetonitrile, α-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-α-(1-methylethyl)-, monohydrochloride**]** ($C_{26}H_{36}N_2O_4 \cdot HCl$ ✧ 477.05). ~~Do not dry before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Add the following:

■**USP Verapamil Related Compound D RS**—[To come.]■1S (*USP30*)

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Change to read:

USP Verteporfin RS ($C_{41}H_{42}N_4O_8$ ✧ 718.79). ~~This is a mixture of *23H,25H* benzo[*b*]porphine 9,13 dipropanoic acid, 18 ethenyl 4,4a dihydro 3,4 bis(methoxycarbonyl) 4a,8,14,19 tetramethyl, 9 methyl ester, *trans* (±) and *23H,25H* benzo[*b*]porphine 9,13 dipropanoic acid, 18 ethenyl 4,4a dihydro 3,4 bis(methoxycarbonyl) 4a,8,14,19 tetramethyl , 13 methyl ester, *trans* (±). Determine the water content titrimetrically at the time of use. Preserve in tight containers, and store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Verteporfin Related Compound A RS [*trans*-(±)-18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropionic acid**]** ($C_{40}H_{40}N_4O_8$ ✧ 704.77). ~~Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Vidarabine RS. ~~This is the monohydrate form of Vidarabine. Do not dry before using. Keep container tightly closed. Protect from light. Store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Vinblastine Sulfate RS. ~~Equilibrate to ambient temperature before opening. After opening ampul, allow the contents to equilibrate for 30 minutes with the ambient humidity before weighing for analyses. Using thermogravimetric analysis, heat a separate equilibrated 10-mg portion at 5° per minute between ambient temperature and 200° under nitrogen flowing at 40 mL per minute (see *Thermal Analysis* ⟨891⟩). From the thermogram, determine the accumulated loss in weight between ambient temperature and a point on the plateau before decomposition is indicated (at about 160°). Keep the containers tightly closed and protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Vincristine Sulfate RS. ~~Store unopened ampul in a cold place. After opening ampul, allow the contents to equilibrate for 30 minutes with the ambient humidity before weighing for analysis. Using thermogravimetric analysis, heat a separate equilibrated 10-mg portion at 5° per minute between ambient temperature and 200° under nitrogen flowing at 40 mL per minute. From the thermogram, determine the accumulated loss in weight between ambient temperature and a point on the plateau before decomposition is indicated (at about 160°). Keep the containers tightly closed and protected from light, and store in a cold place.~~

■■1S (*USP30*)

Change to read:

USP Vinorelbine Related Compound A RS [4-*O*-deacetylvinorelbine**]** ($C_{43}H_{52}N_4O_7 \cdot 2C_4H_6O_6$ ✧ 1037.07). ~~Do not dry. Keep under inert gas with container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Change to read:

USP Vinorelbine Tartrate RS. ~~Do not dry. Keep under inert gas with container tightly closed. Protect from light. Store in a freezer.~~

■■1S (*USP30*)

Add the following:

■**USP Vinyl Acetate RS.**■1S (*USP30*)

Change to read:

USP Vitamin A RS. ~~To use, snip off end of the capsule, expel and weigh the solution. Discard the unused portion after opening individual capsules. Keep container tightly closed, and store in a cool, dry place, or in a refrigerator, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Vitamin D Assay System Suitability RS. ~~Do not dry. Allow it to attain room temperature before opening ampul. Transfer unused contents of ampul to a tightly closed container, and store under nitrogen in the dark, in a cool place.~~

■■1S (*USP30*)

Change to read:

USP Vitexin RS. ~~Do not dry. Keep container tightly closed. Protect from light. Store in a cold, dry place.~~

■■1S (*USP30*)

Change to read:

USP Warfarin RS. ~~This is the acid form of Warfarin. Dry portion in vacuum over phosphorus pentoxide for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Warfarin Related Compound A RS [3-(*o*-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one**]** ($C_{18}H_{16}O_2$ ✧ 264.33). ~~Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

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Change to read:

USP Xanthanoic Acid RS ($C_{14}H_{10}O_3$ ✧ 226.23).~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Xanthone RS ($C_{13}H_8O_2$ ✧ 196.21).~~—Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Xylazine RS.~~—Dry portion at 60° in vacuum for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Xylazine Hydrochloride RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Xylitol RS.~~—Do not dry. Determine the water content titrimetrically at the time of use. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Xylometazoline Hydrochloride RS.~~—Dry portion at 105° for 4 hours before using. Keep container tightly closed. Protect from light.~~

■■1S (*USP30*)

Change to read:

USP Xylose RS.~~—Dry portion in vacuum at 60° to constant weight before using. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Yohimbine Hydrochloride RS.~~—Dry portion at 105° for 2 hours before using. For quantitative applications, use a value of 0.991 mg yohimbine hydrochloride per each mg of this material. Keep container tightly closed.~~

■■1S (*USP30*)

Change to read:

USP Zalcitabine RS.~~—Do not dry. Keep container tightly closed, protected from light.~~

■■1S (*USP30*)

Change to read:

USP Zidovudine RS.~~—Do not dry. Keep container tightly closed and protected from light. Store in a refrigerator.~~

■■1S (*USP30*)

Change to read:

USP Zidovudine Related Compound B RS [3′-chloro-3′-deoxythymidine**]** ($C_{10}H_{13}ClN_2O_4$ ✧ 260.68).~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Zidovudine Related Compound C RS [thymine**]** ($C_5H_6N_2O_2$ ✧ 126.12).~~—Do not dry before using. Keep container tightly closed and protected from light.~~

■■1S (*USP30*)

Change to read:

USP Zileuton RS.~~—Do not dry. Keep container tightly closed. Store at room temperature under nitrogen. Protect from light.~~

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

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

■■1S (*USP30*)

Change to read:

USP Zolazepam Hydrochloride RS. ~~— Do not dry. Keep container tightly closed.~~

■■1S (*USP30*)

Apparatus for Tests and Assays

BRIEFING

〈**41**〉 **Weights and Balances,** *USP 29* page 2499. On the basis of comments received, the Expert Committee for General Chapters is canceling the previous proposal for this general chapter published on page 508 of *PF* 31(2) [Mar.–Apr. 2005]. The following new version is proposed for public comment. In this draft, uncertainty is determined through repeatability and accuracy.

(GC: H. Pappa) RTS—42800-1

Change to read:

INTRODUCTION

~~The intent of this section is to bring the requirements for weights into conformity with American National Standard ANSI/ASTM E617, "Laboratory Weights and Precision Mass Standards." This standard is incorporated by reference and should be consulted for full descriptions and information on the tolerances and construction of weights.[1]~~

■■1S (*USP30*)
Pharmacopeial tests and assays require balances that vary in capacity, sensitivity, and reproducibility.

■Measurement uncertainty from the balance is only one contributor to overall weighing errors. Other contributors to weighing errors include changes in water content of samples during weighing and errors due to a static charge on the sample. This chapter addresses the control of the analytical balance for routine operation.■1S (*USP30*)
Unless otherwise specified, when substances are to be "accurately weighed" for *Assay,* the weighing is to be performed with a weighing device whose measurement uncertainty ~~(random plus systematic error)~~

■■1S (*USP30*)
does not exceed 0.1% of the reading. ~~Measurement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the amount weighed, does not exceed 0.001. Unless otherwise specified, for titrimetric limits tests, the weighing shall be performed to provide the number of significant figures in the weight of the analyte that corresponds to the number of significant figures in the concentration of the titrant.~~

■Assessment of measurement uncertainty is typically done prior to the balance being placed in operation (e.g., during IQ/OQ/PQ) and periodically thereafter. Two steps are performed in measuring uncertainty: (1) measurement of repeatability and (2) verification of accuracy against certified weights.

Repeatability

Assessment of repeatability may be performed with either *Method A* or *Method B*.

Method A—In this method repeatability is determined at the lower end of the desired operating range (i.e., the range of weights for which the balance has been qualified to meet the requirements of this chapter). The measurement of repeatability using this method is satisfactory if two times the standard deviation of not less than 10 replicate weighings divided by the amount weighed does not exceed 0.001:

$$2s/w < 0.001$$

in which s is the standard deviation of not less than 10 replicate weighings; and w is the nominal mass, in mg, of the weight used.

~~[1] Copies of ASTM Standard E 617-81 (Reapproved 1985) may be obtained from the American Society for Testing and Materials, 1916 Race Street, Philadelphia, PA 19103.~~

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Method B—This method may be used to determine the low end of the operating range (e.g., minimum weight). Minimum weight can be derived from the following formula:*

$$(2/U_{rel})s$$

in which U_{rel} represents the uncertainty factor of 0.001; and s is the standard deviation, in mg, of not less than 10 replicate measurements of a mass near the low end of the operating range. Due to scale resolution, it is possible to make measurements with every measurement resulting in the same value. A true scale standard deviation of zero is not statistically possible, though the standard deviation may be less than one display increment d. In this situation, the standard deviation of the scale can be estimated as:

$$s = \frac{d}{\sqrt{3}} = 0.577d$$

Verification of Accuracy

Using multiple weights of suitable accuracy as described in the table *Weights Used for Calibration Check of Balances,* the measured weight is within 0.1% of the certified value over the operating range of the balance. The operating range refers to the range used for performing the assay, and not necessarily the operating range for other weighing operations.

Weights Used for Calibration Check of Balances

Application	Appropriate Class of Weight	Lowest Weight with a Tolerance Within 0.1%*
Calibration of the weights used for other applications or other specialized applications	OIML Classes E1, E2, and ASTM Class 0 (Note: Special control of humidity and temperature is needed.)	OIML E1, 5 mg OIML E2, 10 mg ASTM Class 0, 5 mg
Routine analytical work using microbalances	ASTM Classes 1, 2	ASTM Class 1, 10 mg ASTM Class 2, 20 mg
Routine analytical work using 4–5 place analytical balances	ASTM Classes 3, 4 OIML Classes F1, F2	ASTM Class 3, 50 mg ASTM Class 4, 100 mg OIML Class F1, 50 mg OIML Class F2, 200 mg

* ASTM standard E617 may be obtained from ASTM, 100 Barr Harbor Drive, West Conshohocken, PA 19428. OIML R111 may be obtained from OIML, 11 Rue Targot-75009, Paris, France.

■1S (*USP30*)

~~The class designations below are in order of increasing tolerances.~~

~~Class 1.1 weights are used for calibration of low capacity, high-sensitivity balances. They are available in various denominations from 1 to 500 mg. The tolerance for any denomination in this class is 5 µg. They are recommended for calibration of balances using optical or electrical methods for accurately weighing quantities below 20 mg.~~

~~Class 1 weights are designated as high precision standards for calibration. They may be used for weighing accurately quantities below 20 mg. (For weights of 10 g or less, the requirements of class 1 are met by *USP XXI* class M.)~~

~~Class 2 weights are used as working standards for calibration, built in weights for analytical balances, and laboratory weights for routine analytical work. (The requirements of class 2 are met by *USP XXI* class S.)[2]~~

~~Class 3 and class 4 weights are used with moderate precision laboratory balances. (Class 3 requirements are met by *USP XXI* class S-1; class 4 requirements are met by *USP XXI* class P.)[2]~~

~~A weight class is chosen so that the tolerance of the weights used does not exceed 0.1% of the amount weighed. Generally, class 2 may be used for quantities greater than 20 mg, class 3 for quantities of~~

* Derived from expanded uncertainty equation in NISTIR 6919, *Recommended Guide for Determining and Reporting Uncertainties for Balances and Scales, January 2002.*

~~[2] Note that the designations S and P no longer designate weight classes but rather weight grades, that is, design limitations such as range of density of materials, surface area, surface finish, corrosion resistance, and hardness.~~

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~~greater than 50 mg, and class 4 for quantities of greater than 100 mg. Weights should be calibrated periodically, preferably against an absolute standard weight.~~

■Daily or Time of Use Balance Checks

Analytical balances vary greatly in the features they offer to assure that the balance is maintained in a calibrated state. A calibration check to assure that the balance is in a calibrated state is performed each day or prior to each series of weighings. Typically, the calibration check uses internal or external weights to verify that the balance is still in a calibrated state.■1S (*USP30*)

Chemical Tests and Assays

OTHER TESTS AND ASSAYS

BRIEFING

⟨**311**⟩ **Alginates Assay,** *USP 29* page 2562. On the basis of comments received, it is proposed to revise the *System Suitability* section to revert to the acceptance range of 24.2% to 25.7% for carbon dioxide, the range in the assay that was previously official through *USP 27.* In addition, in the same section, it is proposed to clarify the requirements for the blank determination.

(EGC: C. Sheehan) RTS—44044-1

Change to read:

SYSTEM SUITABILITY

Using D-glucuronolactone as the standard, proceed as directed for *Procedure,* but do not perform preboiling steps. The system is suitable if the following criteria are met: (1) a blank determination results in a net titration value, *C,* between 0.02 and 0.06 mEq, ~~of 0.1 N hydrochloric acid,~~

■■1S (*USP30*)
calculated as follows:

$$A_b - B_b$$

in which A_b is the number of mEq of 0.25 N sodium hydroxide in the 25 mL used, and B_b is the number of mEq of 0.1 N hydrochloric acid used in the blank titration; and (2) the percentage of carbon dioxide, CO_2, obtained from the standard is between ~~24.7% and 25.3%.~~

■24.2% and 25.7%.■1S (*USP30*)

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1047**⟩ **Biotechnology-Derived Articles—Tests,** *USP 29* page 2858. This general information chapter contains the following six sections: *Amino Acid Analysis, Capillary Electrophoresis, Isoelectric Focusing, Peptide Mapping, Polyacrylamide Gel Electrophoresis,* and *Total Protein Assay.* The entire chapter is harmonized with the *Japanese* and *European Pharmacopoeias*. However, the other pharmacopeias divide the listed sections into separate general chapters. For the purpose of having a parallel organization of the harmonized documents, it is proposed to divide and replace the current chapter with the following six general information chapters: *Biotechnology-Derived Articles—Amino Acid Analysis* ⟨1052⟩*, Biotechnology-Derived Articles—Capillary Electrophoresis* ⟨1053⟩*, Biotechnology-Derived Articles—Isoelectric Focusing* ⟨1054⟩*, Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩*, Biotechnology-Derived Articles—Polyacrylamide Electrophoresis* ⟨1056⟩, and *Biotechnology-Derived Articles—Total Protein Assay* ⟨1057⟩. Interested parties are invited to submit comments.

(BB PP: I. DeVeau) RTS—43939-7

Delete the following:

■⟨~~1047~~⟩ ~~BIOTECHNOLOGY DERIVED ARTICLES—TESTS~~

~~The emergence of drug macromolecules obtained through biotechnological processes has led to a set of specialized tests and assays to determine quality, identity, purity, and potency of these articles in addition to the methods traditionally used for other drug products. These specialized tests that are presented below are *Amino Acid Analysis, Capillary Electrophoresis, Isoelectric Focusing, Peptide Mapping, Polyacrylamide Gel Electrophoresis,* and *Total Protein Assay*.~~

~~AMINO ACID ANALYSIS~~

~~Amino acid analysis refers to the methodology used to determine the amino acid composition or content of proteins, peptides, and other pharmaceutical preparations. Proteins and peptides are macromolecules consisting of covalently bonded amino acid residues organized as a linear polymer. The sequence of the amino acids in a protein or peptide determines the properties of the molecule. Proteins are con-~~

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sidered large molecules that commonly exist as folded structures with a specific conformation, while peptides are smaller and may consist of only a few amino acids. Amino acid analysis can be used to quantify protein and peptides, to determine the identity of proteins or peptides based on their amino acid composition, to support protein and peptide structure analysis, to evaluate fragmentation strategies for peptide mapping, and to detect atypical amino acids that might be present in a protein or peptide. It is necessary to hydrolyze a protein/peptide to its individual amino acid constituents before amino acid analysis. Following protein/peptide hydrolysis, the amino acid analysis procedure can be the same as that practiced for free amino acids in other pharmaceutical preparations. The amino acid constituents of the test sample are typically derivatized for analysis.

Apparatus

Methods used for amino acid analysis are usually based on a chromatographic separation of the amino acids present in the test sample. Current techniques take advantage of the automated chromatographic instrumentation designed for analytical methodologies. An amino acid analysis instrument will typically be a low-pressure or high-pressure liquid chromatograph capable of generating mobile phase gradients that separate the amino acid analytes on a chromatographic column. The instrument must have postcolumn derivatization capability, unless the sample is analyzed using precolumn derivatization. The detector is usually a UV-visible or fluorescence detector depending on the derivatization method used. A recording device (e.g., integrator) is used for transforming the analog signal from the detector and for quantitation. It is preferred that instrumentation be dedicated particularly for amino acid analysis.

General Precautions

Background contamination is always a concern for the analyst in performing amino acid analysis. High purity reagents are necessary (e.g., low purity hydrochloric acid can contribute to glycine contamination). Analytical reagents are changed routinely every few weeks using only high pressure liquid chromatography (HPLC) grade solvents. Potential microbial contamination and foreign material that might be present in the solvents are reduced by filtering solvents before use, keeping solvent reservoirs covered, and not placing amino acid analysis instrumentation in direct sunlight.

Laboratory practices can determine the quality of the amino acid analysis. Place the instrumentation in a low traffic area of the laboratory. Keep the laboratory clean. Clean and calibrate pipets according to a maintenance schedule. Keep pipet tips in a covered box; the analysts may not handle pipet tips with their hands. The analysts may wear powder free latex or equivalent gloves. Limit the number of times a test sample vial is opened and closed because dust can contribute to elevated levels of glycine, serine, and alanine.

A well-maintained instrument is necessary for acceptable amino acid analysis results. If the instrument is used on a routine basis, it is to be checked daily for leaks, detector and lamp stability, and the ability of the column to maintain resolution of the individual amino acids. Clean or replace all instrument filters and other maintenance items on a routine schedule.

Reference Standard Material

Acceptable amino acid standards are commercially available[*] for amino acid analysis and typically consist of an aqueous mixture of amino acids. When determining amino acid composition, protein or peptide standards are analyzed with the test material as a control to demonstrate the integrity of the entire procedure. Highly purified bovine serum albumin has been used as a protein standard for this purpose.

[*] Suitable standards are available from NIST (Gaithersburg, MD), Beckman Instruments (Fullerton, CA), Sigma Chemical (St. Louis, MO), Pierce (Rockford, IL), or Hewlett Packard.

Calibration of Instrumentation

Calibration of amino acid analysis instrumentation typically involves analyzing the amino acid standard, which consists of a mixture of amino acids at a number of concentrations, to determine the response factor and range of analysis for each amino acid. The concentration of each amino acid in the standard is known. In the calibration procedure, the analyst dilutes the amino acid standard to several different analyte levels within the expected linear range of the amino acid analysis technique. Then, replicates at each of the different analyte levels can be analyzed. Peak areas obtained for each amino acid are plotted versus the known concentration for each of the amino acids in the standard dilution. These results will allow the analyst to determine the range of amino acid concentrations where the peak area of a given amino acid is an approximately linear function of the amino acid concentration. It is important that the analyst prepare the samples for amino acid analysis so that they are within the analytical limits (e.g., linear working range) of the technique employed in order to obtain accurate and repeatable results.

Four to six amino acid standard levels are analyzed to determine a response factor for each amino acid. The response factor is calculated as the average peak area or peak height per nmol of amino acid present in the standard. A calibration file consisting of the response factor for each amino acid is prepared and is used to calculate the concentration of each amino acid present in the test sample. This calculation involves dividing the peak area corresponding to a given amino acid by the response factor for that amino acid to give the nmol of the amino acid. For routine analysis, a single-point calibration may be sufficient; however, the calibration file is updated frequently and tested by the analysis of analytical controls to ensure its integrity.

Repeatability

Consistent high quality amino acid analysis results from an analytical laboratory require attention to the repeatability of the assay. During analysis of the chromatographic separation of the amino acids or their derivatives, numerous peaks can be observed on the chromatogram that corresponds to the amino acids. The large number of peaks makes it necessary to have an amino acid analysis system that can repeatedly identify the peaks based on retention time and integrate the peak areas for quantitation. A typical repeatability evaluation involves preparing a standard amino acid solution and analyzing many replicates (i.e., six analyses or more) of the same standard solution. The relative standard deviation (RSD) is determined for the retention time and integrated peak area of each amino acid. An evaluation of the repeatability is expanded to include multiple assays conducted over several days by different analysts. Multiple assays include the preparation of standard dilutions from starting materials to determine the variation due to sample handling. Often, the amino acid composition of a standard protein (e.g., bovine serum albumin) is analyzed as part of the repeatability evaluation. By evaluating the replicate variation (i.e., RSD), the laboratory can establish analytical limits to ensure that the analyses from the laboratory are under control. It is desirable to establish the lowest practical variation limits to ensure the best results. Areas to focus on to lower the variability of the amino acid analysis include sample preparation, high background spectral interference due to quality of reagents and/or laboratory practices, instrument performance and maintenance, data analysis and interpretation, and analyst performance and habits. All parameters involved are fully investigated in the scope of the validation work.

Sample Preparation

Accurate results from amino acid analysis require purified protein and peptide samples. Buffer components (e.g., salts, urea, detergents) can interfere with the amino acid analysis and are removed from the sample before analysis. Methods that utilize postcolumn derivatization of the amino acids are generally not affected by buffer components to the extent seen with precolumn derivatization methods. It is desirable to limit the number of sample manipulations to reduce potential background contamination, to improve analyte recovery, and to reduce labor. Common techniques used to remove buffer components from protein samples include the following methods: (1) injecting the protein sample onto a reverse-phase HPLC system, removing

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the protein with a volatile solvent containing a sufficient organic component, and drying the sample in a vacuum centrifuge; (2) dialysis against a volatile buffer or water; (3) centrifugal ultrafiltration for buffer replacement with a volatile buffer or water; (4) precipitating the protein from the buffer using an organic solvent (e.g., acetone); and (5) gel filtration.

Internal Standards

It is recommended that an internal standard be used to monitor physical and chemical losses and variations during amino acid analysis. An accurately known amount of internal standard can be added to a protein solution prior to hydrolysis. The recovery of the internal standard gives the general recovery of the amino acids from the protein solution. Free amino acids, however, do not behave in the same way as protein-bound amino acids during hydrolysis because their rates of release or destruction are variable. Therefore, the use of an internal standard to correct for losses during hydrolysis may give unreliable results. It will be necessary to take this particular point into consideration when interpreting the results. Internal standards can also be added to the mixture of amino acids after hydrolysis to correct for differences in sample application and changes in reagent stability and flow rates. Ideally, an internal standard is an unnaturally occurring primary amino acid that is commercially available and inexpensive. It should also be stable during hydrolysis, its response factor should be linear with concentration, and it needs to elute with a unique retention time without overlapping other amino acids. Commonly used amino acid standards include norleucine, nitrotyrosine, and ⍺ aminobutyric acid.

Protein Hydrolysis

Hydrolysis of protein and peptide samples is necessary for amino acid analysis of these molecules. The glassware used for hydrolysis must be very clean to avoid erroneous results. Glove powders and fingerprints on hydrolysis tubes may cause contamination. To clean glass hydrolysis tubes, boil tubes for 1 hour in 1 N hydrochloric acid or soak tubes in concentrated nitric acid or in a mixture of concentrated hydrochloric acid and concentrated nitric acid (1 : 1). Clean hydrolysis tubes are rinsed with high purity water followed by a rinse with HPLC grade methanol, dried overnight in an oven, and stored covered until use. Alternatively, pyrolysis of clean glassware at 500° for 4 hours may also be used to eliminate contamination from hydrolysis tubes. Adequate disposable laboratory material can also be used.

Acid hydrolysis is the most common method for hydrolyzing a protein sample before amino acid analysis. The acid hydrolysis technique can contribute to the variation of the analysis due to complete or partial destruction of several amino acids. Tryptophan is destroyed; serine and threonine are partially destroyed; methionine might undergo oxidation; and cysteine is typically recovered as cystine (but cystine recovery is usually poor because of partial destruction or reduction to cysteine). Application of adequate vacuum (less than 200 µm of mercury or 26.7 Pa) or introduction of an inert gas (argon) in the headspace of the reaction vessel can reduce the level of oxidative destruction. In peptide bonds involving isoleucine and valine, the amido bonds of Ile-Ile, Val-Val, Ile-Val, and Val-Ile are partially cleaved; and asparagine and glutamine are deamidated, resulting in aspartic acid and glutamic acid, respectively. The loss of tryptophan, asparagine, and glutamine during an acid hydrolysis limits quantitation to 17 amino acids. Some of the hydrolysis techniques described are used to address these concerns. Some of the hydrolysis techniques described (i.e., *Methods 4–11*) may cause modifications to other amino acids. Therefore, the benefits of using a given hydrolysis technique are weighed against the concerns with the technique and are tested adequately before employing a method other than acid hydrolysis.

A time-course study (i.e., amino acid analysis at acid hydrolysis times of 24, 48, and 72 hours) is often employed to analyze the starting concentration of amino acids that are partially destroyed or slow to cleave. By plotting the observed concentration of labile amino acids (i.e., serine and threonine) versus hydrolysis time, the line can be extrapolated to the origin to determine the starting concentration of these amino acids. Time-course hydrolysis studies are also used with amino acids that are slow to cleave (e.g., isoleucine and valine). During the hydrolysis time course, the analyst will observe a plateau in these residues. The level of this plateau is taken as the residue concentration. If the hydrolysis time is too long, the residue concentration of the sample will begin to decrease, indicating destruction by the hydrolysis conditions.

An acceptable alternative to the time-course study is to subject an amino acid calibration standard to the same hydrolysis conditions as the test sample. The amino acid in free form may not completely represent the rate of destruction of labile amino acids within a peptide or protein during the hydrolysis. This is especially true for peptide bonds that are slow to cleave (e.g., Ile-Val bonds). However, this technique will allow the analyst to account for some residue destruction. Microwave acid hydrolysis has been used and is rapid but it requires special equipment as well as special precautions. The optimal conditions for microwave hydrolysis must be investigated for each individual protein/peptide sample. The microwave hydrolysis technique typically requires only a few minutes, but even a deviation of 1 minute may give inadequate results (e.g., incomplete hydrolysis or destruction of labile amino acids). Complete proteolysis, using a mixture of proteases, has been used but can be complicated, requires the proper controls, and is typically more applicable to peptides than proteins. [NOTE—During initial analyses of an unknown protein, experiments with various hydrolysis time and temperature conditions are conducted to determine the optimal conditions.]

METHOD 1

Acid hydrolysis using hydrochloric acid containing phenol is the most common procedure used for protein/peptide hydrolysis preceding amino acid analysis. The addition of phenol to the reaction prevents the halogenation of tyrosine.

Hydrolysis Solution: 6 N hydrochloric acid containing 0.1% to 1.0% of phenol.

Procedure—

Liquid Phase Hydrolysis—Place the protein or peptide sample in a hydrolysis tube, and dry. [NOTE—The sample is dried so that water in the sample will not dilute the acid used for the hydrolysis.] Add 200 µL of *Hydrolysis Solution* per 500 µg of lyophilized protein. Freeze the sample tube in a dry ice-acetone bath, and flame seal in vacuum. Samples are typically hydrolyzed at 110° for 24 hours in vacuum or inert atmosphere to prevent oxidation. Longer hydrolysis times (e.g., 48 and 72 hours) are investigated if there is a concern that the protein is not completely hydrolyzed.

Vapor Phase Hydrolysis—This is one of the most common acid hydrolysis procedures, and it is preferred for microanalysis when only small amounts of the sample are available. Contamination of the sample from the acid reagent is also minimized by using vapor phase hydrolysis. Place vials containing the dried samples in a vessel that contains an appropriate amount of *Hydrolysis Solution*. The *Hydrolysis Solution* does not come in contact with the test sample. Apply an inert atmosphere or vacuum (less than 200 µm of mercury or 26.7 Pa) to the headspace of the vessel, and heat to about 110° for a 24-hour hydrolysis time. Acid vapor hydrolyzes the dried sample. Any condensation of the acid in the sample vials is minimized. After hydrolysis, dry the test sample in vacuum to remove any residual acid.

METHOD 2

Tryptophan oxidation during hydrolysis is decreased by using mercaptoethanesulfonic acid (MESA) as the reducing acid.

Hydrolysis Solution: 2.5 M MESA solution.

Vapor Phase Hydrolysis—About 1 to 100 µg of the protein/peptide under test is dried in a hydrolysis tube. The hydrolysis tube is placed in a larger tube with about 200 µL of the *Hydrolysis Solution*. The larger tube is sealed in vacuum (about 50 µm of mercury or 6.7 Pa) to vaporize the *Hydrolysis Solution*. The hydrolysis tube is heated to between 170° to 185° for about 12.5 minutes. After hydrolysis, the hydrolysis tube is dried in vacuum for 15 minutes to remove the residual acid.

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~~METHOD 3~~

~~Tryptophan oxidation during hydrolysis is prevented by using thioglycolic acid (TGA) as the reducing acid.~~

~~**Hydrolysis Solution:**—a solution containing 7 M hydrochloric acid, 10% of trifluoroacetic acid, 20% of thioglycolic acid, and 1% of phenol.~~

~~**Vapor Phase Hydrolysis**—About 10 to 50 µg of the protein/peptide under test is dried in a sample tube. The sample tube is placed in a larger tube with about 200 µL of the *Hydrolysis Solution*. The larger tube is sealed in vacuum (about 50 µm of mercury or 6.7 Pa) to vaporize the TGA. The sample tube is heated to 166° for about 15 to 30 minutes. After hydrolysis, the sample tube is dried in vacuum for 5 minutes to remove the residual acid. Recovery of tryptophan by this method may be dependent on the amount of sample present.~~

~~METHOD 4~~

~~Cysteine-cystine and methionine oxidation is performed with performic acid before the protein hydrolysis.~~

~~**Oxidation Solution**—The performic acid is prepared fresh by mixing formic acid and 30 percent hydrogen peroxide (9 : 1), and incubated at room temperature for 1 hour.~~

~~**Procedure**—The protein/peptide sample is dissolved in 20 µL of formic acid, and heated at 50° for 5 minutes; then 100 µL of the *Oxidation Solution* is added. In this reaction, cysteine is converted to cysteic acid and methionine is converted to methionine sulfone. The oxidation is allowed to proceed for 10 to 30 minutes. The excess reagent is removed from the sample in a vacuum centrifuge. This technique may cause modifications to tyrosine residues in the presence of halides. The oxidized protein can then be acid hydrolyzed using *Method 1* or *Method 2*.~~

~~METHOD 5~~

~~Cysteine-cystine oxidation is accomplished during the liquid phase hydrolysis with sodium azide.~~

~~**Hydrolysis Solution:**—6 N hydrochloric acid containing 0.2% of phenol, to which sodium azide is added to obtain a final concentration of 0.2% (w/v). The added phenol prevents halogenation of tyrosine.~~

~~**Liquid Phase Hydrolysis**—The protein/peptide hydrolysis is conducted at about 110° for 24 hours. During the hydrolysis, the cysteine-cystine present in the sample is converted to cysteic acid by the sodium azide present in the *Hydrolysis Solution*. This technique allows better tyrosine recovery than *Method 4*, but it is not quantitative for methionine. Methionine is converted to a mixture of the parent methionine and its two oxidative products, methionine sulfoxide and methionine sulfone.~~

~~METHOD 6~~

~~Cysteine-cystine oxidation is accomplished with dimethyl sulfoxide (DMSO).~~

~~**Hydrolysis Solution:**—6 N hydrochloric acid containing 0.1% to 1.0% of phenol, to which DMSO is added to obtain a final concentration of 2% (v/v).~~

~~**Vapor Phase Hydrolysis**—The protein/peptide hydrolysis is conducted at about 110° for 24 hours. During the hydrolysis, the cysteine-cystine present in the sample is converted to cysteic acid by the DMSO present in the *Hydrolysis Solution*. As an approach to limit variability and compensate for partial destruction, it is recommended to evaluate the cysteic acid recovery from oxidative hydrolyses of standard proteins containing 1 to 8 mol of cysteine. The response factors from protein/peptide hydrolysates are typically about 30% lower than those for nonhydrolyzed cysteic acid standards. Because histidine, methionine, tyrosine, and tryptophan are also modified, a complete compositional analysis is not obtained with this technique.~~

~~METHOD 7~~

~~Cysteine-cystine reduction and alkylation is accomplished by a vapor phase pyridylethylation reaction.~~

~~**Reducing Solution**—Transfer 83.3 µL of pyridine, 16.7 µL of 4-vinylpyridine, 16.7 µL of tributylphosphine, and 83.3 µL of water to a suitable container, and mix.~~

~~**Procedure**—Add the protein/peptide (between 1 and 100 µg) to a hydrolysis tube, and place in a larger tube. Transfer the *Reducing Solution* to the large tube, seal in vacuum (about 50 µm of mercury or 6.7 Pa), and incubate at about 100° for 5 minutes. Then remove the inner hydrolysis tube, and dry it in a vacuum desiccator for 15 minutes to remove residual reagents. The pyridylethylated protein/peptide can then be acid hydrolyzed using previously described procedures. The pyridylethylation reaction is performed simultaneously with a protein standard sample containing 1 to 8 mol of cysteine to improve accuracy in the pyridylethyl-cysteine recovery. Longer incubation times for the pyridylethylation reaction can cause modifications to the α-amino-terminal group and the ε-amino group of lysine in the protein.~~

~~METHOD 8~~

~~Cysteine-cystine reduction and alkylation is accomplished by a liquid phase pyridylethylation reaction.~~

~~**Stock Solutions**—Prepare and filter three solutions: 1 M Tris hydrochloride (pH 8.5) containing 4 mM edetate disodium (*Stock Solution 1*), 8 M guanidine hydrochloride (*Stock Solution 2*), and 10% of 2-mercaptoethanol in water (*Stock Solution 3*).~~

~~**Reducing Solution**—Prepare a mixture of *Stock Solution 2* and *Stock Solution 1* (3 : 1) to obtain a buffered solution of 6 M guanidine hydrochloride in 0.25 M Tris hydrochloride.~~

~~**Procedure**—Dissolve about 10 µg of the test sample in 50 µL of the *Reducing Solution*, and add about 2.5 µL of *Stock Solution 3*. Store under nitrogen or argon for 2 hours at room temperature in the dark. To achieve the pyridylethylation reaction, add about 2 µL of 4-vinylpyridine to the protein solution, and incubate for an additional 2 hours at room temperature in the dark. The protein/peptide is desalted by collecting the protein/peptide fraction from a reverse-phase HPLC separation. The collected sample can be dried in a vacuum centrifuge before acid hydrolysis.~~

~~METHOD 9~~

~~Cysteine-cystine reduction and alkylation is accomplished by a liquid phase carboxymethylation reaction.~~

~~**Stock Solutions**—Prepare as directed for *Method 8*.~~

~~**Carboxymethylation Solution**—Prepare a solution containing 100 mg of iodoacetamide per mL of alcohol.~~

~~**Buffer Solution**—Use the *Reducing Solution,* prepared as directed for *Method 8*.~~

~~**Procedure**—Dissolve the test sample in 50 µL of the *Buffer Solution,* and add about 2.5 µL of *Stock Solution 3*. Store under nitrogen or argon for 2 hours at room temperature in the dark. Add the *Carboxymethylation Solution* in a 1.5-fold ratio per total theoretical content of thiols, and incubate for an additional 30 minutes at room temperature in the dark. [NOTE—If the thiol content of the protein is unknown, then add 5 µL of 100 mM iodoacetamide for every 20 nmol of protein present.] The reaction is stopped by adding excess of 2-mercaptoethanol. The protein/peptide is desalted by collecting the protein/peptide fraction from a reverse-phase HPLC separation. The collected sample can be dried in a vacuum centrifuge before acid hydrolysis. The *S*-carboxyamidomethylcysteine formed will be converted to *S*-carboxymethyl cysteine during acid hydrolysis.~~

METHOD 10

Cysteine-cystine is reacted with dithiodiglycolic acid or dithiodipropionic acid to produce a mixed disulfide. [NOTE—The choice of dithiodiglycolic acid or dithiodipropionic acid depends on the required resolution of the amino acid analysis method.]

Reducing Solution: a solution containing 10 mg of dithiodiglycolic acid (or dithiodipropionic acid) per mL of 0.2 M sodium hydroxide.

Procedure—Transfer about 20 µg of the test sample to a hydrolysis tube, and add 5 µL of the *Reducing Solution*. Add 10 µL of isopropyl alcohol, and then remove all of the sample liquid by vacuum centrifugation. The sample is then hydrolyzed using *Method 1*. This method has the advantage that other amino acid residues are not derivatized by side reactions, and the sample does not need to be desalted prior to hydrolysis.

METHOD 11

Asparagine and glutamine are converted to aspartic acid and glutamic acid, respectively, during acid hydrolysis. Asparagine and aspartic acid residues are added and represented by *Asx*, while glutamine and glutamic acid residues are added and represented by *Glx*. Proteins/peptides can be reacted with bis(1,1 trifluoroacetoxy)iodobenzene (BTI) to convert the asparagine and glutamine residues to diaminopropionic acid and diaminobutyric acid residues, respectively, upon acid hydrolysis. These conversions allow the analyst to determine the asparagine and glutamine content of a protein/peptide in the presence of aspartic acid and glutamic acid residues.

Reducing Solutions—Prepare and filter three solutions: a solution of 10 mM trifluoroacetic acid (*Solution 1*), a solution of 5 M guanidine hydrochloride and 10 mM trifluoroacetic acid (*Solution 2*), and a freshly prepared solution of dimethylformamide containing 36 mg of BTI per mL (*Solution 3*).

Procedure—In a clean hydrolysis tube, transfer about 200 µg of the test sample, and add 2 mL of *Solution 1* or *Solution 2* and 2 mL of *Solution 3*. Seal the hydrolysis tube in vacuum. Heat the sample at 60° for 4 hours in the dark. The sample is then dialyzed with water to remove the excess reagents. Extract the dialyzed sample three times with equal volumes of *n*-butyl acetate, and then lyophilize. The protein can then be acid hydrolyzed using previously described procedures. The α,β-diaminopropionic and α,γ-diaminobutyric acid residues do not typically resolve from the lysine residues upon ion-exchange chromatography based on amino acid analysis. Therefore, when using ion-exchange as the mode of amino acid separation, the asparagine and glutamine contents are the quantitative difference in the aspartic acid and glutamic acid assayed contents with un-derivatized and BTI-derivatized acid hydrolysis. [NOTE—The threonine, methionine, cysteine, tyrosine, and histidine assayed content can be altered by BTI derivatization; a hydrolysis without BTI will have to be performed if the analyst is interested in the protein/peptide content of these other amino acid residues.]

Methodologies of Amino Acid Analysis

Many amino acid analysis techniques exist, and the choice of any one technique often depends on the sensitivity required from the assay. In general, about one half of the amino acid analysis techniques employed rely on the separation of the free amino acids by ion-exchange chromatography followed by postcolumn derivatization (e.g., with ninhydrin or *o*-phthalaldehyde). Postcolumn detection techniques can be used with samples that contain small amounts of buffer components, such as salts and urea, and generally require between 5 and 10 µg of protein sample per analysis. The remaining amino acid techniques typically involve precolumn derivatization of the free amino acids (e.g., phenyl isothiocyanate; 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbonate; (dimethylamino)azobenzenesulfonyl chloride; 9-fluorenyl methylchloroformate; and 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole) followed by reverse-phase HPLC. Precolumn derivatization techniques are very sensitive and usually require between 0.5 and 1.0 µg of protein sample per analysis but may be influenced by buffer salts in the samples. Precolumn derivatization techniques may also result in multiple derivatives of a given amino acid, which complicates the result interpretation. Postcolumn derivatization techniques are generally influenced less by performance variation of the assay than precolumn derivatization techniques.

The following *Methods* may be used for quantitative amino acid analysis. Instruments and reagents for these procedures are available commercially. Furthermore, many modifications of these methodologies exist with different reagent preparations, reaction procedures, chromatographic systems, etc. Specific parameters may vary according to the exact equipment and procedure used. Many laboratories will utilize more than one amino acid analysis technique to exploit the advantages offered by each. In each of these *Methods*, the analog signal is visualized by means of a data acquisition system, and the peak areas are integrated for quantification purposes.

METHOD 1—POSTCOLUMN NINHYDRIN DETECTION

Ion-exchange chromatography with postcolumn ninhydrin detection is one of the most common methods employed for quantitative amino acid analysis. As a rule, a Li-based cation-exchange system is employed for the analysis of the more complex physiological samples, and the faster Na-based cation-exchange system is used for the more simplistic amino acid mixtures obtained with protein hydrolysates (typically containing 17 amino acid components). Separation of the amino acids on an ion-exchange column is accomplished through a combination of changes in pH and cation strength. A temperature gradient is often employed to enhance separation.

When the amino acid reacts with ninhydrin, the reactant has characteristic purple or yellow color. Amino acids, except imino acids, give a purple color, and show maximum absorption at 570 nm. The imino acids, such as proline, give a yellow color, and show maximum absorption at 440 nm. The postcolumn reaction between ninhydrin and amino acid eluted from the column is monitored at 440 nm and 570 nm, and the chromatogram obtained is used for the determination of amino acid composition.

The detection limit is considered to be 10 pmol for most of the amino acid derivatives, but 50 pmol for proline. Response linearity is obtained in the range of 20 to 500 pmol with correlation coefficients exceeding 0.999. To obtain good compositional data, samples larger than 1 µg before hydrolysis are best suited for this amino acid analysis of protein/peptide.

One method for postcolumn ninhydrin detection is shown below. Many other methods are also available, with instruments and reagents available commercially.

Mobile Phase Preparation—

Solution A—Transfer about 1.7 g of anhydrous sodium citrate and 1.5 mL of hydrochloric acid to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust, if necessary, with hydrochloric acid to a pH of 3.0.

Solution B—Transfer about 1.7 g of anhydrous sodium citrate and 0.7 mL of hydrochloric acid to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust, if necessary, with hydrochloric acid to a pH of 4.3.

Solution C—Prepare a solution containing 5% of sodium chloride, 1.9% of anhydrous sodium citrate, and 0.1% of phenol in water, and adjust to a pH of 6.

Column Regeneration Solution—Prepare a solution containing 0.8% of sodium hydroxide in water, and adjust to a pH of 13.

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

Postcolumn Reagent—Transfer about 18 g of ninhydrin and 0.7 g of hydrindantin to 900 mL of a solution containing 76.7% of dimethyl sulfoxide, 0.7% of dihydrate lithium acetate, and 0.1% of acetic acid, and mix for at least 3 hours under inert gas, such as nitrogen. [NOTE—This reagent is stable for 30 days if kept between 2° and 8° under inert gas.]

Buffer Solution—Prepare a solution containing 2% of anhydrous sodium citrate, 1% of hydrochloric acid, 0.5% of thiodiglycol, and 0.1% of benzoic acid in water, and adjust to a pH of 2.

Chromatographic System—The liquid chromatograph is equipped with a detector with appropriate interference filters at 440, 570, or 690 nm and a 4.0-mm × 120-mm column that contains 7.5-µm sulfonated styrene-divinylbenzene copolymer packing. The flow rate is about 14 mL per hour. The system is programmed as fol-

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lows. Initially equilibrate the column with *Solution A;* at 25 minutes, the composition of the *Mobile Phase* is changed to 100% *Solution B;* and at 37 minutes, the composition is changed to 100% *Solution C*. At 75 minutes into the run, the last amino acid has been eluted from the column, and the column is regenerated with *Column Regeneration Solution* for 1 minute. The column is then equilibrated with *Solution A* for 11 minutes before the next injection. The column temperature is programmed as follows. The initial temperature is 48°; after 11.5 minutes, the temperature is increased to 65° at a rate of 3° per minute; at about 35 minutes, the temperature is increased to 77° at a rate of 3° per minute; and finally at about 52 minutes, the temperature is decreased to 48° at a rate of 3° per minute.

Procedure and **Posteolumn Reaction**— Reconstitute the lyophilized protein/peptide hydrolysate in the *Buffer Solution,* inject an appropriate amount into the chromatograph, and proceed as directed for *Chromatographic System.* As the amino acids are eluted from the column, they are mixed with the *Posteolumn Reagent,* which is delivered at a flow rate of 7 mL per hour, through a tee. After mixing, the column effluent and the *Posteolumn Reagent* pass through a tubular reactor at a temperature of 135°, where a characteristic purple or yellow color is developed. From the reactor, the liquid passes through a colorimeter with a 12-mm flow-through cuvette. The light emerging from the cuvette is split into three beams for analysis by the detector with interference filters at 440, 570, or 690 nm. The 690-nm signal may be electronically subtracted from the other signals for improved signal-to-noise ratios. The 440-nm (imino acids) and the 570-nm (amino acids) signals may be added in order to simplify data handling.

METHOD 2—POSTCOLUMN OPA FLUOROMETRIC DERIVATIZATION

Ion-exchange chromatography with posteolumn *o*-phthalaldehyde (OPA) fluorometric detection is used. The procedure employs an ion-exchange column for separation of free amino acids followed by post-column oxidation with sodium hypochlorite and derivatization using OPA and *N*-acetyl-L-cysteine. The sodium hypochlorite oxidation step allows secondary amines, such as proline, to react with the OPA reagent.

OPA reacts with primary amines in the presence of thiol compound to form highly fluorescent isoindole products. This reaction is utilized for the posteolumn derivatization in analysis of amino acids by ion-exchange chromatography. The rule of the separation is the same as *Method I.* Instruments and reagents for this form of amino acid analysis are available commercially. Many modifications of this method exist.

Although OPA does not react with secondary amines (imino acids, such as proline) to form fluorescent substances, the oxidation with sodium hypochlorite allows secondary amines to react with OPA. The procedure employs a strongly acidic cation exchange column for separation of free amino acids followed by posteolumn oxidation with sodium hypochlorite and posteolumn derivatization using OPA and thiol compound, such as *N*-acetyl-L-cysteine and 2-mercaptoethanol. The derivatization of primary amino acids are not noticeably affected by the continuous supply of sodium hypochlorite.

Separation of the amino acids on an ion exchange column is accomplished through a combination of changes of pH and cation strength. After posteolumn derivatization of eluted amino acids with OPA, the reactant passes through the fluorometric detector. Fluorescence intensity of OPA-derivatized amino acids are monitored with an excitation wavelength of 348 nm and an emission wavelength of 450 nm.

The detection limit is considered to be a few tens of picomole level for most of the amino acid derivatives. Response linearity is obtained in the range of a few picomole level to a few tens of nanomole level. To obtain good compositional data, a sample greater than 500 ng before hydrolysis is best suited for the amino acid analysis of protein/peptide.

One method of posteolumn OPA fluorometric detection is shown below.

Mobile Phase Preparation—

Solution A— Prepare a solution of sodium hydroxide, citric acid, and alcohol in HPLC grade water having a 0.2 N sodium concentration and containing 7% of alcohol (w/v), adjusted to a pH of 3.2.

Solution B— Prepare a solution of sodium hydroxide and citric acid in HPLC grade water having a 0.6 N sodium concentration, adjusted to a pH of 10.0.

Solution C:— 0.2 N sodium hydroxide.

Mobile Phase— Use variable mixtures of *Solution A*, *Solution B,* and *Solution C* as directed for *Chromatographic System*.

Posteolumn Reagent Preparation—

Alkaline Buffer— Prepare a solution containing 384 mM sodium carbonate, 216 mM boric acid, and 108 mM potassium sulfate, and adjust to a pH of 10.0.

Hypochlorite Reagent— To 1 L of *Alkaline Buffer,* add 0.4 mL of sodium hypochlorite solution (10% chlorine concentration). [NOTE—The hypochlorite solution is stable for 2 weeks.]

OPA Reagent— Transfer 2 g of *N*-acetyl-L-cysteine and 1.6 g of OPA to a 15-mL volumetric flask, dissolve in and dilute with alcohol to volume, and mix. Transfer this solution and 4 mL of 10% aqueous polyethylene (23) lauryl ether[a] to a 1-liter volumetric flask, dilute with 980 mL of *Alkaline Buffer,* and mix.

Chromatographic System— The liquid chromatograph is equipped with a fluorometric detector set to an excitation wavelength of 348 nm and an emission wavelength of 450 nm and a 4.0-mm × 150-mm column that contains 7.5-µm packing L17. The flow rate is about 0.3 mL per minute, and the column temperature is set at 50°. The system is programmed as follows. The column is equilibrated with *Solution A;* over the next 20 minutes, the composition of the *Mobile Phase* is changed linearly to 85% *Solution A* and 15% *Solution B;* then there is a step change to 40% *Solution A* and 60% *Solution B;* over the next 18 minutes, the composition is changed linearly to 100% *Solution B* and held for 7 minutes; then there is a step change to 100% *Solution C,* and this is held for 6 minutes; then there is a step change to *Solution A,* and this composition is maintained for the next 8 minutes.

Procedure and Posteolumn Reaction— Inject about 1.0 nmol of each amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System*. As the effluent leaves the column, it is mixed with the *Hypochlorite Reagent*. The mixture passes through the first posteolumn reactor which consists of stainless steel 0.5-mm × 2-m tubing. A second posteolumn reactor of similar design is placed immediately downstream from the first posteolumn reactor and is used for the OPA posteolumn reaction. The flow rates for both the *Hypochlorite Reagent* and the *OPA Reagent* are 0.2 mL per minute, resulting in a total flow rate (i.e., *Hypochlorite Reagent*, *OPA Reagent,* and column effluent) of 0.7 mL per minute exiting from the posteolumn reactors. Posteolumn reactions are conducted at 55°. This results in a residence time of about 33 seconds in the OPA posteolumn reactor. After posteolumn derivatization, the column effluent passes through the fluorometric detector.

METHOD 3—PRECOLUMN DETERMINATION

Precolumn derivatization of amino acids with phenylisothiocyanate (PITC) followed by reverse phase HPLC separation with UV detection is used.

PITC reacts with amino acids to form phenylthiocarbamyl (PTC) derivatives which can be detected with high sensitivity at 254 nm. Therefore, precolumn derivatization of amino acids with PITC followed by a reverse phase HPLC separation with UV detection is used to analyze the amino acid composition.

After the reagent is removed under vacuum, the derivatized amino acids can be stored dry and frozen for several weeks with no significant degradation. If the solution for injection is kept cold, no noticeable loss in chromatographic response occurs after three days.

Separation of the PTC-amino acids on a reverse phase HPLC with ODS column is accomplished through a combination of changes in concentrations of acetonitrile and buffer ionic strength. PTC-amino acids eluted from the column are monitored at 254 nm.

The detection limit is considered to be 1 pmol for most of the amino acid derivatives. Response linearity is obtained in the range of 20 to 500 pmol with correlation coefficients exceeding 0.999. To obtain

[a] A suitable grade is available commercially as "Palladium Catalyst, Type I (5% Palladium on Caleium Carbonate)," from Engelhard Industries, Inc., fax number (864) 885-1375.

good compositional data, a sample larger than 500 ng of protein/peptide before hydrolysis is best suited for this amino analysis of proteins/peptides.

One method of precolumn PITC derivatization is described below.

Mobile Phase Preparation

Solution A: 0.05 M ammonium acetate, adjusted with phosphoric acid to a pH of 6.8.

Solution B: Prepare 0.1 M ammonium acetate, adjust with phosphoric acid to a pH of 6.8, and then prepare a mixture of this solution and acetonitrile (1 : 1).

Solution C: a mixture of acetonitrile and water (70 : 30).

Mobile Phase: Use variable mixtures of *Solution A, Solution B,* and *Solution C* as directed for *Chromatographic System*.

Derivatization Reagent Preparation

Coupling Buffer: a mixture of acetonitrile, pyridine, triethylamine, and water (10 : 5 : 2 : 3).

Sample Solvent: a mixture of water and acetonitrile (7 : 2).

Sample Derivatization Procedure Dissolve the lyophilized test sample in 100 µL of the *Coupling Buffer,* and then dry in a vacuum centrifuge to remove any hydrochloride if a protein hydrolysis step was used. Dissolve the test sample in 100 µL of *Coupling Buffer*, add 5 µL of PITC, and incubate at room temperature for 5 minutes. The test sample is again dried in a vacuum centrifuge, and is dissolved in 250 µL of *Sample Solvent*.

Chromatographic System The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 250-mm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 52°. The system is programmed as follows. The column is equilibrated with *Solution A;* over the next 15 minutes, the composition of the *Mobile Phase* is changed linearly to 85% *Solution A* and 15% *Solution B;* over the next 15 minutes, the composition is changed linearly to 50% *Solution A* and 50% *Solution B;* then there is a step change to 100% *Solution C,* and this is held for 10 minutes; then there is a step change to 100% *Solution A,* and the column is allowed to equilibrate before the next injection.

Procedure Inject about 1.0 nmol of each PITC-amino acid under test (10 µL sample in *Sample Solvent*) into the chromatograph, and proceed as directed for *Chromatographic System*.

METHOD 4—PRECOLUMN AQC DERIVATIZATION

Precolumn derivatization of amino acids with 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbamate (AQC) followed by reverse-phase HPLC separation with fluorometric detection is used.

AQC reacts with amino acids to form stable, fluorescent unsymmetric urea derivatives (AQC-amino acids) which are readily amenable to analysis by reverse-phase HPLC. Therefore, precolumn derivatization of amino acids with AQC followed by reverse-phase HPLC separation is used to analyze the amino acid composition.

Separation of the AQC-amino acids on an ODS column is accomplished through a combination of changes in the concentrations of acetonitrile and salt. Selective fluorescence detection of the derivatives with an excitation wavelength at 250 nm and an emission wavelength at 395 nm allows for the direct injection of the reaction mixture with no significant interference from the only major fluorescent reagent by-product, 6-aminoquinoline. Excess reagent is rapidly hydrolyzed ($t_{1/2}$ < 15 seconds) to yield 6-aminoquinoline *N*-hydroxysuccinimide and carbon dioxide, and after 1 minute no further derivatization can take place.

Peak areas for AQC-amino acids are essentially unchanged for at least 1 week at room temperature, and the derivatives have more than sufficient stability to allow for overnight automated chromatographic analysis.

The detection limit is considered to be ranging from about 40 fmol to 320 fmol for each amino acid, except for Cys. The detection limit for Cys is approximately 800 fmol. Response linearity is obtained in the range of 2.5 µM to 200 µM with correlation coefficients exceeding 0.999. Good compositional data can be obtained from the analysis of derivatized protein hydrolysates containing as little as 30 ng of protein/peptide.

One method of precolumn AQC derivatization is shown below.

Mobile Phase Preparation

Solution A: Prepare a solution having a composition of 140 mM sodium acetate and 17 mM triethylamine, and adjust with phosphoric acid to a pH of 5.02.

Solution B: a mixture of acetonitrile and water (60 : 40).

Mobile Phase: Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic System*.

Sample Derivatization Procedure Dissolve about 2 µg of the test sample in 20 µL of 15 mM hydrochloric acid, and dilute with 0.2 M borate buffer (pH 8.8) to 80 µL. The derivatization is initiated by the addition of 20 µL of 10 mM AQC in acetonitrile, and allowed to proceed for 10 minutes at room temperature.

Chromatographic System The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 250 nm and an emission wavelength of 395 nm and a 3.9-mm × 150-mm column that contains 4-µm packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 37°. The system is programmed as follows. The column is equilibrated with *Solution A;* over the next 0.5 minute, the composition of the *Mobile Phase* is changed linearly to 98% *Solution A* and 2% *Solution B;* then over the next 14.5 minutes to 93% *Solution A* and 7% *Solution B;* then over the next 4 minutes to 87% *Solution A* and 13% *Solution B;* over the next 14 minutes to 68% *Solution A* and 32% *Solution B;* then there is a step change to 100% *Solution B* for a 5-minute wash; over the next 10 minutes, there is a step change to 100% *Solution A;* and the column is allowed to equilibrate before the next injection.

Procedure Inject about 0.05 nmol of each AQC-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System*.

METHOD 5—PRECOLUMN OPA DERIVATIZATION

Precolumn derivatization of amino acids with OPA followed by reverse-phase HPLC separation with fluorometric detection is used. This technique does not detect amino acids that exist as secondary amines (e.g., proline).

OPA in conjunction with a thiol reagent reacts with primary amine groups to form highly fluorescent isoindole products. 2-Mercaptoethanol and 3-mercaptopropionic acid can be used as thiol. OPA itself does not fluoresce and consequently produces no interfering peaks. In addition, its solubility and stability in aqueous solution, along with the rapid kinetics for the reactions, make it amenable to automated derivatization and analysis using an autosampler to mix the sample with the reagent. However, lack of reactivity with secondary amino acids has been a predominant drawback. This method does not detect amino acids that exist as secondary amines (e.g., proline). To compensate for this drawback, this technique may be combined with another technique described in *Method 7* or *Method 8*.

Precolumn derivatization of amino acids with OPA is followed by reverse-phase HPLC separation. Because of the instability of the OPA-amino acid derivative, HPLC separation and analysis are performed immediately following derivatization. The liquid chromatograph is equipped with a fluorometric detector for the detection of derivatized amino acids. Fluorescence intensity of the OPA-derivatized amino acids are monitored with an excitation wavelength of 348 nm and an emission wavelength of 450 nm.

The detection limits as low as 50 fmol via fluorescence have been reported, although the practical limit of analysis remains at 1 pmol. One method of precolumn OPA derivatization is shown below.

Mobile Phase Preparation

Solution A: a mixture of 100 mM sodium acetate (pH 7.2), methanol, and tetrahydrofuran (900 : 95 : 5).

Solution B: methanol.

Mobile Phase: Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic System*.

Derivatization Reagent Dissolve 50 mg of OPA in 1.25 mL of methanol (protein sequencing grade). Add 50 µL of 2-mercaptoethanol and 11.2 mL of 0.4 M sodium borate (pH 9.5), and mix. [NOTE—This reagent is stable for 1 week.]

In-Process Revision

Sample Derivatization Procedure— Transfer about 5 µL of the test sample to an appropriate container, add 5 µL of the *Derivatization Reagent*, and mix. After 1 minute, add not less than 20 µL of 0.1 M sodium acetate (pH 7.0). Use 20 µL of this solution for analysis. [NOTE—Use of an internal standard (e.g., norleucine) is recommended for quantitative analysis because of potential reagent volume variations in the sample derivatization. The sample derivatization is performed in an automated on-line fashion. Because of the instability of the OPA-amino acid derivative, HPLC separation and analysis are performed immediately following derivatization.]

Chromatographic System— The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 348 nm and an emission wavelength of 450 nm and a 4.6-mm × 75-mm column that contains 3-µm packing L3. The flow rate is about 1.7 mL per minute, and the column temperature is maintained at 37°. The system is programmed as follows. The column is equilibrated with 92% *Solution A* and 8% *Solution B;* over the next 2 minutes, the composition of the *Mobile Phase* is changed to 83% *Solution A* and 17% *Solution B,* and held for an additional 3 minutes; then changed to 54% *Solution A* and 46% *Solution B* over the next 5 minutes, and held for an additional 2 minutes; then changed to 34% *Solution A* and 66% *Solution B* over the next 2 minutes, and held for 1 minute; then over the next 0.3 minute changed to 20% *Solution A* and 80% *Solution B*, and held for an additional 2.6 minutes; and then finally over 0.6 minute changed to 92% *Solution A* and 8% *Solution B,* and held for an additional 0.6 minute.

Procedure— Inject about 0.02 nmol of each OPA-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System.*

METHOD 6—POSTCOLUMN DABS-CL DERIVATIZATION

Precolumn derivatization of amino acids with (dimethylamino)azobenzenesulfonyl chloride (DABS-Cl) followed by reverse-phase HPLC separation with visible-light detection is used.

DABS-Cl is a chromophoric reagent employed for the labeling of amino acids. Amino acids labeled with DABS-Cl (DABS-amino acids) are highly stable and show the maximum absorption at 436 nm.

DABS-amino acids, all 19 naturally occurring amino acids derivatives, can be separated on an ODS column of a reverse-phase HPLC by employing gradient systems consisting of acetonitrile and aqueous buffer mixture. Separated DABS-amino acids eluted from the column are detected at 436 nm in the visible region.

This method can analyze the imino acids, such as proline, together with the amino acids, at the same degree of sensitivity. DABS-Cl derivatization method permits the simultaneous quantification of tryptophan residues by previous hydrolysis of the protein/peptide with sulfonic acids, such as mercaptoethanesulfonic acid, *p*-toluenesulfonic acid, or methanesulfonic acid, described for *Method 2* in *Protein Hydrolysis* under *Amino Acid Analysis.* The other acid-labile residues, asparagine and glutamine, can also be analyzed by previous conversion into diaminopropionic acid and diaminobutyric acid, respectively, by treatment of protein/peptide with BTI, described for *Method 11* in *Protein Hydrolysis* under *Amino Acid Analysis.*

The non-proteinogenic amino acid, norleucine, cannot be used as an internal standard in this method as this compound is eluted in a chromatographic region crowded with peaks of primary amino acids. Nitrotyrosine can be used as an internal standard because it is eluted in a clean region.

The detection limit of DABS-amino acid is about 1 pmol. As little as 2 to 5 pmol of an individual DABS-amino acid can be quantitatively analyzed with reliability, and only 10 ng to 30 ng of the dabsylated protein hydrolysate is required for each analysis.

One method for precolumn DABS-Cl derivatization is shown below.

Mobile Phase Preparation—

Solution A:— 25 mM sodium acetate (pH 6.5) containing 4% of dimethylformamide.

Solution B:— acetonitrile.

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

Derivatization Reagent Preparation—

Sample Buffer:— 50 mM sodium bicarbonate, adjusted to a pH of 8.1.

Derivatization Reagent— Dissolve 1.3 mg of DABS-Cl in 1 mL of acetonitrile. [NOTE—This reagent is prepared fresh shortly before the derivatization step.]

Sample Dilution Buffer— Prepare a mixture of 50 mM sodium phosphate (pH 7.0) and alcohol (1 : 1).

Sample Derivatization Procedure— Dissolve the test sample in 20 µL of *Sample Buffer*, add 40 µL of *Derivatization Reagent*, and mix. The sample container is sealed with a silicon rubber stopper, and heated to 70° for 10 minutes. During the sample heating, the mixture will become completely soluble. After the derivatization, dilute the test sample with an appropriate quantity of the *Sample Dilution Buffer.*

Chromatographic System— The liquid chromatograph is equipped with a 436-nm detector and a 4.6-mm × 250-mm column that contains packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 40°. The system is programmed as follows. The column is equilibrated with 85% *Solution A* and 15% *Solution B;* over the next 20 minutes, the composition of the *Mobile Phase* is changed to 60% *Solution A* and 40% *Solution B;* over the next 12 minutes, the composition is changed to 30% *Solution A* and 70% *Solution B,* and held for an additional 2 minutes.

Procedure— Inject about 0.05 nmol of the DABS-amino acids into the chromatograph, and proceed as directed for *Chromatographic System.*

METHOD 7—PRECOLUMN FMOC-CL DERIVATIZATION

Precolumn derivatization of amino acids with 9-fluorenylmethyl chloroformate (FMOC-Cl) followed by reverse-phase HPLC separation with fluorometric detection is used.

FMOC-Cl reacts with both primary and secondary amino acids to form highly fluorescent products. The reaction of FMOC-Cl with amino acid proceeds under mild conditions, in aqueous solution, and is completed in 30 seconds. The derivatives are stable, with only the histidine derivative showing any breakdown. Although FMOC-Cl is fluorescent itself, the reagent excess and fluorescent side products can be eliminated without loss of FMOC-amino acids.

FMOC-amino acids are separated by reverse-phase HPLC using an ODS column. The separation is carried out by gradient elution varied linearly from a mixture of acetic acid–buffer, methanol, and acetonitrile (50 : 40 : 10) to a mixture of acetonitrile and acetic acid–buffer (50 : 50), and 20 amino acid derivatives that are separated in 20 minutes. Each derivative eluted from the column is monitored by a fluorometric detector set at an excitation wavelength of 260 nm and an emission wavelength of 313 nm.

The detection limit is in the low fmol range. A linearity range of 0.1 µM to 50 µM is obtained for most amino acids.

One method for precolumn FMOC-Cl derivatization is shown below.

Mobile Phase Preparation—

Acetic Acid Buffer— Transfer 3 mL of glacial acetic acid and 1 mL of triethylamine to a 1-liter volumetric flask, and dilute with HPLC grade water to volume. Adjust with sodium hydroxide to a pH of 4.20.

Solution A:— a mixture of *Acetic Acid Buffer,* methanol, and acetonitrile (50 : 40 : 10).

Solution B:— a mixture of acetonitrile and *Acetic Acid Buffer* (50 : 50).

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

Derivatization Reagent Preparation—

Borate Buffer— Prepare a 1 M boric acid solution, and adjust with sodium hydroxide to a pH of 6.2.

FMOC-Cl Reagent— Dissolve 155 mg of 9-fluorenylmethyl chloroformate in 40 mL of acetone, and mix.

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Sample Derivatization Procedure— To 0.4 mL of the test sample add 0.1 mL of *Borate Buffer* and 0.5 mL of *FMOC-Cl Reagent*. After about 40 seconds, extract the mixture with 2 mL of pentane, and then extract again with fresh pentane. The aqueous solution with amino acid derivatives is then ready for injection.

Chromatographic System— The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 260 nm and an emission wavelength of 313 nm and a 4.6-mm × 125-mm column that contains 3-µm packing L1. The flow rate is about 1.3 mL per minute. The system is programmed as follows. The column is equilibrated with *Solution A*, and this composition is maintained for 3 minutes; over the next 9 minutes, it is changed to 100% *Solution B;* then over the next 0.5 minute, the flow rate is increased to 2 mL per minute, and held until the final FMOC-amino acid is eluted from the column. The total run time is about 20 minutes.

Procedure— Inject not less than 0.01 nmol of each FMOC-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System*. The FMOC-histidine derivative will generally give a lower response than the other derivatives.

METHOD 8—PRECOLUMN NBD-F DERIVATIZATION

Precolumn derivatization of amino acids with 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole (NBD-F) followed by reverse-phase HPLC separation with fluorometric detection is used.

7-Fluoro-4-nitrobenzo-2-oxa-1,3-diazole (NBD-F) reacts with both primary and secondary amino acids to form highly fluorescent products. Amino acids are derivatized with NBD-F by heating to 60° for 5 minutes.

NBD-amino acid derivatives are separated on an ODS column of reverse-phase HPLC by employing a gradient elution system consisting of acetonitrile and aqueous buffer mixture, and 17 amino acid derivatives that are separated in 35 minutes. *E*-aminocaproic acid can be used as an internal standard because it is eluted in a clean chromatographic region. Each derivative eluted from the column is monitored by a fluorometric detector set at an excitation wavelength of 480 nm and an emission wavelength of 530 nm.

The sensitivity of this method is almost the same as that for the precolumn OPA derivatization method (*Method 5*), excluding proline to which OPA is not reactive and might be advantageous for NBD-F against OPA.

The detection limit for each amino acid is about 10 fmol. Profile analysis was achieved for about 1.5 mg of protein hydrolysates in the final precolumn labeling reaction mixture for HPLC.

One method for precolumn NBD-F derivatization is shown below.

Mobile Phase Preparation—

Solution A:— a solution of 10mM sodium citrate containing 75 mM sodium perchlorate, adjusted with hydrochloric acid to a pH of 6.2.

Solution B:— a mixture of acetonitrile and water (50 : 50).

Derivatization Reagent Preparation—

Sample Buffer:— a 0.1 M boric acid solution, adjusted with sodium hydroxide to a pH of 9.2.

Derivatization Reagent— Dissolve 5 mg of NBD-F in 1.0 mL of alcohol, and mix.

Sample Derivatization Procedure— Dissolve the test sample in 20 µL of *Sample Buffer*, add 10 µL of *Derivatization Reagent*, and mix. The sample container is heated at 60° for 5 minutes. After the derivatization, dilute the test sample with 300 µL of *Solution A*.

Chromatographic System— The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 480 nm and an emission wavelength of 530 nm and a 4.6-mm × 150-mm column that contains 5-µm particle size ODS silica packing. The flow rate is about 1.0 mL per minute, and the column temperature is maintained at 40°. The system is programmed as follows. The column is equilibrated with 94% *Solution A* and 6% *Solution B;* over the next 16 minutes, the composition is changed linearly to 63% *Solution A* and 37% *Solution B;* over the next 5 minutes, the composition is changed linearly to 62% *Solution A* and 38% *Solution B;* over the next 9 minutes, the composition is changed linearly to 100% *Solution B*, and held for an additional 5 minutes; then finally over 2 minutes, the composition is changed linearly to 94% *Solution A* and 6% *Solution B;* and then the column is allowed to equilibrate before the next injection.

Procedure— Inject about 15 pmol of each NBD-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System*.

Data Calculation and Analysis

When determining the amino acid content of a protein/peptide hydrolysate, it should be noted that the acid hydrolysis step destroys tryptophan and cysteine. Serine and threonine are partially destroyed by acid hydrolysis, while isoleucine and valine residues may be only partially cleaved. Methionine can undergo oxidation during acid hydrolysis, and some amino acids (e.g., glycine and serine) are common contaminants. Application of adequate vacuum (less than 200 um µm of mercury or 26.7 Pa) or introduction of inert gas (argon) in the headspace of the reaction vessel during vapor phase hydrolysis can reduce the level of oxidative destruction. Therefore, the quantitative results obtained for cysteine, tryptophan, threonine, isoleucine, valine, methionine, glycine, and serine from a protein/peptide hydrolysate may be variable and may warrant further investigation and consideration.

CALCULATIONS

Amino-Acid Mole Percent— This is the number of specific amino acid residues per 100 residues in a protein. This result may be useful for evaluating amino acid analysis data when the molecular weight of the protein/peptide under investigation is unknown. This information can be used to corroborate the identity of a protein and has other applications. Carefully identify and integrate the peaks obtained as directed for each *Procedure*. Calculate the mole percent for each amino acid present in the test sample by the formula:

$$100r_i/r,$$

in which r_i is the peak response, in nmol, of the amino acid under test, and r is the sum of peak responses, in nmol, for all amino acids present in the test sample. Comparison of the mole percent of the amino acids under test to data from known proteins can help establish or corroborate the identity of the sample protein.

Unknown Protein Samples— This data analysis technique can be used to estimate the protein concentration of an unknown protein sample using the amino acid analysis data. Calculate the mass, in µg, of each recovered amino acid by the formula:

$$mM_w/1000$$

in which m is the recovered quantity, in nmol, of the amino acid under test; and M_w is the average molecular weight, in mg, for that amino acid, corrected for the weight of the water molecule that was eliminated during peptide bond formation. The sum of the masses of the recovered amino acids will give an estimate of the total mass of the protein analyzed after appropriate correction for partially and completely destroyed amino acids. If the molecular weight of the unknown protein is available (i.e., by SDS-PAGE analysis or mass spectroscopy), the amino acid composition of the unknown protein can be predicted. Calculate the number of residues of each amino acid by the formula:

$$m/(1000M/M_w)$$

in which m is the recovered quantity, in nmol, of the amino acid under test; M is the total mass, in µg, of the protein; and M_w is the molecular weight, in mg, of the unknown protein.

Known Protein Samples— This data analysis technique can be used to investigate the amino acid composition and protein concentration of a protein sample of known molecular weight and amino acid composition using the amino acid analysis data. When the composition of the protein being analyzed is known, one can exploit the fact that some amino acids are recovered well, while other amino acid recoveries may be compromised because of complete or partial destruction (e.g., tryptophan, cysteine, threonine, serine, methionine), incomplete bond cleavage (i.e., for isoleucine and valine), and free amino acid contamination (i.e., by glycine and serine).

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Because those amino acids that are recovered best represent the protein, these amino acids are chosen to quantify the amount of protein. Well recovered amino acids are, typically, aspartate asparagine, glutamate glutamine, alanine, leucine, phenylalanine, lysine, and arginine. This list can be modified based on experience with one's own analysis system. Divide the quantity, in nmol, of each of the well-recovered amino acids by the expected number of residues for that amino acid to obtain the protein content based on each well recovered amino acid. Average the protein content results calculated. The protein content determined for each of the well-recovered amino acids should be evenly distributed about the mean. Discard protein content values for those amino acids that have an unacceptable deviation from the mean. Typically, a greater than 5% variation from the mean is considered unacceptable, but this is arbitrary. Recalculate the mean protein content from the remaining values to obtain the protein content of the sample. Divide the content of each amino acid by the calculated mean protein content to determine the amino acid composition of the sample by analysis.

Calculate the relative compositional error, in percentage, by the formula:

$$100m/m_s$$

in which m is the experimentally determined quantity, in nmol per amino acid residue, of the amino acid under test; and m_s is the known residue value for that amino acid. The average relative compositional error is the average of the absolute values of the relative compositional errors of the individual amino acids, typically excluding tryptophan and cysteine from this calculation. The average relative compositional error can provide important information on the stability of analysis run over time. The agreement in the amino acid composition between the protein sample and the known composition can be used to corroborate the identity and purity of the protein in the sample.

CAPILLARY ELECTROPHORESIS

Capillary electrophoresis is a physical method of analysis based on the migration, inside a capillary, of charged analytes dissolved in an electrolyte solution, under the influence of a direct-current electric field. In this section we are describing four capillary electrophoresis methods, *Free-Solution Capillary Electrophoresis, Capillary Gel Electrophoresis, Capillary Isoelectric Focusing,* and *Micelle Electrokinetic Chromatography.*

General Principle

The migration velocity of the analyte under an electric field of intensity, E, is determined by the electrophoretic mobility of the analyte and the electroosmotic mobility of the buffer inside the capillary. The electrophoretic mobility of a solute (μ_{ep}) depends on the characteristics of the solute (electrical charge, molecular size, and shape) and the characteristics of the buffer in which the migration takes place (type and ionic strength of the electrolyte, pH, viscosity, and additives). The electrophoretic velocity (V_{ep}) of a solute, assuming a spherical shape, is as follows:

$$V_{ep} = \mu_{ep} E = \left(\frac{q}{6\pi\eta r}\right)\left(\frac{V}{L}\right),$$

in which q is the effective charge of the particle; η is the viscosity of the buffer; r is the size of the solute ion; V is the applied voltage; and L is the total length of the capillary.

When an electric field is applied through the capillary filled with buffer, a flow of solvent is generated inside the capillary called electroosmotic flow. Its velocity depends on the electroosmotic mobility (μ_{eo}) which in turn depends on the charge density on the capillary internal wall and the buffer characteristics. The electroosmotic velocity (V_{eo}) is as follows:

$$V_{eo} = \mu_{eo} E = \left(\frac{\varepsilon\zeta}{\eta}\right)\left(\frac{V}{L}\right),$$

in which ε is the dielectric constant of the buffer; ζ is the zeta potential of the capillary surface; and the other terms are as defined above.

The electrophoretic and electroosmotic mobilities of the analyte may act in the same direction or in opposite directions, depending on the charge (positive or negative) of the solute, and the velocity of the solute (v) is as follows:

$$V = V_{ep} \pm V_{eo}.$$

The sum or the difference between the two velocities (V_{ep} and V_{eo}) is used depending on whether the mobilities act in the same or opposite directions. Under conditions with a fast V_{eo}, with respect to the V_{ep} of the solutes, both negative and positive charged analytes can be separated in the same run. The time (t) taken by the solute to migrate the distance (l) from the injection end of the capillary to the detection point (capillary effective length) is as follows:

$$t = \frac{l}{V_{ep} \pm V_{eo}} = \frac{l(L)}{V(\mu_{ep} \pm \mu_{eo})},$$

in which the other terms are as defined above.

In general, the fused-silica capillaries used in electrophoresis bear negative charges on the inner wall, producing electroosmotic flow towards the cathode. The electroosmotic flow has to remain constant from run to run to obtain good reproducibility in the migration velocity of the solutes. For some applications, it might be necessary to reduce or suppress the electroosmotic flow by modifying the inner wall of the capillary or by changing the pH of the buffer solution.

When the sample is introduced in the capillary, each analyte ion of the sample migrates within the background electrolyte as an independent zone according to its electrophoretic mobility. The spreading of each solute band (zone dispersion) results from a different phenomena. Under ideal conditions, the sole contribution to the solute zone broadening is molecular diffusion of the solute along the capillary (longitudinal diffusion). In this case, the efficiency of the zone is expressed as the number of theoretical plates (N), as follows:

$$N = \frac{(\mu_{ep} \pm \mu_{eo})(Vl)}{2DL},$$

in which D is the molecular diffusion of the solute in the buffer; and the other terms are as defined above.

From a practical point of view, other phenomena such as heat dissipation, sample adsorption onto the capillary wall, mismatched conductivity between sample and buffer, length of the injection plug, detector cell size, and unleveled buffer reservoirs can also significantly contribute to band dispersion. Separation between two bands (expressed by the resolution, R_s) can be achieved by modification of the

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electrophoretic mobility of the analytes, by the electroosmotic mobility induced by capillary, and by increasing the efficiency for the band of each analyte as follows:

$$R_S = \frac{\sqrt{N}(\mu_{epa} - \mu_{epa})}{4(\mu_{ep} \pm \mu_{eo})},$$

in which μ_{epa} and μ_{epa} are the electrophoretic mobilities of the two compounds to be separated; $\bar{\mu}_{ep}$ is the average electrophoretic mobility of the two solutes calculated as:

$$\bar{\mu}_{ep} = \tfrac{1}{2}(\mu_{epa} - \mu_{epa}),$$

and the other terms are as defined above.

Apparatus

An apparatus for capillary electrophoresis is composed of a high voltage controllable power supply; two buffer reservoirs held at the same level and containing specified anodic and cathodic solutions; two electrodes assemblies (cathode and anode) immersed in the buffer reservoirs and connected to the power supply; a separation capillary usually made of fused silica, with sometimes an optical viewing window aligned with detector, depending on the detector, with the ends of the capillary placed in the buffer reservoirs and the capillary being filled with a solution specified in a given monograph; a suitable injection system; a detector capable of monitoring the amount of substance of interest passing through a segment of the separation capillary at a given time, generally based on absorption spectrophotometry (UV and visible), fluorimetry, conductimetric, amperometric, or mass spectrometric detection, depending on the specific applications, or even indirect detection to detect non-UV absorbing and nonfluorescent compounds; and a thermostatic system capable of maintaining the temperature inside the capillary.

The method of injection of samples and its automation is critical for precise quantitative analysis. Methods of injection include gravity, pressure or vacuum, or electrokinetic injection. The amount of each sample component introduced electrokinetically depends on its electrophoretic mobility, thus possibly biasing the results.

It is expected that the capillary, the buffer solutions, the preconditioning method, the sample solution, and the migration conditions will be specified in the individual monograph. The electrolytic solution employed may be filtered to remove particles and degassed to avoid bubble formation that could interfere with the detection system. To achieve reproducible migration time of the solutes, if would be necessary to develop, for each analytical method, a rigorous rinsing routine after each injection.

Free Solution Capillary Electrophoresis

In free solution capillary electrophoresis, analytes are separated in a capillary containing only buffer without any anticonvective medium. In this technique, separation takes place because the different components of the sample migrate as discrete bands with different velocities. The velocity of each band depends on the electrophoretic mobility of the solute and the electroosmotic flow on the capillary. Coated capillaries, with reduced electroosmotic flow, can be used to increase the separation capacity of those substances absorbing on fused silica surfaces.

This mode of capillary electrophoresis is appropriate for the analysis of small (MW < 2000) and large molecules (2000 < MW < 100,000). Due to the high efficiency achieved, molecules having only minute differences in their charge-to-mass ratio can be separated. This method also allows the separation of chiral compounds by adding chiral selectors to the separation buffer. The optimization of the separations requires consideration of a number of instrumental and electrolytic solution parameters.

INSTRUMENTAL PARAMETERS

Voltage — The separation time is universally proportional to applied voltage. However, an increase in the voltage used can cause excessive heat production, giving rise to temperature and viscosity gradients in the buffer inside the capillary, which causes band broadening and decreases resolution.

Temperature — The main effect of temperature is observed on buffer viscosity and electrical conductivity, thus affecting migration velocity. In some cases, an increase in capillary temperature can cause a conformational change of some proteins, modifying their migration time and the efficiency of the separation.

Capillary — The length and internal diameter of the capillary affects the analysis time, the efficiency of separations, and the load capacity. Increasing both effective length and total length can decrease the electric fields, at a constant voltage, which will increase migration time. For a given buffer and electric field, heat dissipation (thus sample band broadening) depends on the internal diameter of the capillary. The latter also affects the detection limit, depending on the sample volume injected into the capillary and the detection system used.

The adsorption of sample components on the capillary wall limits efficiency; therefore, methods to avoid these interactions should be considered in the development of a separation method. This is critical in samples containing proteins. Strategies have been devised to avoid adsorption of proteins on the capillary wall. These strategies include both the use of extreme pH and the absorption of positively charged buffer additives that only require modification of the buffer composition. Other strategies include the coating of the internal wall of the capillary with a polymer covalently bonded to the silica that prevents interaction between the proteins and the negatively charged silica surface. Capillaries with coatings consisting of neutral hydrophilic, cationic, and anionic polymers are commercially available.

ELECTROLYTIC SOLUTION PARAMETERS

Buffer Type and Concentrations — Suitable buffers for capillary electrophoresis have an appropriate buffer capacity in the pH range of choice and low mobility to minimize current generation.

To minimize peak shape distortion, it is important to match buffer ion mobility to solute mobility, whenever possible. The type of sample solvent used is important to achieve on-column sample focusing which increases separation efficiency and improves detection. Also, an increase in buffer concentration at a given pH will decrease electroosmotic flow and solute velocity.

Buffer pH — The pH of the buffer can affect separation by modifying the charge of the analyte or other additives and by changing the electroosmotic flow. For protein and peptide separation, a change in the pH of the buffer from above the isoelectric point to below the isoelectric point changes the net charge of the solute from negative to positive. An increase in the buffer pH generally increases the electroosmotic flow.

Organic Solvents — Organic modifiers, such as methanol, acetonitrile, and others, are added to the aqueous buffer to increase the solubility of the solute or other additives and/or to affect the ionization degree of the sample components. The addition of these organic modifiers to the buffer generally causes a decrease in the electroosmotic flow.

Additives for Chiral Separations — To separate optical isomers, a chiral selector is added to the separation buffer. The most commonly used chiral selectors are cyclodextrins, although in some cases crown ethers, certain polysaccharides, or even proteins can be used. Because chiral recognition is governed by the different interactions between the chiral selector and each of the enantiomers, the resolution achieved for the chiral compounds depends largely on the type of chiral selector used. While developing a given separation it may be useful to test cyclodextrins having a different cavity size (α, β, or Γ-cyclodextrin) or modified cyclodextrins with neutral (methyl, ethyl, hydroxyalkyl, etc.) or ionizable (aminomethyl, carboxymethyl, sulfobutylether, etc.) moities. The resolution of chiral separations is also controlled by the concentration of the chiral selector, the composition

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and pH of the buffer, and the separation temperature. Organic additives, such as methanol or urea, can also affect the resolution of separation.

Capillary Gel Electrophoresis

Separation takes place inside a capillary filled with a polymer acting as a molecular sieve. The smaller components in the sample move faster along the capillary than the larger ones. This method can be used for separation of biopolymers proteins, and DNA fragments, according to their molecular mass.

CHARACTERISTICS OF CHEMICAL AND PHYSICAL GELS

Chemical Gels—Chemical gels are prepared inside the capillary by reaction of monomers. One example of such a gel is a cross-linked polyacrylamide. This type of gel is bonded to the fused silica wall and cannot be removed without destroying the capillary. For protein analysis, the separation buffer usually contains sodium dodecyl sulfate and the sample is denatured by heating in a mixture of sodium dodecyl sulfate and 2-mercaptoethanol or dithiothreitol before injection. Optimization of separation in a cross-linked gel is obtained by modifying the separation buffer (see *Free-Solution Capillary Electrophoresis*) and by controlling the gel porosity during the gel preparation. For a cross-linked polyacrylamide gel, the porosity can be modified by changing the concentration of acrylamide and/or the ratio of the cross-linker. As a rule, a decrease in the porosity of the gel leads to a decrease in the mobility of the solutes. Due to the rigidity of this type of gel, only electrokinetic injection can be used.

Physical Gels—Physical gels are hydrophilic polymers (i.e., linear polyacrylamide, cellulose derivatives, dextran, etc.) which can be dissolved in aqueous separation buffers, giving rise to a separation medium that also acts as a molecular sieve. These polymeric separation media are easier to prepare than cross-linked polymers. They can be prepared in a vial and filled by pressure in a wall-coated capillary with no electroosmotic flow. Replacing the gel before every injection generally improves the separation reproducibility. The porosity of the physical gels can be increased by using polymers of higher molecular weight (at a given polymer concentration) or by decreasing the polymer concentration (for a given polymer molecular weight). A decrease in gel porosity leads to a decrease in the mobility of the solute for the same buffer. Both hydrodynamic and electromigration injection techniques can be used, since the dissolution of these polymers in the buffer gives low-viscosity solutions.

Capillary Isoelectric Focusing

The molecules migrate under the influence of the electric field, so long as they are charged, in a pH gradient generated by ampholytes having pI values in a wide range (poly-aminocarboxylic acids) dissolved in the separation buffer. The three basic steps in capillary isoelectric focusing are loading, focusing, and mobilization.

Loading—

Loading in One Step—The sample is mixed with ampholytes and introduced into the capillary by pressure or vacuum.

Sequential Loading—A leading buffer, then the ampholytes, then the sample mixed with ampholytes, again ampholytes alone, and finally the terminating buffer are introduced into the capillary. The volume of the sample must be small enough so as to not modify the pH gradient.

Focusing—When the voltage is applied, ampholytes migrate toward the cathode or the anode according to their net charge, creating the pH gradient from anode (lower pH) to cathode (higher pH). The components to be separated migrate until they reach a pH corresponding to their isoelectric point and the current drops to very low values.

Mobilization—The bands of separated components migrate past the detector by one of the three following methods.

Method 1—During *Focusing*, under the influence of the electroosmotic flow when this flow is small enough to allow the focusing of the components.

Method 2—By application of positive pressure after *Focusing*.

Method 3—After *Focusing*, by adding salts in the cathode reservoir or the anode reservoir (depending on the direction chosen for mobilization), in order to alter the pH in the capillary when the voltage is applied. As the pH is changed, the proteins and ampholytes are mobilized in the direction of the reservoir which contains added salts and pass the detector.

The separation achieved is expressed as ΔpI and depends on the pH gradient (dpH), the number of ampholytes having different pI values, the diffusion coefficient (D), the intensity of the electric field (E), and the variation of the electrophoretic mobility of the analyte with the pH, and is as follows:

$$\Delta pI = 3\sqrt{\frac{D(dpH/dx)}{E(-d\mu/dpH)}},$$

in which dpH/dx is the pH gradient; and $d\mu/dpH$ is the variation of the solution mobility with the pH in the region close to the pI.

Optimization Parameters—The major parameters that need to be considered in the development of separations are voltage, capillary, and solutes.

Voltage—Use of high fields from 300 V/cm to 1,000 V/cm during *Focusing*.

Capillary—Depending on the *Mobilization* strategy selected (see above), the electroosmotic flow must be reduced or suppressed. Coated capillaries tend to reduce the electroosmotic flow.

Solutions—The anode buffer reservoir is filled with a solution of a lower pH than the pI of the most acidic ampholyte and the cathode reservoir is filled with a solution with a higher pH than the pI of the most basic ampholyte. Phosphoric acid for the anode and sodium hydroxide for the cathode are frequently used.

Addition of a polymer, like methylcellulose, in the ampholyte solution tends to suppress convective forces (if any) and electroosmotic flow by increasing the viscosity. Commercial ampholytes covering many pH ranges are available and may also be mixed to obtain an expanded pH range. Broad pH ranges are used to estimate the isoelectric point whereas narrower ranges are employed to improve accuracy. Calibration can be made by correlating migration time with the isoelectric point of a series of standard protein markers. During *Focusing*, precipitation of proteins at their isoelectric point can be prevented, if necessary, using buffer additives such as glycerol, surfactants, urea, or Zwitterionic buffers. However, depending on the concentration, urea can denature proteins.

Micellar Electrokinetic Chromatography (MEKC)

Separation takes place in an electrolytic solution which contains a surfactant, generally ionic, at a concentration above the critical micellar concentration. The solute molecules are distributed between the aqueous buffer and the pseudo-stationary phase composed by the micelles according to the solute's partition coefficient. The technique can be considered as a hybrid of electrophoresis and chromatography. It is an electrophoretic technique that can be used for the separation of both neutral and charged solutes maintaining the efficiency, speed, and instrumental suitability of capillary electrophoresis. One of the most widely used surfactants is sodium dodecyl sulfate, although other anionic and cationic surfactants, such as cetyl trimethyl ammonium salts, have also been used.

At neutral and alkaline pH, a strong electroosmotic flow is generated and moves the separation buffer ions in the direction of the cathode. If sodium dodecyl sulfate is used as surfactant, the electrophoretic migration of the anionic micelle is in the opposite direction, toward the anode. As a result, the overall micelle migration velocity is slowed compared to the bulk flow of the electrolytic solution. In the case of neutral solutes, since the analyte can partition between the micelle and the aqueous buffer and has no electrophoretic mobility, the analyte migration velocity will only depend on the partition coefficient between the micelle and the aqueous buffer. In the electropherotogram, the peak corresponding to each uncharged solute is always between that of the electroosmotic flow marker and that of the micelle, and the time elapsed between these two peaks is called the separation window. For electrically charged solutes, the migration

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velocity depends on both the partition coefficient of the solute between the micelle and the aqueous buffer and on the electrophoretic mobility of the solute in the absence of micelles.

The separation mechanism is essentially chromatographic, and migration of the solute and resolution can be expressed in terms of the capacity factor of the solute (K'), which is the ratio between the total number of moles of solute in the micelle to those in the mobile phase. For a neutral compound, K' is as follows:

$$K' = \frac{t_r - t_o}{t_o(1 - t_r/t_m)} = K\left(\frac{V_S}{V_M}\right),$$

in which t_r is the migration time of the solute; t_o is the analysis time of the unretained solute obtained by injecting an electroosmotic flow marker which does not enter the micelle (i.e., methanol); t_m is the micelle migration time measured by injecting a micelle marker, such as Sudan III, which migrates continuously associated in the micelle; K is the partition coefficient of the solute; V_S is the volume of the micelles phase; and V_M is the volume of the mobile phase.

The resolution between two closely migrating compounds (R_S) is as follows:

$$R_S = \left(\frac{\sqrt{N}}{4}\right)\left(\frac{\alpha - 1}{\alpha}\right)\left(\frac{K'_b}{K'_b}\right)\left(\frac{1 - (t_o/t_m)}{1 + (t_o/t_m)K'_a}\right),$$

in which N is the number of theoretical plates for one of the compounds; α is the selectivity obtained; K'_a and K'_b are capacity factors for both components; and the other terms are as defined above.

Similar, but not identical, equations give K' and R_S values for electrically charged compounds.

Optimization Parameters — The main parameters to be considered in the development of separations by MEKC are instrumental and electrolytic solution parameters.

INSTRUMENTAL PARAMETERS

Voltage — Separation time is inversely proportional to applied voltage. An increase in voltage can cause excessive heat production that gives rise to temperature gradients and viscosity gradients of the buffer in the cross section of the capillary. This effect can be significant with high conductivity buffers, such as those containing micelles. Poor heat dissipation causes band broadening and decreases resolution.

Temperature — Variations in capillary temperature affect the partition coefficient of the solute between the buffer and the micelle, the critical micelle concentration, and the viscosity of the buffer. These parameters contribute to the migration time of the solutes.

Capillary — Length and internal diameter contribute to analysis time and efficiency of separations. Increasing both effective length and total length can decrease the electrical fields, working at constant voltage, and will increase migration time and improve the separation efficiency. The internal diameter controls heat dissipation, at a given buffer and electrical field, and provides a broadening of the sample band.

ELECTROLYTIC SOLUTION PARAMETERS

Surfactant Type and Concentration — The type of surfactant, as the stationary phase in chromatography, affects the resolution since it modifies separation selectively. The log K' of a neutral compound increases linearly with the concentration of detergent in the mobile phase. Resolution in MEKC reaches a maximum when K' approaches the value of

$$\sqrt{t_m t_{mc}},$$

modifying the concentration of surfactant in the mobile phase changes the resolution.

Buffer pH — pH does not modify the partition coefficient of non-ionized solutes, but it can modify the electroosmotic flow in uncoated capillaries. A decrease in the buffer pH decreases the electroosmotic flow and therefore increases the resolution of the neutral solutes, giving rise to longer analysis time.

Organic Solvents — To improve separation of hydrophobic compounds, organic modifiers (methanol, propanol, acetonitrile, etc.) can be added to the separation electrolytic solution. The addition of these modifiers generally decreases migration time and selectivity of the separation. The addition of organic modifiers affects micelle formation, thus a given surfactant concentration can be used only with a certain percentage of organic modifier before the micellezation equilibrium is eliminated or adversely affected, resulting in the absence of micelles and therefore the absence of the partition mechanism of MEKC. The elimination of micelles in the presence of a high content of organic solvent does not always mean that the separation will no longer be possible, since in some cases, the hydrophobic interaction between the ionic surfactant monomer and the neutral solutes form solvophobic complexes that can be separated electrophoretically.

Additives for Chiral Separations — A chiral selector is included in the micellar system, either covalently bound to the surfactant or added to the micellar separation electrolyte. Micelles which have a moiety with chiral discrimination properties include salts, *N*-dodecanoyl L-anine acids, bile salts, etc. Chiral resolution can also be achieved using chiral discriminators, such as cyclodextrins added to the electrolytic solutions which contain micellized achiral surfactants.

Other Additives — Selectivity can be modified by adding chemicals to the buffer. Addition of several types of cyclodextrins to the buffer are also used to reduce the interaction of hydrophobic solutes with the micelle, increasing the selectivity for this type of compound. The addition of substances able to modify solute-micelle interactions by adsorption on the latter, has been used to improve the selectivity of the separations in MEKC. These additives may consist of a second surfactant (ionic or non-ionic) which gives rise to mixed micelles, metallic cations which dissolve in the micelle, and give co-ordination complexes with the solutes.

QUANTITATIVE ANALYSIS

Peak areas must be divided by the corresponding migration time to give the corrected area in order to compensate for the shift in migration time from run to run, thus reducing the variation of the response. It will also compensate for the different responses of sample constituents with different migration times. Where an internal standard is used, check that no peak of the substance to be examined is masked by that of the internal standard.

Calculations — From the values obtained, calculate the content of a component or components being determined. When indicated, the percentage of one (or more) components of the sample to be examined is calculated by determining the areas of the peak(s) as a percentage of the total corrected areas of all the peaks, excluding those due to solvents or any added reagents. The use of an automatic integration system (integrator or data acquisition and processing system) is recommended.

Capillary Electrophoresis System Suitability

The choice of suitability parameters to be used will depend on the type of capillary electrophoresis that is performed. These parameters are the capacity factor (K') used only for *Micelles Electrokinetic Chromatography*, the number of theoretical plates (n), the symmetry factor (A_s), and the resolution (R_s). Note that in previous sections, the

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theoretical expression for n and R_s have been described, but more practical equations that allow for the determination of these suitability parameters using the electropherotograms are described below.

The number of theoretical plates (n) may be calculated from the formula:

$$n = 5.54\,(t/b_{0.5})^2,$$

in which t is the distance, in mm, along the baseline between the point of injection and the perpendicular dropped from the maximum of the peak in question; and $b_{0.5}$ is the peak width, in mm, at half height.

The resolution (R_s) may be calculated from the formula:

$$R_s = 1.18(t_{s2} - t_{s1})/b_{0.5,2} - b_{0.5,1}),$$

in which t_{s1} and t_{s2} are the distances, in mm, along the baseline, between the point of injection and the perpendicular dropped from the maxima of two adjacent peaks ($t_{s2} > t_{s1}$); and $b_{0.5,1}$ and $b_{0.5,2}$ are the peak widths, in mm, at half height.

The resolution (R_s) may be also calculated by measuring the height of the valley (c) between two partly resolved peaks in a standard preparation, the height of the smaller peak (d), and by specifying $(c/d) \leq x$, in which x is the limit indicated in the individual monograph.

The symmetry factor of a peak (A_s) may be calculated using the formula:

$$A_s = b_{0.05}/2A,$$

in which $b_{0.05}$ is the width of the peak at one-twentieth of the peak height; and A is the distance between the perpendicular dropped from the peak maximum and the leading edge of the peak at one-twentieth of the peak height.

Other system suitability parameters include tests for area repeatability (i.e., standard deviation of areas or of area/migration time) and tests for migration time repeatability (i.e., standard deviation of migration time). For migration time repeatability, it will be necessary to provide for a test to measure the suitability of the capillary washing procedures. To avoid the lack of repeatability of the migration time, an alternative practice is to use a migration time relative to an internal standard.

A test for the verification of the signal-to-noise ratio for a standard preparation or the determination of the limit of quantitation is a useful system suitability parameter. The detection limit and quantitation limit correspond to a signal-to-noise ratio greater than 3 and 10, respectively. The signal-to-noise ratio (S/N) is calculated as follows:

$$S/N = 2H/h_n,$$

in which H is the height of the peak corresponding to the component concerned in the electropherotogram obtained with the specified reference solution; and h_n is the absolute value of the largest noise fluctuation from the baseline in an electropherotogram obtained after injection of a blank and observed over a distance equal to twenty times the width at the half-height of the peak in the electropherotogram obtained with the reference solution, and situated equally around the place where this peak would be found.

ISOELECTRIC FOCUSING

Isoelectric focusing (IEF) is a method of electrophoresis that separates proteins according to their isoelectric points. Separation is carried out in a slab of polyacrylamide or agarose gel that contains a mixture of amphoteric electrolytes (ampholytes). When subjected to an electrical field, the ampholytes migrate in the gel to create a pH gradient. In some cases, gels containing an immobilized pH gradient, prepared by incorporating weak acids and bases to specific regions of the gel network during the preparation of the gel, are used. When the applied proteins reach the gel fraction that has a pH that is the same as their isoelectric point, their charge is neutralized and migration ceases. Gradients can be made over various ranges of pH, according to the mixture of ampholytes chosen.

General Principles

When a protein is at the position of its isoelectric point, it has no net charge and cannot be moved in a gel matrix by the electric field. It may, however, move from that position by diffusion. The pH gradient forces a protein to remain in its isoelectric point position, thus concentrating it; this concentration effect is called "focusing". Increasing the applied voltage or reducing the sample load results in improved resolution of bands. The applied voltage is limited by the heat generated because the heat must be dissipated. The use of thin gels and an efficient cooling plate controlled by a thermostatic circulator prevents the burning of the gel while allowing sharp focusing. The separation is estimated by determining the minimum pI difference, which is necessary to separate two neighboring bands, as follows:

$$\Delta pI = 3\sqrt{\frac{D(dpH/dx)}{E(-d\mu/dpH)}},$$

in which D is the diffusion coefficient of the protein; dpH/dx is the pH gradient; E is the intensity of the electric field, in volts per centimeter; and $-d\mu/dpH$ is the variation of the solute mobility with the pH in the region close to the pI. Since D and $-d\mu/dpH$ for a given protein cannot be altered, the separation can be improved by using a narrower pH range and by increasing the intensity of the electric field.

From an operational point, special attention must be paid to sample characteristics and/or preparation. Salt in a sample can be problematic and it is best to prepare the sample, if possible, in deionized water or 2% ampholytes using dialysis or gel filtration if necessary. Potentials of 2500 volts have been used and are considered optimal under a given set of conditions. Up to 30 watts of constant power can be applied and will generally give complete separation in 1.5 to 3.0 hours. The time required for completion of focusing in thin layer polyacrylamide gels is determined by placing a colored protein (e.g., hemoglobin) at different positions on the gel surface and by applying the electric field: the steady state is reached when all applications give an identical band pattern. In some procedures the completion of the focusing is indicated by the time elapsed after the sample application.

Resolution between protein bands on an IEF gel prepared with carrier ampholytes can be quite good. Better resolution may be achieved by using immobilized pH gradients where the buffering species, which are analogous to carrier ampholytes, are copolymerized within the gel matrix. Proteins exhibiting pIs differing by as little as 0.02 pH units may be resolved using a gel prepared with carrier ampholytes, while immobilized pH gradients can resolve protein differing by approximately 0.001 pH units.

The IEF gel can be used as an identity test when migration on the gel is compared to a standard preparation and IEF calibration proteins, the IEF gel can be used as a limit test when the density of a band on IEF is compared subjectively with the density of bands appearing in a standard preparation, or it can be used as a semi-quantitative test when the density is measured using a densitometer or similar instrumentation to determine the relative concentration of protein in the bands.

Apparatus

An apparatus for isoelectric focusing consists of a controllable direct current generator, of stabilized output; a rigid plastic isoelectric focusing chamber that contains a cooled plate of suitable material to support the gel; and a plastic cover with platinum electrodes that are connected to the gel by means of paper wicks of suitable width, length, and thickness, impregnated with solutions of anodic and cathodic electrolytes.

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Procedure

Unless otherwise indicated in a given monograph, the following procedure in thick polyacrylamide slab gels is to be used.

Preparation of the Gels—

Assembly—Composed of a glass plate (A) on which a polyester film (B) is placed to facilitate handling of the gel, one or more spacers (C), a second glass plate (D), and clamps to hold the structure together (see *Figure 1*).

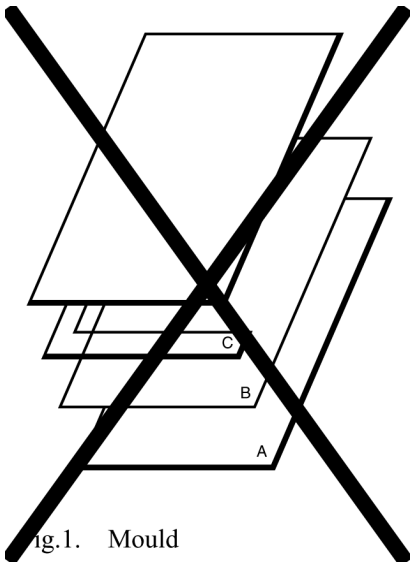

Fig.1. Mould

7.5% Polyacrylamide Gel—Dissolve 29.1 g of acrylamide and 0.9 g of methylenebisacrylamide in 100 mL of water. To 2.5 volumes of this solution, add the mixture of ampholytes specified in the individual monograph, and make up to 10 volumes with water. Mix carefully, and degas the solution.

Preparation of the Assembly—Place the polyester film on the lower glass plate, apply the spacer, place the second glass plate, and fit the clamps. Before use, place the mixture on a magnetic stirrer, and add 0.25 volumes of a 10% solution of ammonium persulfate and 0.25 volumes of tetramethylenediamine. Immediately fill the space between the glass plates of the assembly with the gel.

Fixing Solution for Isoelectric Focusing Polyacrylamide Gel—Mix 35 g of sulfosalicylic acid and 100 g of trichloroacetic acid in 1000 mL of water.

Coomassie Staining Solution and *Destaining Solution*—Use the same solutions indicated in *Polyacrylamide Gel Electrophoresis*.

Procedure—Dismantle the assembly, and using the polyester film, transfer the gel onto the cooled support wetted with a few milliliters of a suitable liquid, taking care to avoid forming air bubbles. Prepare the test solutions and reference solutions as specified in the individual monograph. Place strips of paper for sample application, about 10 mm × 5 mm in size, on the gel, and impregnate each with the prescribed amount of the test and reference solutions. If the protein concentration of the solution is too low, several strips may be superimposed (up to four). Also apply the prescribed quantity of a solution of proteins with known isoelectric points as pH markers to calibrate the gel. In some procedures, the gel has pre-cast slots where a solution of the sample is applied instead of using impregnated paper strips. Cut two strips of paper to the length of the gel, and impregnate them with the electrolyte solutions: acid for the anode and alkaline for the cathode. The compositions of the anode and cathode solutions are given in the individual monograph. Apply these paper wicks to each side of the gel several millimeters from the edge. Fit the cover so that the electrodes are in contact with the wicks (with respect to the anodic and cathodic poles). Proceed with the isoelectric focusing by applying the electrical parameters described in the individual monograph. Switch off the current when the migration of the mixture of standard proteins has stabilized. Using forceps, remove the sample application strips and the two electrode wicks. Immerse the gel in *Fixing Solution for Isoelectric Focusing Polyacrylamide Gel*. Incubate with gentle shaking at room temperature for 30 minutes. Drain off the solution, and add 200 mL of *Destaining Solution*. Incubate with shaking for 1 hour. Drain the gel, add *Coomassie Staining Solution*. Incubate for 30 minutes. Destain the gel by passive diffusion with *Destaining Solution* until the bands are well visualized against a clear background. Locate the position and intensity of the bands in the electropherogram as prescribed in the individual monograph.

Alternative Procedure—When a monograph references the general method for isoelectric focusing above, variations in methodology or procedure may be used, subject to validation. These variations include the use of commercially available pre-cast gels; the use of immobilized pH gradients; the use of rod gels; and the use of cassettes of different dimensions, including ultra-thin (0.2 mm) gels; the variations in the sample application procedure, including different sample volumes or the use of sample application masks or wicks other than paper; the use of alternate running conditions, including variations in the electric field depending on gel dimensions and equipment, and the use of fixed migration times rather than subjective interpretation of band stability; the inclusion of a pre-focusing step; the use of automated instrumentation; and the use of agarose gels.

Validation of Procedure

Where alternative methods to the general method are employed, they must be validated. The following criteria may be used to validate the separation: the formation of a stable pH gradient of desired characteristics, evaluated using colored pH markers of known isoelectric points; the comparison with electropherogram provided with the chemical reference substance for the preparation to be examined; and any other validation criteria as prescribed in the individual monograph.

Specified Variations to the General Method

Variations to the general method required for the analysis of specific substances may be specified in detail in individual monographs. Variations may include the addition of urea in the running gel (3 M concentration is often satisfactory to keep protein in solution but up to 8 M can be used). Some proteins precipitate at their isoelectric point. In this case, urea is included in the gel formulation to keep the protein in solution. If urea is used, only fresh solutions should be used to prevent carbamylation of the protein. Other variations include the use of alternative staining methods and the use of gel additives such as nonionic detergents (e.g., octylglucoside) or zwitterionic detergents (e.g., CHAPS or CHAPSO) to prevent proteins from aggregating or precipitating.

NOTE—The following are general precautionary items that can be used to improve the method. Samples can be applied to any area on the gel, but in general, they should be applied to areas where they are expected to focus. To protect the proteins from extreme pH environments, samples should not be applied close to either electrode. During method development, the analyst can try applying the protein in three positions on the gel (i.e., middle and both ends); the pattern of a protein applied at opposite ends of the gel may not be identical. A phenomenon known as cathodic drift, where the pH gradient decays over time, may occur if a gel is focused too long. Although not well understood, electroendoosmosis and absorption of carbon dioxide may be factors that lead to cathodic drift. Cathodic drift is observed as focused protein migrating off the cathode end of the gel. Immobilized pH gradients may be used to address this problem. Efficient cooling (approximately 4°) of the bed that the gel lies on during focusing is important. High field strengths used during isoelectric focusing can lead to overheating and affect the quality of the focused gel.

PEPTIDE MAPPING

Purpose and Scope

Peptide mapping is an identity test for proteins, especially those obtained by r-DNA technology. It involves the chemical or enzymatic treatment of a protein resulting in the formation of peptide fragments followed by separation and identification of the resultant fragments in

a reproducible manner. It is a powerful test that is capable of identifying single amino acid changes resulting from events such as errors in the reading of complementary DNA (cDNA) sequences or point mutations. Peptide mapping is a comparative procedure because the information obtained, compared to a reference standard or reference material similarly treated, confirms the primary structure of the protein, is capable of detecting whether alterations in structure have occurred, and demonstrates process consistency and genetic stability. Each protein presents unique characteristics which must be well understood so that the scientific and analytical approaches permit validated development of a peptide map that provides sufficient specificity.

This section provides detailed assistance in the application of peptide mapping and its validation to characterize the desired protein product, to evaluate the stability of the expression construct of cells used for recombinant DNA products, to evaluate the consistency of the overall process, and to assess product stability, as well as to ensure the identity of the protein product, or to detect the presence of protein variant. The validation scheme presented differentiates between qualification of the method at an early stage in the regulatory process, Investigational New Drug (IND) level, and full validation in support of New Drug Application (NDA), Product License Application (PLA), or Marketing Authorization Application (MAA). The validation concepts described are consistent with the general information chapter *Validation of Compendial Methods* ⟨1225⟩ and with the International Conference on Harmonization (ICH) document on *Analytical Methods Validation*.

The Peptide Map

Peptide mapping is not a general method, but involves developing specific maps for each unique protein. Although the technology is evolving rapidly, there are certain methods that are generally accepted. Variations of these methods will be indicated, when appropriate, in specific monographs.

A peptide map may be viewed as a fingerprint of a protein and is the end product of several chemical processes that provide a comprehensive understanding of the protein being analyzed. Four major steps are necessary for the development of the procedure: isolation and purification of the protein, if the protein is part of a formulation; selective cleavage of the peptide bonds; chromatographic separation of the peptides; and analysis and identification of the peptides. A test sample is digested and assayed in parallel with a reference standard or reference material. Complete cleavage is more likely to occur when enzymes such as endoproteases (e.g., trypsin) are used instead of chemical cleavage reagents. A map should contain enough peptides to be meaningful. On the other hand, if there are too many fragments, the map might lose its specificity because many proteins will then have the same profiles.

ISOLATION AND PURIFICATION

Isolation and purification are necessary for analysis of bulk drugs or dosage forms containing interfering excipients and carrier proteins and, when required, will be specified in the monograph. Quantitative recovery of protein from the dosage form should be validated.

SELECTIVE CLEAVAGE OF PEPTIDE BONDS

The selection of the approach used for the cleavage of peptide bonds will depend on the protein under test. This selection process involves determination of the type of cleavage to be employed—enzymatic or chemical—and the type of cleavage agent within the chosen category. Several cleavage agents and their specificity are shown in *Table 1*. This list is not all-inclusive and will be expanded as other cleavage agents are identified.

Table 1. Examples of Cleaving Agents

Type	Agent	Specificity
Enzymatic	Trypsin (EC 3.4.21.4)	*C* terminal side of Arg and Lys
	Chymotrypsin (EC 3.4.21.1)	*C* terminal side of hydrophobic residues (e.g., Leu, Met, Ala, aromatics)
	Pepsin (EC 3.4.23.1)	Nonspecific digest
	Lysyl endopeptidase (Lys-C Endopeptidase) (EC 3.4.21.50)	*C* terminal side of Lys
	Glutamyl endopeptidase (from *S. aureus* strain V8) (EC 3.4.21.19)	*C* terminal side of Glu and Asp
	Peptidyl-Asp metaplo-endopeptidase (Endoproteinase Asp-N) (EC 3.4.24.33)	*N* terminal side of Asp
	(Clostripain) (EC 3.4.28.8)	*C* terminal side of Arg
Chemical	Cyanogen bromide	*C* terminal side of Met
	2-Nitro-5-thio-cyano- benzoic acid	*N* terminal side of Cys
	O-Iodosobenzoic acid	*C* terminal side of Trp and Tyr
	Dilute acid	Asp and Pro
	BNPS-skatole	Trp

Pretreatment of Sample—Depending on the size or the configuration of the protein, different approaches in the pretreatment of samples can be used. For monoclonal antibodies, the heavy and light chains will need to be separated before mapping. If trypsin is used as a cleavage agent for proteins with a molecular mass greater than 100,000 Da, lysine residues must be protected by citraconylation or maleylation; otherwise, too many peptides will be generated.

Pretreatment of the Cleavage Agent—Pretreatment of cleavage agents—especially enzymatic agents—might be necessary for purification purposes to ensure reproducibility of the map. For example, trypsin used as a cleavage agent will have to be treated with tosyl-L-phenylalanine chloromethyl ketone to inactivate chymotrypsin. Other methods, such as purification of trypsin by HPLC or immobilization of enzyme on a gel support, have been successfully used when only a small amount of protein is available.

Pretreatment of the Protein—Under certain conditions, it might be necessary to concentrate the sample or to separate the protein from added substances and stabilizers used in the formulation of the product, if these interfere with the mapping procedure. Physical procedures used for pretreatment can include ultrafiltration, column chromatography, and lyophilization.

Other pretreatments, such as the addition of chaotropic agents (e.g., urea), can be used to unfold the protein prior to mapping. To allow the enzyme to have full access to cleavage sites and permit some unfolding of the protein, it is often necessary to reduce and alkylate the disulfide bonds prior to digestion.

Digestion with trypsin can introduce ambiguities in the tryptic map due to side reactions occurring during the digestion reaction, such as nonspecific cleavage, deamidation, disulfide isomerization, oxidation of methionine residues, or formation of pyroglutamic groups created

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from the deamidation of glutamine at the *N* terminal side of a peptide. Furthermore, peaks may be produced by autohydrolysis of trypsin. Their intensities depend on the ratio of trypsin to protein. To avoid autohydrolysis, solutions of proteases may be prepared at a pH that is not optimal (e.g., at pH 5 for trypsin), which would mean that the enzyme would not become active until diluted with the digest buffer.

Establishment of Optimal Digestion Conditions— Factors that affect the completeness and effectiveness of digestion of proteins are those that could affect any chemical or enzymatic reactions.

pH— The pH of the digestion mixture is empirically determined to ensure the optimization of the performance of the given cleavage agent. For example, when using cyanogen bromide as a cleavage agent, a highly acidic environment (e.g., pH 2, formic acid) is necessary; however, when using trypsin as a cleavage agent, a slightly alkaline environment (pH 8) is optimal. As a general rule, the pH of the reaction milieu should not alter the chemical integrity of the protein during the digestion and should not change during the course of the fragmentation reaction.

Temperature— A temperature between 25° and 37° is adequate for most digestions. The temperature used is intended to minimize chemical side reactions. The type of protein under test will dictate the temperature of the reaction milieu, because some proteins are more susceptible to denaturation as the temperature of the reaction increases. For example, digestion of recombinant bovine somatropin is conducted at 4°, because at higher temperatures it will precipitate during digestion.

Time— If a sufficient amount of sample is available, a time course study is considered in order to determine the optimum time to obtain a reproducible map and avoid incomplete digestion. Time of digestion varies from 2 to 30 hours. The reaction is stopped by the addition of an acid that does not interfere in the tryptic map, or by freezing.

Amount of Cleavage Agent— Although excessive amounts of cleavage agent are used to accomplish a reasonably rapid digestion time (i.e., 6 to 20 hours), the amount of cleavage agent is minimized to avoid its contribution to the chromatographic map pattern. A protein to protease ratio between 20 : 1 and 200 : 1 is generally used. It is recommended that the cleavage agent can be added in two or more stages to optimize cleavage. Nonetheless, the final reaction volume remains small enough to facilitate the next step in peptide mapping—the separation step. To sort out digestion artifacts that might be interfering with the subsequent analysis, a blank determination is performed, using a digestion control with all the reagents, except the test protein.

CHROMATOGRAPHIC SEPARATION

Many techniques are used to separate peptides for mapping. The selection of a technique depends on the protein being mapped. Techniques that have been successfully used for separation of peptides are shown in *Table 2*.

Table 2. Techniques Used for the Separation of Peptides

Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC)
Ion-Exchange Chromatography (IEC)
Hydrophobic Interaction Chromatography (HIC)
Polyacrylamide-Gel Electrophoresis (PAGE), nondenaturating
Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis (SDS-PAGE)
Capillary Electrophoresis (CE)
Paper Chromatography
High-Voltage Paper Electrophoresis (HVPE)

In this section, a most widely used reverse-phase HPLC (RP-HPLC) method is described as one of the procedures of chromatographic separation.

The purity of solvents and mobile phases is a critical factor in HPLC separation. HPLC-grade solvents and water that are commercially available are recommended for RP-HPLC. Dissolved gases present a problem in gradient systems where the solubility of the gas in a solvent may be less in a mixture than in a single solvent. Vacuum degassing and agitation by sonication are often used as useful degassing procedures. The solid particles in the solvents are drawn into the HPLC system, they can damage the sealing of pump valves or clog the top of the chromatographic column. Both pre- and post-pump filtration is also recommended.

Chromatographic Column— The selection of a chromatographic column is empirically determined for each protein. Columns with 100Å or 300Å pore size with silica support can give optimal separation. For smaller peptides, octylsilane chemically bonded to totally porous silica articles, 3 to 10 µm in diameter (L7) and octadecylsilane chemically bonded to porous silica or ceramic microparticles, 3 to 10 µm in diameter (L1) column packings are more efficient than the butyl silane chemically bonded to totally porous silica particles, 5 to 10 µm in diameter (L26) packing.

Solvent— The most commonly used solvent is water with acetonitrile as the organic modifier to which less than 0.1% of trifluoroacetic acid is added. If necessary, add isopropyl alcohol or *n*-propyl alcohol to solubilize the digest components, provided that the addition does not unduly increase the viscosity of the components.

Mobile Phase— Buffered mobile phases containing phosphate are used to provide some flexibility in the selection of pH conditions, since shifts of pH in the 3.0 to 5.0 range enhance the separation of peptides containing acidic residues (e.g., glutamic and aspartic acids). Sodium or potassium phosphates, ammonium acetate, phosphoric acid, and a pH between 2 and 7 (or higher for polymer based supports) have also been used with acetonitrile gradients. Acetonitrile containing trifluoroacetic acid is also used quite often.

Gradient Selection— Gradients can be linear, nonlinear, or include step functions. A shallow gradient is recommended in order to separate complex mixtures. Gradients are optimized to provide clear resolution of one or two peaks that will become "marker" peaks for the test.

Isocratic Selection— Isocratic HPLC systems using a single mobile phase are used on the basis of their convenience of use and improved detector responses. Optimal composition of a mobile phase to obtain clear resolution of each peak is sometimes difficult to establish. Mobile phases for which slight changes in component ratios or in pH significantly affect retention times of peaks in peptide maps should not be used in isocratic HPLC systems.

Other Parameters— Temperature control of the column is usually necessary to achieve good reproducibility. The flow rates for the mobile phases range from 0.1 to 2.0 mL per minute, and the detection of peptides is performed with a UV detector at 200 to 230 nm. Other methods of detection have been used (e.g., postcolumn derivatization), but they are not as robust or as versatile as UV detection.

System Suitability— The section *System Suitability* under *Chromatography* ⟨621⟩ provides an experimental means for measuring the overall performance of the test method. The acceptance criteria for system suitability depend on the identification of critical test parameters that affect data interpretation and acceptance. These critical parameters are also criteria that monitor peptide digestion and peptide analysis. An indicator that the desired digestion endpoint was achieved is the comparison with a reference standard or reference material, which is treated exactly as the article under test. The use of a USP Reference Standard in parallel with the protein under test is critical in the development and establishment of system suitability limits. In addition, a specimen chromatogram should be included with the USP Reference Standard or reference material for comparison purposes. Other indicators may include visual inspection of protein or peptide solubility, the absence of intact protein, or measurement of responses of a digestion dependent peptide. The critical system suitability parameters for peptide analysis will depend on the particular mode of peptide separation and detection, and on the data analysis requirements.

When peptide mapping is used as an identification test, the system suitability requirements for the identified peptides covers selectivity and precision. In this case, as well as when identification of variant proteins is done, the identification of the primary structure of the peptide fragments in the peptide map provides both a verification of the known primary structure and the identification of protein variants by comparison with the peptide map of the USP Reference Standard or reference material for the specified protein. The use of a digested USP Reference Standard or reference material for a given protein in the determination of peptide resolution is the method of choice. For an analysis of a variant protein, a characterized mixture of a variant

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and a reference standard can be used, especially if the variant peptide is located in a less resolved region of the map. The index of pattern consistency can be simply the number of major peptides detected. Peptide pattern consistency can be best defined by the resolution of peptide peaks. Chromatographic parameters—such as peak to peak resolution, maximum peak width, peak tailing factors, and column efficiency—may be used to define peptide resolution. Depending on the protein under test and the method of separation used, single peptide or multiple peptide resolution requirements may be necessary.

The replicate analysis of the digest of the USP Reference Standard or reference material for the protein under test yields measures of precision and quantitative recovery. Recovery of the identified peptides is generally ascertained by the use of internal or external peptide standards. The precision is expressed as the relative standard deviation (RSD). Differences in the recovery and precision of the identified peptides are expected; therefore, the system suitability limits will have to be established for both the recovery and the precision of the identified peptides. These limits are unique for a given protein and will be specified in the individual monograph.

Visual comparison of the relative retention times, the peak responses, the number of peaks, and the overall elution pattern is completed initially. It is then complemented and supported by mathematical analysis of the peak response ratios and by the chromatographic profile of a 1 : 1 (v/v) mixture of sample and USP Reference Standard or reference material digest. If all peaks in the sample digest and in the USP Reference Standard or reference material digest have the same relative retention times and peak response ratios, then the identity of the sample under test is confirmed.

If peaks that initially eluted with significantly different relative retention times are then observed as single peaks in the 1 : 1 mixture, the initial difference would be an indication of system variability. However, if separate peaks are observed in the 1 : 1 mixture, this would be evidence of the nonequivalence of the peptides in each peak. If a peak in the 1 : 1 mixture is significantly broader than the corresponding peak in the sample and USP Reference Standard or reference material digest, it may indicate the presence of different peptides. The use of computer-aided pattern recognition software for the analysis of peptide mapping data has been proposed and applied, but issues related to the validation of the computer software preclude its use in a compendial test in the near future. Other automated approaches have been used that employ mathematical formulas, models, and pattern recognition. Such approaches, for example, the automated identification of compounds by IR spectroscopy and the application of diode-array UV spectral analysis for identification of peptides, have been proposed. These methods have limitations due to inadequate resolutions, co-elution of fragments, or absolute peak response differences between USP Reference Standard or reference material and sample fragments.

The numerical comparison of the retention times and peak areas or peak heights can be done for a selected group of relevant peaks that have been correctly identified in the peptide maps. Peak areas can be calculated using one peak showing relatively small variation as an internal reference, keeping in mind that peak area integration is sensitive to baseline variation and likely to introduce error in the analysis. Alternatively, the percentage of each peptide peak height relative to the sum of all peak heights can be calculated for the sample under test. The percentage is then compared to that of the corresponding peak of the USP Reference Standard or reference material. The possibility of autohydrolysis of trypsin is monitored by producing a blank peptide map that is the peptide map obtained when a blank solution is treated with trypsin.

The minimum requirement for the qualification of peptide mapping is an approved test procedure that includes system suitability as a test control. In general, for an IND, qualification of peptide mapping for a protein is sufficient. As the regulatory approval process for the protein progresses, additional qualifications of the test can include a partial validation of the analytical procedure to provide assurance that the method will perform as intended in the development of a peptide map for the specified protein.

ANALYSIS AND IDENTIFICATION OF PEPTIDES

This section gives guidance on the use of peptide mapping during development in support of regulatory applications.

The use of a peptide map as a qualitative tool does not require the complete characterization of the individual peptide peaks. However, validation of peptide mapping in support of regulatory applications requires rigorous characterization of each of the individual peaks in the peptide map. Methods to characterize peaks range from *N* terminal sequencing of each peak followed by amino acid analysis to the use of mass spectroscopy (MS).

For characterization purposes, when *N* terminal sequencing and amino acids analysis are used, the analytical separation is scaled up. Since scale-up might affect the resolution of peptide peaks, it is necessary, using empirical data, to assure that there is no loss of resolution due to scale up. Eluates corresponding to specific peptide peaks are collected, vacuum concentrated, and chromatographed again, if necessary. Amino acid analysis of fragments may be limited by the peptide size. If the *N* terminus is blocked, it may need to be cleared before sequencing. *C* terminal sequencing of proteins in combination with carboxypeptidase and MALDITOF MS can also be used for characterization purposes.

The use of MS for characterization of peptide fragments is by direct infusion of isolated peptides or by the use of on-line LC-MS for structure analysis. In general, it includes electrospray and matrix-assisted laser desorption ionization coupled to time of flight analyzer (MALDITOF) as well as fast atom bombardment (FAB). Tandem MS has also been used to sequence a modified protein and to determine the type of amino acid modification that has occurred. The comparison of mass spectra of the digests before and after reduction provides a method to assign the disulfide bonds to the various sulfhydryl containing peptides.

If regions of the primary structure are not clearly demonstrated by the peptide map, it might be necessary to develop a secondary peptide map. The goal of a validated method of characterization of a protein through peptide mapping is to reconcile and account for at least 95% of the theoretical composition of the protein structure.

The Use of Peptide Mapping for Genetic Stability Evaluation

A validated peptide map can be used to assess the integrity of the predicted primary sequence of a protein product (i.e., its genetic stability). It can also be used to determine lot-to-lot consistency of the biotechnology-derived product process. Furthermore, the performance of the protein expression of the production system is best assessed by peptide mapping of the expressed protein. Peptide maps of protein produced at various times of the protein expression process, including a point well beyond the normal protein expression time, compared with those of a USP Reference Standard or reference material, will evaluate the genetic stability of the expression system as a function of time.

Variant protein sequences can arise from a genetic variation at the DNA level (point mutation) or as an error in the translation process. A validated peptide map is the best approach to the detection of protein variants. However, the limitations of the peptide mapping itself must be taken into consideration. The detection of a structured variant is possible only if the corresponding peptide variant is easily isolated and characterized. To establish genetic stability will require the use of a battery of biochemical methods, provided that the variants have properties different from those of the "normal" protein.

Validation

CRITICAL FACTORS

Validation of peptide mapping requires that a protocol be designed, outlining in detail the experiment to be conducted and the criteria for acceptance of the map. Criteria for acceptance of mapping include detection limit, specificity, linearity, range, accuracy, precision, and reagent stability. Reproducibility of the peptide map is a critical element in the utilization of such a map as an identity test and for confirming genetic stability. Those technical aspects of peptide mapping that influence the reproducibility of the map will be discussed.

The setting of limits, with respect to quantification (peak area or height) and identification (retention times) for the selected group of relevant peaks is based on empirical observations. These limits detect significant differences between the sample and USP Reference Standard or reference material within a series of analyses.

Another critical issue is the recovery of peptides and its impact on peak area determination and reproducibility and on the establishment of acceptance criteria. The recovery criteria address all aspects of test methodology, from digestion to chromatographic conditions. Determination of peptide recovery includes quantitative amino acid analysis, spike addition, radiolabeling, and UV summation. An overall recovery of about 80% is considered satisfactory. Recovery of individual peptides is more problematic and is handled on a case-by-case basis. The critical factors considered in the validation of a peptide map are as follows.

Written Test Procedures—These procedures include a detailed description of the analytical method in which reagents, equipment, sample preparation, method of analysis, and analysis of the data are defined.

Validation Protocol—A protocol is prepared that contains a procedure for test validation.

Acceptance Criteria—The criteria can be minimal at the early stages, but need to be better defined as validation studies progress.

Reporting of Results—Results from the validation study are documented with respect to the analytical parameters listed in the validation protocol.

Revalidation of the Test Procedure—If the method used requires alteration that could affect the analytical parameter previously assessed in the validation of the procedure, the test procedure must be revalidated. Significant changes in the processing of the article, in laboratories performing the analysis, in formulation of the bulk or the finished products, and in any other significant parameter will require revalidation of the methods.

REQUIREMENTS

Precision—

Intratest Precision—This is a measure of the reproducibility of peptide mapping. The two critical steps in peptide mapping are fragmentation (i.e., digestion) and separation of peptides. An acceptable precision occurs where the absolute retention times and the relative peak areas are constant from run to run, and the average variation in retention time is small relative to that of a selected internal reference peak. The reproducibility of the map can be enhanced if a temperature-controlled column oven is used, if an extensive equilibration of the system is performed prior to the start of the test, if a blank (control digest mixture without protein) is run first to minimize "first-run effects," and if a USP Reference Standard or a reference material digest is interspersed periodically with test samples to evaluate chromatographic drift.

The criteria for validation of the fragmentation step are similar to those described below for separation of peptides, but they are met for consecutive tests of a series of separately prepared digests of the protein under test.

The criteria for validation of the separation of peptides step include the following:

1. The average standard deviation of the absolute retention times of all major peaks for a set of consecutive tests of the same digest does not exceed a specified acceptance criterion.
2. The average standard deviation of absolute peak area for all fully resolved major peaks does not exceed a specified percentage.

Intertest Precision—This is a measure of the reproducibility of the peptide mapping when the test is performed on different days, by different analysts, in different laboratories, with reagents or enzymes from different suppliers or different lots from the same supplier, with different instruments, on columns of different makes or columns of the same make from different lots, and on individual columns of the same make from the same lot. Although it would be desirable, from a scientific perspective, to validate all of these variables in terms of their impacts on precision, a practical approach is to validate the test using those variables most likely to be encountered under operational conditions. Additional variables can be included when needed.

The experimental design allows the analyst to make comparisons using peak retention times and areas that are expressed relative to a highly reproducible internal reference peak within the same chromatogram. The relative peak area is expressed as the ratio of the peak area to that of the internal reference peak. The relative retention time can be expressed as the difference between the absolute retention time and that of the reference peak. The use of relative values eliminates the need to make separate corrections for differences due to injector-to-injector volumes, units of measure for peak areas, column dimensions, and instrument dead volumes. The variability in the retention times and peak areas for the *Intertest Precision* experiments is expected to be slightly higher than the variability observed for *Intratest Precision*.

Robustness—Factors such as composition of the *Mobile Phase*, protease quality or chemical reagent purity, column variation and age, and digest stability are likely to affect the overall performance of the test and its reproducibility. Tolerances for each of the key parameters are evaluated and baseline limits established in case the test is used for routine lot release purposes.

Mobile Phase—The composition of the *Mobile Phase* is optimized to obtain the maximum resolution of peptides throughout the elution profile. A balance between optimal resolution and overall reproducibility is desired. A lower pH might improve peak separation but might shorten the life of the column, resulting in lack of reproducibility. Peptide maps at a pH above and below the pH of the procedure are compared to the peptide map obtained at the pH of the procedure and checked for significant differences; they are also reviewed with respect to the acceptance criteria established in the validation protocol.

Protease Quality or Chemical Reagent Purity—A sample of the USP Reference Standard or reference material for the protein under test is prepared and digested with different lots of cleavage agent. The chromatograms for each digest are compared in terms of peak areas, shape, and number. The same procedure can be applied to other critical chemicals or pretreatment procedures used during sample preparation, such as reducing and carboxymethylation reagents.

Column Considerations—Column-to-column variability, even within a single lot, can affect the performance of the column in the development of peptide maps. Column size may also lead to significant differences. A USP Reference Standard or reference material of the protein under test is digested and the digest is chromatographed on different lots of column from a single manufacturer. The maps are then evaluated in terms of the overall elution profile, retention times, selectivity resolution, and recovery. To evaluate the overall lifetime of the column in terms of robustness, perform a peptide mapping test on different columns and vary significantly the number of injections (e.g., from 10 injections to 250 injections). The resulting maps can then be compared for significant differences in peak broadening, peak area, and overall resolution. As a column ages, an increase in back pressure might be observed that might affect the peptide maps.

A sensible precaution in the use of peptide mapping columns is to select alternative columns in case the original columns become unavailable or are discontinued. Perform a peptide mapping test using equivalent columns from different manufacturers, and examine the maps. Differences in particle shape and size, pore size and volume, carbon load, and end-capping can lead to significant differences in retention times, elution profile selectivity, resolution, and recovery. Slight modifications in the gradient profile may be required to achieve equivalency of mapping when using columns from different manufacturers. [NOTE—The equivalency between instrumentation used for the validation of the test and for routine quality control testing should be considered. It might be preferable to use the same HPLC system for all applications. Otherwise, equivalency of the systems is determined, which may require some changes in the chromatographic test conditions.]

Digest Stability—The length of time a digest can be kept before it is chromatographed, as well as the conditions under which the digest is stored before chromatography, is assessed. Several aliquots from a single digest are stored at different storage conditions and chromatographed. These maps are then evaluated for significant differences.

Reproducibility—Determination of various parameters indicated above is repeated using the same USP Reference Standard or reference material and test sample in at least two different laboratories by two analysts equipped with similar HPLC systems. The generated peptide maps are evaluated for significant differences.

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~~POLYACRYLAMIDE GEL ELECTROPHORESIS~~

~~Polyacrylamide gel electrophoresis (PAGE) is used for the qualitative characterization of proteins in biological preparations, for control of purity, and for quantitative determinations. This procedure is limited to the analysis of proteins with a weight range of 14,000 to 100,000 Da. It is possible to extend the weight range of an electrophoresis gel by various techniques (e.g., gradient gels or particular buffer systems), but such techniques will not be discussed in this chapter. Analytical gel electrophoresis is an appropriate method with which to identify and to assess the homogeneity of proteins in drug substances. These methods are routinely used for the estimation of protein subunit molecular weights and for the determination of the subunit compositions of purified proteins.~~

~~Ready-to-use gels and reagents are commercially available and can be used instead of those described in this chapter, provided that they give equivalent results and that they meet the validation requirements.~~

~~General Principle of Electrophoresis~~

~~Under the influence of an electrical field, charged particles migrate in the direction of the electrode bearing the opposite polarity. In gel electrophoresis, the movements of the particles are retarded by interactions with the surrounding gel matrix, which acts as a molecular sieve. The opposing interactions of the electrical force and molecular sieving result in differential migration rates according to sizes, shapes, and charges of particles. Because of their different physicochemical properties, different macromolecules of a mixture will migrate at different speeds during electrophoresis and thus will be separated into discrete fractions. Electrophoretic separations can be conducted in systems without support phases (e.g., free solution separation in capillary electrophoresis) and in stabilizing media, such as thin-layer plates, films, or gels.~~

~~Characteristics of Polyacrylamide Gels for Protein Electrophoresis~~

~~The sieving properties of polyacrylamide gels are established by the three-dimensional network of fibers and pores that is formed as the bifunctional bisacrylamide cross-links adjacent to polyacrylamide chains. Polymerization is catalyzed by a free-radical generating system composed of ammonium persulfate and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED).~~

~~As the acrylamide concentration of a gel increases, its effective pore size decreases. The effective pore size of a gel is operationally defined by its sieving properties, that is, by the resistance it imparts to the migration of macromolecules. There are limits to the acrylamide concentrations that can be used. At high acrylamide concentrations, gels break much more easily and are difficult to handle. As the pore size of a gel decreases, the migration rate of a protein through the gel decreases. By adjusting the pore size of a gel, through manipulating the acrylamide concentration, the resolution of the method can be optimized for a given protein product. Thus, a given gel is physically characterized by its respective composition of acrylamide and bisacrylamide.~~

~~In addition to the composition of the gel, the state of the protein is an important component to the electrophoretic mobility. In the case of proteins, the electrophoretic mobility is dependent on the pK value of the charged groups and the size of the molecule. It is influenced by the type, the concentration, and pH of the buffer, by the temperature and the field strength, and by the nature of the support material.~~

~~Denaturation with Sodium Dodecyl Sulfate~~

~~Denaturing PAGE using sodium dodecyl sulfate (SDS) is the most common mode of electrophoresis used in assessing the pharmaceutical quality of protein products. Typically, analytical electrophoresis of proteins is carried out under conditions that ensure dissociation of the proteins into their individual polypeptide subunits and that minimize aggregation of these subunits. The strongly anionic detergent SDS is used in combination with heat to dissociate the proteins before they are loaded on the gel. The denatured polypeptides bind SDS, become negatively charged, and exhibit a consistent charge-to-weight ratio regardless of protein type. Because the amount of SDS bound is almost always proportional to the molecular weight of the polypeptide and is typically independent of its sequence, SDS-polypeptide complexes migrate through polyacrylamide gels in reasonable accordance with the size of the polypeptide.~~

~~The electrophoretic mobilities of the resultant detergent-polypeptide complexes all assume the same functional relationship to the molecular weights of polypeptides. Migration of SDS derivatives is toward the anode in a predictable manner, with low molecular weight complexes migrating faster than larger ones. This means that the molecular weight of a protein can be estimated from its relative mobility in calibrated SDS-PAGE and that a single band in such a gel is a criterion of purity.~~

~~Modifications to the polypeptide backbone, such as *N*- or *O*-linked glycosylation, however, have a significant impact on the apparent molecular weight of a protein. This is due to SDS not binding to a carbohydrate moiety in a manner similar to the polypeptide. Thus, a consistent charge-to-weight ratio is not maintained. The apparent molecular weight of proteins having undergone post-translational modifications is not a true reflection of the weight of the polypeptide chain.~~

~~REDUCING CONDITIONS~~

~~Polypeptide subunits and their three-dimensional structure can be maintained in proteins by the presence of disulfide bonds. A goal of SDS-PAGE analysis under reducing conditions is to disrupt this structure by reducing disulfide bonds. Complete denaturation and dissociation of proteins by treatment with 2-mercaptoethanol or dithiothreitol (DTT) will result in unfolding of the polypeptide backbone and subsequent complexation with SDS. Under these conditions, the molecular weight of the polypeptide subunits can be calculated by linear regression in the presence of suitable molecular weight standards.~~

~~NONREDUCING CONDITIONS~~

~~For some analyses, complete dissociation of protein to peptide subunits is not desirable. In the absence of treatment with reducing agents, disulfide covalent bonds remain intact, preserving the oligomeric form of the protein. Oligomeric SDS-protein complexes migrate more slowly than their SDS-polypeptide subunits. In addition, nonreduced proteins may not be completely saturated with SDS and, hence, may not bind the detergent in a constant weight ratio. This makes molecular weight determinations of these molecules less straightforward than analyses of fully denatured polypeptides, because it is necessary that both standards and unknown proteins be in similar configurations for valid comparisons. However, the staining of a single band in such a gel is a criterion of purity.~~

~~CHARACTERISTICS OF A DISCONTINUOUS BUFFER SYSTEM~~

~~The most popular electrophoretic method for the characterization of a complex mixture of proteins involves the use of a discontinuous buffer system consisting of two contiguous, but distinct, gels: a resolving or separating (lower) gel and a stacking (upper) gel. The two gels are cast with different porosities, pHs, and ionic strengths. In addition, different mobile ions are used in the gel and electrode buffers. The buffer discontinuity concentrates large volumes of sample in the stacking gel, resulting in improved resolution. When power is applied, a voltage drop develops across the sample solution that drives the proteins into the stacking gel. Glycinate ions from the electrode buffer follow the proteins into the stacking gel. A moving boundary region is rapidly formed with the highly mobile chloride ions in the front and the relatively slow glycinate ions in the rear. A localized~~

high-voltage gradient forms between the leading and trailing ion fronts, causing the SDS-protein complexes to form into a thin zone (stack) and migrate between the chloride and glycinate phases. Within a broad limit, regardless of the height of the applied sample, all SDS-proteins condense into a very narrow region and enter the resolving gel as a well-defined, thin zone of high protein density. The large-pore stacking gel does not retard the migration of most proteins and serves mainly as an anticonvective medium. At the interface between the stacking and resolving gels, the proteins experience a sharp retardation due to the restrictive pore size of the resolving gel. Once in the resolving gel, proteins continue to be slowed by the sieving of the matrix. The glycinate ions overtake the proteins, which then move in a space of uniform pH formed by the TRIS and glycine. Molecular sieving causes the SDS-polypeptide complexes to separate on the basis of their molecular weights.

PREPARATION OF GELS

In a discontinuous buffer SDS-polyacrylamide gel, it is important to pour the resolving gel, let the gel set, and then pour the stacking gel because the composition of acrylamide-bisacrylamide, buffer, and pH are different.

Gel Stock Solutions—

30% Acrylamide-Bisacrylamide Solution—Prepare a solution containing 290 g of acrylamide and 10 g of methylene bisacrylamide per L of warm water, and filter. [NOTE—Acrylamide and methylene bisacrylamide are slowly converted during storage to acrylic acid and bisacrylic acid, respectively. This deamidation reaction is catalyzed by light and alkali. The pH of the solution must be 7.0 or lower. Store the solution in dark bottles at room temperature. Fresh solutions are prepared every month.]

Ammonium Persulfate Solution—Prepare a small quantity of solution having a concentration of 100 g of ammonium persulfate per L, and store at 4°. [NOTE—Ammonium persulfate provides the free radicals that drive polymerization of acrylamide and bisacrylamide. Ammonium persulfate decomposes slowly; therefore, prepare fresh solutions weekly.]

TEMED—Use an electrophoresis-grade reagent. [NOTE—*TEMED* accelerates the polymerization of acrylamide and bisacrylamide by catalyzing the formation of free radicals from ammonium persulfate. Because *TEMED* works only as a free base, polymerization is inhibited at low pH.]

SDS Solution—Use an electrophoresis-grade reagent. Prepare a solution having a concentration of about 100 g of SDS per L, and store at room temperature.

1.5 M Buffer Solution—Transfer about 90.8 g of tris(hydroxymethyl)aminomethane (TRIS) to a 500-mL flask, dissolve in 400 mL of water, adjust with hydrochloric acid to a pH of 8.8, dilute with water to volume, and mix.

1 M Buffer Solution—Transfer about 60.6 g of TRIS to a 500-mL flask, add 400 mL of water, adjust with hydrochloric acid to a pH of 6.8, dilute with water to volume, and mix.

Plate Preparation—Clean two glass plates (10 cm × 8 cm), the polytef comb, the two spacers, and the silicone rubber tubing (0.6 mm × 35 cm) with mild detergent, rinse thoroughly with water, and blot dry.

Lubricate the spacers and the tubing with nonsilicone grease. Apply the spacers along each of the two short sides of the glass plate 2 mm away from the edges and 2 mm away from the long side corresponding to the bottom of the gel.

Begin to lay the tubing on the glass plate by using one spacer as a guide. Carefully twist the tubing at the bottom of the spacer, and follow the long side of the glass plate. While holding the tubing with one finger along the long side, twist the tubing again, and lay it on the second short side of the glass plate, using the spacer as a guide.

Place the second glass plate in perfect alignment, and hold the mold together by hand pressure. Apply two clamps on each of the two short sides of the mold. Carefully apply four clamps on the longer side of the gel mold, thus forming the bottom of the gel mold. Verify that the tubing is running along the edge of the glass plates and has not been extruded while placing the clamps. The gel mold is now ready for pouring the gel.

Resolving Gel—In a conical flask, prepare the appropriate volume of solution containing the desired concentration of acrylamide as directed in *Table 3*. Mix the components in the order shown. Before adding the *Ammonium Persulfate Solution* and the *TEMED*, pour the solution in a disposable filtration unit equipped with a nitrocellulose filter having a 0.45-µm porosity, and apply vacuum. Allow the solution to degas by swirling the filtration unit, and disconnect the vacuum when no more bubbles are formed in the solution. Add appropriate amounts of *Ammonium Persulfate Solution* and *TEMED*, as directed in *Table 3*, swirl, and pour immediately into the gap between the two glass plates of the mold. Leave sufficient space for the stacking gel (the length of the teeth of the comb plus 1 cm). Using a pipet, carefully overlay the solution with water-saturated isobutyl alcohol. Leave the gel in a vertical position at room temperature for polymerization.

Table 3. Preparation of Resolving Gel

Solution Components	Component Volumes (mL) per Gel Mold Volume Below							
	5 mL	10 mL	15 mL	20 mL	25 mL	30 mL	40 mL	50 mL
6% Acrylamide								
Water	2.6	5.3	7.9	10.6	13.2	15.9	21.2	26.5
30% Acrylamide-Bisacrylamide Solution	1.0	2.0	3.0	4.0	5.0	6.0	8.0	10.0
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.004	0.008	0.012	0.016	0.02	0.024	0.032	0.04
8% Acrylamide								
Water	2.3	4.6	6.9	9.3	11.5	13.9	18.5	23.2
30% Acrylamide-Bisacrylamide Solution	1.3	2.7	4.0	5.3	6.7	8.0	10.7	13.3
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.003	0.006	0.009	0.012	0.015	0.018	0.024	0.03
10% Acrylamide								
Water	1.9	4.0	5.9	7.9	9.9	11.9	15.9	19.8
30% Acrylamide-Bisacrylamide Solution	1.7	3.3	5.0	6.7	8.3	10.0	13.3	16.7
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02

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Table 3. Preparation of Resolving Gel *(Continued)*

Solution Components	Component Volumes (mL) per Gel Mold Volume Below							
	5 mL	10 mL	15 mL	20 mL	25 mL	30 mL	40 mL	50 mL
12% Acrylamide								
Water	1.6	3.3	4.9	6.6	8.2	9.9	13.2	16.5
30% Acrylamide-Bisacrylamide Solution	2.0	4.0	6.0	8.0	10.0	12.0	16.0	20.0
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02
14% Acrylamide								
Water	1.4	2.7	3.9	5.3	6.6	8.0	10.6	13.8
30% Acrylamide-Bisacrylamide Solution	2.3	4.6	7.0	9.3	11.6	13.9	18.6	23.2
1.5 M Buffer Solution	1.2	2.5	3.6	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02
15% Acrylamide								
Water	1.1	2.3	3.4	4.6	5.7	6.9	9.2	11.5
30% Acrylamide-Bisacrylamide Solution	2.5	5.0	7.5	10.0	12.5	15.0	20.0	25.0
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02

After polymerization is complete (about 30 minutes later), pour off the overlay, and wash the top of the gel several times with water to remove the isobutyl alcohol overlay and any unpolymerized acrylamide. Drain as much fluid as possible from the top of the gel, and then remove any remaining water with the edge of a paper towel.

Stacking Gel—In a conical flask, prepare the appropriate volume of solution containing the desired concentration of acrylamide, as directed in *Table 4*. Mix the components in the order shown. Before adding the *Ammonium Persulfate Solution* and the *TEMED*, pour the solution into a disposable filtration unit equipped with a nitrocellulose filter having a 0.45 µm porosity, and apply vacuum. Allow the solution to degas by swirling the filtration unit, and disconnect the vacuum when no more bubbles are formed in the solution. Add appropriate amounts of *Ammonium Persulfate Solution* and *TEMED* as directed in *Table 4*, swirl, and pour immediately into the gap between the two glass plates of the mold directly onto the surface of the polymerized Resolving Gel. Immediately insert a clean polytef comb into the stacking gel solution, being careful to avoid trapping air bubbles. Add more stacking gel solution to fill the spaces of the comb completely. Leave the gel in a vertical position, and allow to polymerize at room temperature. After polymerization is complete (about 30 minutes later), carefully remove the polytef comb, and proceed as directed below.

Table 4. Preparation of Stacking Gel

Solution Components	Component Volumes (mL) per Gel Mold Volume Below							
	1 mL	2 mL	3 mL	4 mL	5 mL	6 mL	8 mL	10 mL
Water	0.68	1.4	2.1	2.7	3.4	4.1	5.5	6.8
30% Acrylamide-Bisacrylamide Solution	0.17	0.33	0.5	0.67	0.83	1.0	1.3	1.7
1.0 M Buffer Solution	0.13	0.25	0.38	0.5	0.63	0.75	1.0	1.25
SDS Solution	0.01	0.02	0.03	0.04	0.05	0.06	0.08	0.1
Ammonium Persulfate Solution	0.01	0.02	0.03	0.04	0.05	0.06	0.08	0.1
TEMED	0.001	0.002	0.003	0.004	0.005	0.006	0.008	0.01

ELECTROPHORETIC SEPARATION

Sample Buffer 1—Dissolve 1.89 g of TRIS, 5.0 g of SDS, 50 mg bromophenol blue, and 25.0 mL glycerol in 100 mL of water. Adjust with hydrochloric acid to a pH of 6.8, and dilute with water to 125 mL. Before use, dilute with an equal volume of water or sample, and mix.

Sample Buffer 2 (for reducing conditions)—Prepare as directed under *Sample Buffer 1* except to add 12.5 mL of 2-mercaptoethanol before adjusting the pH. Alternatively, prepare as directed for *Sample Buffer 1* except to start with about 1.93 g of TRIS and add a suitable quantity of DTT to obtain a final 100 µM DTT concentration.

Running Buffer—Dissolve 151.4 g of TRIS, 721.0 g of aminoacetic acid, and 50.0 g of SDS in water, dilute with water to 5000 mL, and mix to obtain a stock solution. Immediately before use, dilute this stock solution with water to 10 times its volume, mix, and adjust to a pH between 8.1 and 8.8.

Procedure—Rinse the wells immediately with water or with the *Running Buffer* to remove any unpolymerized acrylamide. (If necessary, straighten the teeth of the *Stacking Gel* with a blunt hypodermic needle attached to a syringe.) Remove the clamps on one short side, carefully pull out the tubing, and replace the clamps. Proceed similarly on the other short side. Remove the tubing from the bottom part of the gel.

Mount the completed gel in the electrophoresis apparatus. Add the electrophoresis buffers to the top and bottom reservoirs. Remove any bubbles that become trapped at the bottom of the gel between the glass plates. [NOTES—This is best done with a bent hypodermic needle attached to a syringe. Never pre-run the gel before loading the samples, because this will destroy the discontinuity of the buffer systems. Before loading the sample, carefully rinse the slot with *Running Buffer*.]

Prepare the test and standard solutions in the recommended *Sample Buffer*, and treat as directed in the individual monograph. Apply the appropriate volume of each solution to the *Stacking Gel* wells.

Start the electrophoresis using the conditions recommended by the manufacturer of the equipment. Electrophoresis running time and current or voltage may need to be varied in order to achieve optimum separation. Check that the dye front is moving into the resolving gel. When the dye has reached the bottom of the gel, stop the electrophoresis. Remove the gel assembly from the apparatus, and separate the glass plates. Remove the spacers, cut off and discard the *Stacking Gel,* and immediately proceed with staining.

DETECTION OF PROTEINS IN GELS

Coomassie staining is the most common protein staining method with a detection level in the order of 1 to 10 µg of protein per band. Silver staining is the most sensitive method for staining proteins in gels, as a band containing 10 to 100 ng can be detected, but the method is more cumbersome and less rugged. All of the steps in gel staining are performed at room temperature with gentle agitation (e.g., on a rocking platform shaker, or equivalent). Gloves must be worn when staining the gels to prevent fingerprint residue staining.

Reagents—

Coomassie Staining Solution—Prepare a solution of Coomassie brilliant blue R-250 having a concentration of 1.25 g per L in a mixture of water, methanol, and glacial acetic acid (5 : 4 : 1). Filter, and store at room temperature.

Destaining Solution—Prepare a mixture of water, methanol, and glacial acetic acid (5 : 4 : 1).

Fixing Solution 1—Prepare a mixture of water, methanol, and trichloroacetic acid (5 : 4 : 1).

Fixing Solution 2—Transfer 250 mL of methanol to a 500-mL volumetric flask, add 0.27 mL of formaldehyde, dilute with water to volume, and mix.

Silver Nitrate Reagent—To a mixture of 40 mL of 1 M sodium hydroxide and 3 mL of ammonium hydroxide, add, dropwise, 8 mL of a 200 g per L solution of silver nitrate with stirring; dilute to 200 mL with water, and mix.

Developing Solution—Transfer 2.5 mL of a citric acid solution (2 in 100) and 0.27 mL of formaldehyde to a 500.0-mL volumetric flask, dilute with water to volume, and mix.

Stopping Solution—Prepare a 10% (v/v) solution of acetic acid.

Coomassie Staining—Immerse the gel in an excess of *Coomassie Staining Solution,* and incubate for at least 1 hour. Remove the *Coomassie Staining Solution.* Destain the gel with an excess of *Destaining Solution.* Change the *Destaining Solution* several times, until the stained protein bands are clearly distinguishable on a clear background. The more thoroughly the gel is destained, the smaller the amount of protein that can be detected. Destaining can be accelerated by including a few g of anion-exchange resin or a small sponge in the *Destaining Solution.* [NOTE—The acid-alcohol solutions used in this procedure do not completely fix proteins in the gel. This can lead to losses of some low-molecular-weight proteins during the staining and destaining of thin gels. Permanent fixation is obtainable by incubating the gel in *Fixing Solution 1* for 1 hour before it is immersed in the *Coomassie Staining Solution.*]

Silver Staining—Immerse the gel in an excess of *Fixing Solution 2,* and incubate for 1 hour. Remove *Fixing Solution 2,* add fresh *Fixing Solution 2,* and incubate for at least 1 hour, or overnight if convenient. Discard *Fixing Solution 2,* and wash the gel in an excess of water for 1 hour. Soak the gel for 15 minutes in a 1% solution of glutaraldehyde (v/v). Wash the gel twice, for 15 minutes each time, with an excess of water. Soak the gel in fresh *Silver Nitrate Reagent* for 15 minutes, in darkness. Wash the gel three times, for 5 minutes each time, with an excess of water. Immerse the gel for about 1 minute in *Developing Solution* until satisfactory staining has been obtained. Stop the development by incubation in the *Stopping Solution* for 15 minutes, then rinse the gel with water, and proceed with drying as indicated below.

DRYING OF GELS

For Coomassie staining, after the destaining step, incubate the gel in a glycerol solution (1 in 10) for at least 2 hours. For silver staining, add to the final rinsing step a 5-minute incubation in a glycerol solution (1 in 50).

Immerse two sheets of porous cellophane in water, and incubate for 5 to 10 minutes. Place one of the sheets on a drying frame. Carefully lift the gel and place it on the cellophane sheet. Remove any trapped air bubbles, and pour a few mL of water around the edges of the gel. Place the second sheet on top, and remove any trapped air bubbles. Complete the assembly of the drying frame. Place in a drying oven, leave at room temperature until dry, or use a commercial gel dryer.

MOLECULAR WEIGHT DETERMINATION

Molecular weights of proteins are determined by comparison of their mobilities with those of several marker proteins of known molecular weight. Mixtures of proteins with precisely known molecular weights blended for uniform staining are available for calibrating gels. They are available in various molecular weight ranges. Concentrated stock solutions of proteins of known molecular weight are diluted in a sample buffer and loaded on the same gel as the protein sample to be tested.

Immediately after the gel has been run, the position of the bromophenol blue tracking dye is marked to identify the leading edge of the electrophoretic ion front. This can be done by cutting notches in the edges of the gel or by inserting a needle soaked in india ink into the gel at the dye front. After staining, measure the migration distances of each protein band (markers and unknowns) from the top of the *Resolving Gel.* Divide the migration distance of each protein by the distance traveled by the tracking dye. The normalized migration distances so obtained are called the relative mobilities of the proteins (relative to the dye front) and conventionally denoted as R_m. Construct a (semilogarithmic) plot of the logarithm of the molecular weights (M_w) of the protein standards as functions of the R_m values. [NOTE—The graphs are slightly sigmoid.] From the graph so obtained, estimate the unknown molecular weights by linear regression analysis or interpolation, as long as unknown samples are positioned along the linear part of the graph.

If the proteins of the molecular weight marker are not distributed along 80% of the length of the gel and over the required separation range (i.e., the range covering the product and its dimer or the products and its related impurities), and the separation obtained for the relevant protein bands does not show a linear relationship between the logarithm of the molecular weight and the R_m, then the test is not valid.

QUANTIFICATION OF IMPURITIES

Where the impurity limit is specified in the individual monograph, a reference solution corresponding to that level of impurity is prepared by diluting the test solution. For example, where the limit is 5.0%, a reference solution is a 1 in 20 dilution of the test solution. No impurity—any band other than the main band—in the electropherogram obtained from the test solution is more intense than the main band obtained with the reference solution.

Under validated conditions and when using the Coomassie staining procedure, impurities may be quantified by normalization to the main band using an integrating densitometer. In this case, the responses must be validated for linearity.

TOTAL PROTEIN ASSAY

The following procedures are provided as illustrations of the determination of total protein content in pharmacopeial preparations. Other techniques, such as HPLC, are also acceptable if total protein recovery is demonstrated. Many of the total protein assay methods described below can be performed successfully using kits from commercial sources. [NOTE—Where water is required, use distilled water.]

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Method 1

Protein in solution absorbs UV light at a wavelength of 280 nm, due to the presence of aromatic amino acids, mainly tyrosine and tryptophan. This property is the basis of this method. Protein determination at 280 nm is mainly a function of the tyrosine and tryptophan content of the protein. If the buffer used to dissolve the protein has a high absorbance relative to that of water, there is an interfering substance in the buffer. This interference can be compensated for when the spectrophotometer is adjusted to zero buffer absorbance. If the interference results in a large absorbance that challenges the limit of sensitivity of the spectrophotometer, the results may be compromised. Furthermore, at low concentrations protein can be absorbed onto the cuvette, thereby reducing the content in solution. This can be prevented by preparing samples at higher concentrations or by using a nonionic detergent in the preparation. [NOTE—Keep the *Test Solution*, the *Standard Solution*, and the buffer at the same temperature during testing.]

Test Solution— Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration of 0.2 to 2 mg per mL.

Standard Solution— Unless otherwise specified in the individual monograph prepare a solution of USP Reference Standard or reference material for the protein under test in the same buffer and at the same concentration as the *Test Solution*.

Procedure— Concomitantly determine the absorbances of the *Standard Solution* and the *Test Solution* in quartz cells at a wavelength of 280 nm, with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the buffer as the blank. To obtain accurate results, the response should be linear in the range of protein concentrations to be assayed.

Light-Scattering— The accuracy of the UV spectroscopic determination of protein can be decreased by the scattering of light by the test specimen. If the proteins in solution exist as particles comparable in size to the wavelength of the measuring light (250 to 300 nm), scattering of the light beam results in an apparent increase in absorbance of the test specimen. To calculate the absorbance at 280 nm due to light scattering, determine the absorbances of the *Test Solution* at wavelengths of 320, 325, 330, 335, 340, 345, and 350 nm. Using the linear regression method, plot the log of the observed absorbance versus the log of the wavelength, and determine the standard curve best fitting the plotted points. From the graph so obtained, extrapolate the absorbance value due to light scattering at 280 nm. Subtract the absorbance from light-scattering from the total absorbance at 280 nm to obtain the absorbance value of the protein in solution. Filtration with a filter having a 0.2-µm porosity or clarification by centrifugation may be performed to reduce the effect of light scattering, especially if the solution is noticeably turbid.

Calculations— Calculate the concentration, C_u, of protein in the test specimen by the formula:

$$C_u(A_u/A_s),$$

in which C_s is the concentration of the *Standard Solution;* and A_u and A_s are the corrected absorbances of the *Test Solution* and the *Standard Solution,* respectively (see *Spectrophotometry and Light-Scattering* ⟨851⟩).

Method 2

This method, commonly referred to as the Lowry assay, is based on the reduction by protein of the phosphomolybdic-tungstic mixed acid chromogen in the Folin-Ciocalteu's phenol reagent, resulting in an absorbance maximum at 750 nm. The Folin-Ciocalteu's phenol reagent reacts primarily with tyrosine residues in the protein, which can lead to variation in the response of the assay to different proteins. Because the method is sensitive to interfering substances, a procedure for precipitation of the protein from the test specimen may be used. Where separation of interfering substances from the protein in the test specimen is necessary, proceed as directed below for *Interfering Substances* prior to preparation of the *Test Solution*. The effect of interfering substances can be minimized by dilution, provided the concentration of the protein under test remains sufficient for accurate measurement.

Standard Solutions— Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution*. Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 5 and 100 µg of protein per mL, the concentrations being evenly spaced.

Test Solution— Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions*. An appropriate buffer will produce a pH in the range of 10.0 to 10.5.

Blank— Use the buffer used for the *Test Solution* and the *Standard Solutions*.

Reagents and **Solutions**—

Copper Sulfate Reagent— Dissolve 100 mg of cupric sulfate and 200 mg of sodium tartrate in water, dilute with water to 50 mL, and mix. Dissolve 10 g of sodium carbonate in water to a final volume of 50 mL, and mix. Slowly pour the sodium carbonate solution into the copper sulfate solution with mixing. Prepare this solution fresh daily.

SDS Solution— Dissolve 5 g of sodium dodecyl sulfate in water, and dilute with water to 100 mL.

Sodium Hydroxide Solution— Dissolve 3.2 g of sodium hydroxide in water, dilute with water to 100 mL, and mix.

Alkaline Copper Reagent— Prepare a mixture of *Copper Sulfate Reagent*, *SDS Solution*, and *Sodium Hydroxide Solution* (1 : 2 : 1). This reagent may be stored at room temperature for up to 2 weeks.

Diluted Folin-Ciocalteu's Phenol Reagent— Mix 10 mL of Folin-Ciocalteu's phenol TS with 50 mL of water. Store in an amber bottle, at room temperature.

Procedure— To 1 mL of each *Standard Solution*, the *Test Solution*, and the *Blank*, add 1 mL of *Alkaline Copper Reagent*, and mix. Allow to stand at room temperature for 10 minutes. Add 0.5 mL of the *Diluted Folin-Ciocalteu's Phenol Reagent* to each solution, mix each tube immediately, and allow to stand at room temperature for 30 minutes. Determine the absorbances of the solutions from the *Standard Solutions* and the *Test Solution* at the wavelength of maximum absorbance at 750 nm, with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the solution from the *Blank* to set the instrument to zero.

Calculations— [NOTE—The relationship of absorbance to protein concentration is nonlinear; however, if the standard curve concentration range is sufficiently small, it will approach linearity.] Using the linear regression method, plot the absorbances of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From the standard curve so obtained and the absorbance of the *Test Solution*, determine the concentration of protein in the *Test Solution*.

INTERFERING SUBSTANCES

In the following procedure, deoxycholate-trichloroacetic acid is added to a test specimen to remove interfering substances by precipitation of proteins before testing. This technique also can be used to concentrate proteins from a dilute solution.

Sodium Deoxycholate Reagent— Prepare a solution of sodium deoxycholate in water having a concentration of 150 mg in 100 mL.

Trichloroacetic Acid Reagent— Prepare a solution of trichloroacetic acid in water having a concentration of 72 g in 100 mL.

Procedure— Add 0.1 mL of *Sodium Deoxycholate Reagent* to 1 mL of a solution of the protein under test. Mix on a vortex mixer, and allow to stand at room temperature for 10 minutes. Add 0.1 mL of *Trichloroacetic Acid Reagent*, and mix on a vortex mixer. Centrifuge at 3000 × *g* for 30 minutes, decant the liquid, and remove any residual liquid with a pipet. Redissolve the protein pellet in 1 mL of *Alkaline Copper Reagent*. Proceed as directed for the *Test Solution*.

NOTE—Color development reaches a maximum in 20 to 30 minutes during incubation at room temperature, after which there is a gradual loss of color. Most interfering substances cause a lower color yield;

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however, some detergents cause a slight increase in color. A high salt concentration may cause a precipitate to form. Because different protein species may give different color response intensities, the standard protein and test protein should be the same.

Method 3

This method, commonly referred to as the Bradford assay, is based on the absorption shift from 470 nm to 595 nm observed when the brilliant blue G dye binds to protein. The brilliant blue G dye binds most readily to arginyl and lysyl residues in the protein, which can lead to variation in the response of the assay to different proteins.

Standard Solutions—Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution*. Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 100 µg and 1 mg of protein per mL, the concentrations being evenly spaced.

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions*.

Blank—Use the buffer used to prepare the *Test Solution* and the *Standard Solutions*.

Coomassie Reagent—Dissolve 100 mg of brilliant blue G[3] in 50 mL of alcohol. [NOTE—Not all dyes have the same brilliant blue G content, and different products may give different results.] Add 100 mL of phosphoric acid, dilute with water to 1 L, and mix. Pass the solution through filter paper (Whatman No. 1 or equivalent), and store the filtered reagent in an amber bottle at room temperature. [NOTE—Slow precipitation of the dye will occur during storage of the reagent. Filter the reagent before use.]

Procedure—Add 5 mL of the *Coomassie Reagent* to 100 µL of each *Standard Solution*, the *Test Solution*, and the *Blank*, and mix by inversion. Avoid foaming, which will lead to poor reproducibility. Determine the absorbances of the solutions from the *Standard Solutions* and the *Test Solution* at 595 nm, with a suitable spectrophotometer (see *Spectrophotometry and Light Scattering* ⟨851⟩), using the *Blank* to set the instrument to zero. [NOTE—Do not use quartz (silica) spectrophotometer cells: the dye binds to this material. Because different protein species may give different color response intensities, the standard protein and test protein should be the same.]

There are relatively few interfering substances, but detergents and ampholytes in the test specimen should be avoided. Highly alkaline specimens may interfere with the acidic reagent.

Calculations—[NOTE—The relationship of absorbance to protein concentration is nonlinear; however, if the standard curve concentration range is sufficiently small, it will approach linearity.] Using the linear regression method, plot the absorbances of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From the standard curve so obtained and the absorbance of the *Test Solution*, determine the concentration of protein in the *Test Solution*.

Method 4

This method, commonly referred to as the bicinchoninic acid or BCA assay, is based on reduction of the cupric (Cu^{2+}) ion to cuprous (Cu^{1+}) ion by protein. The bicinchoninic acid reagent is used to detect the cuprous ion. The method has few interfering substances. When interfering substances are present, their effect may be minimized by dilution, provided that the concentration of the protein under test remains sufficient for accurate measurement.

Standard Solutions—Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution*. Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 10 and 1200 µg of protein per mL, the concentrations being evenly spaced.

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions*.

Blank—Use the buffer used to prepare the *Test Solution* and the *Standard Solutions*.

Reagents—

BCA Reagent—Dissolve about 10 g of bicinchoninic acid, 20 g of sodium carbonate monohydrate, 1.6 g of sodium tartrate, 4 g of sodium hydroxide, and 9.5 g of sodium bicarbonate in water. Adjust, if necessary, with sodium hydroxide or sodium bicarbonate to a pH of 11.25. Dilute with water to 1 L, and mix.

Copper Sulfate Reagent—Dissolve about 2 g of cupric sulfate in water to a final volume of 50 mL.

Copper-BCA Reagent—Mix 1 mL of *Copper Sulfate Reagent* and 50 mL of *BCA Reagent*.

Procedure—Mix 0.1 mL of each *Standard Solution*, the *Test Solution*, and the *Blank* with 2 mL of the *Copper-BCA Reagent*. Incubate the solutions at 37° for 30 minutes, note the time, and allow to come to room temperature. Within 60 minutes following the incubation time, determine the absorbances of the solutions from the *Standard Solutions* and the *Test Solution* in quartz cells at 562 nm, with a suitable spectrophotometer (see *Spectrophotometry and Light Scattering* ⟨851⟩), using the *Blank* to set the instrument to zero. After the solutions are cooled to room temperature, the color intensity continues to increase gradually. If substances that will cause interference in the test are present, proceed as directed for *Interfering Substances* under *Method 2*. Because different protein species may give different color response intensities, the standard protein and test protein should be the same.

Calculations—[NOTE—The relationship of absorbance to protein concentration is nonlinear; however, if the standard curve concentration range is sufficiently small, it will approach linearity.] Using the linear regression method, plot the absorbances of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From the standard curve so obtained and the absorbance of the *Test Solution*, determine the concentration of protein in the *Test Solution*.

Method 5

This method, commonly referred to as the Biuret assay, is based on the interaction of cupric (Cu^{2+}) ion with protein in an alkaline solution and the resultant development of absorbance at 545 nm.

Standard Solutions—Unless otherwise specified in the individual monograph, prepare a solution of Albumin Human for which the protein content has been previously determined by nitrogen analysis (using the nitrogen-to-protein conversion factor of 6.25) or of the USP Reference Standard or reference material for the protein under test in sodium chloride solution (9 in 1000). Dilute portions of this solution with sodium chloride solution (9 in 1000) to obtain not fewer than three *Standard Solutions* having concentrations between 0.5 and 10 mg per mL, the concentrations being evenly spaced. [NOTE—Low responses may be observed if the sample under test has significantly different level of proline than that of Albumin Human. A different standard protein may be employed in such cases.]

Test Solution—Prepare a solution of the test protein in sodium chloride solution (9 in 1000) having a concentration within the range of the concentrations of the *Standard Solutions*.

Blank—Use sodium chloride solution (9 in 1000).

Biuret Reagent—Dissolve about 3.46 g of cupric sulfate in 10 mL of hot water, and allow to cool (*Solution 1*). Dissolve about 34.6 g of sodium citrate dihydrate and 20.0 g of sodium carbonate in 80 mL of hot water, and allow to cool (*Solution 2*). Mix *Solution 1* and *Solution 2*, and dilute with water to 200 mL. This *Biuret Reagent* is stable at room temperature for 6 months. Do not use the reagent if it develops turbidity or contains any precipitate.

Procedure—To one volume of a solution of the *Test Solution* add an equal volume of sodium hydroxide solution (6 in 100), and mix. Immediately add a volume of *Biuret Reagent* equivalent to 0.4 vol-

[3] Dye purity is important in the reagent preparation. It is intended to propose a reagent footnote to indicate that Serva Blue G (Crescent Chemical Company, Hauppauge, NY) is an acceptable grade.

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ume of the *Test Solution*, and mix. Allow to stand at a temperature between 15° and 25° for not less than 15 minutes. Within 90 minutes after the addition of the *Biuret Reagent,* determine the absorbances of the *Standard Solutions* and the solution from the *Test Solution* at the wavelength of maximum absorbance at 545 nm, with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the *Blank* to set the instrument to zero. [NOTE—Any solution that develops turbidity or a precipitate is not acceptable for calculation of protein concentration.]

Calculations—Using the least-squares linear regression method, plot the absorbances of the *Standard Solutions* versus the protein concentrations, determine the standard curve best fitting the plotted points, and calculate the correlation coefficient for the line. [NOTE—Within the given range of the standards, the relationship of absorbance to protein concentration is approximately linear.] A suitable system is one that yields a line having a correlation coefficient of not less than 0.99. From the standard curve and the absorbance of the *Test Solution,* determine the concentration of protein in the test specimen, making any necessary correction.

Interfering Substances—To minimize the effect of interfering substances, the protein can be precipitated from the initial test specimen as follows. Add 0.1 volume of 50 percent trichloroacetic acid to 1 volume of a solution of the test specimen, withdraw the supernatant layer, and dissolve the precipitate in a small volume of 0.5 N sodium hydroxide. Use the solution so obtained to prepare the *Test Solution.*

Comments—This test shows minimal difference between equivalent IgG and albumin samples. Addition of the sodium hydroxide and the *Biuret Reagent* as a combined reagent, insufficient mixing after the addition of the sodium hydroxide, or an extended time between the addition of the sodium hydroxide solution and the addition of the *Biuret Reagent* will give IgG samples a higher response than albumin samples. The trichloroacetic acid method used to minimize the effects of interfering substances can also be used to determine the protein content in test specimens at concentrations below 500 µg per mL.

Method 6

This fluorometric method is based on the derivatization of the protein with *o*-phthalaldehyde (OPA), which reacts with the primary amines of the protein (i.e., NH_2- terminal amino acid and the ε-amino group of the lysine residues). The sensitivity of the test can be increased by hydrolyzing the protein before testing. Hydrolysis makes the α-amino group of the constituent amino acids of the protein available for reaction with the *o*-phthalaldehyde reagent. The method requires very small quantities of the protein.

Primary amines, such as tris(hydroxymethyl)aminomethane and amino acid buffers, react with *o*-phthalaldehyde and must be avoided or removed. Ammonia at high concentrations will react with *o*-phthalaldehyde as well. The fluorescence obtained when amine reacts with *o*-phthalaldehyde can be unstable. The use of automated procedures to standardize this procedure may improve the accuracy and precision of the test.

Standard Solutions—Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution.* Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 10 and 200 µg of protein per mL, the concentrations being evenly spaced.

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions.*

Blank—Use the buffer used to prepare the *Test Solution* and the *Standard Solutions.*

Reagents—

Borate Buffer—Dissolve about 61.83 g of boric acid in water, and adjust with potassium hydroxide to a pH of 10.4. Dilute with water to 1 L, and mix.

Stock OPA Reagent—Dissolve about 120 mg of *o*-phthalaldehyde in 1.5 mL of methanol, add 100 mL of *Borate Buffer*, and mix. Add 0.6 mL of polyoxyethylene (23) lauryl ether, and mix. This solution is stable at room temperature for at least 3 weeks.

OPA Reagent—To 5 mL of *Stock OPA Reagent* add 15 µL of 2-mercaptoethanol. Prepare at least 30 minutes prior to use. This reagent is stable for one day.

Procedure—Adjust each of the *Standard Solutions* and the *Test Solution* to a pH between 8 and 10.5. Mix 10 µL of the *Test Solution* and each of the *Standard Solutions* with 100 µL of *OPA Reagent,* and allow to stand at room temperature for 15 minutes. Add 3 mL of 0.5 N sodium hydroxide, and mix. Using a suitable fluorometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), determine the fluorescent intensities of solutions from the *Standard Solutions* and the *Test Solution* at an excitation wavelength of 340 nm and an emission wavelength between 440 and 455 nm. [NOTE—The fluorescence of an individual specimen is read only once because irradiation decreases the fluorescent intensity.]

Calculations—The relationship of fluorescence to protein concentration is linear. Using the linear regression method, plot the fluorescent intensities of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From the standard curve so obtained and the fluorescent intensity of the *Test Solution,* determine the concentration of protein in the test specimen.

Method 7

This method is based on nitrogen analysis as a means of protein determination. Interference caused by the presence of other nitrogen-containing substances in the test specimen can affect the determination of protein by this method. Nitrogen analysis techniques destroy the protein under test but are not limited to protein presentation in an aqueous environment.

Procedure 1—Determine the nitrogen content of the protein under test as directed under *Nitrogen Determination* ⟨461⟩. Commercial instrumentation is available for the Kjeldahl nitrogen assay.

Procedure 2—Commercial instrumentation is available for nitrogen analysis. Most nitrogen analysis instruments use pyrolysis (i.e., combustion of the sample in oxygen at temperatures approaching 1000°), which produces nitric oxide (NO) and similar oxides of nitrogen (NO_x) from the nitrogen present in the test protein. Some instruments convert the nitric oxides to nitrogen gas, which is quantified with a thermal conductivity detector. Other instruments mix nitric oxide (NO) with ozone (O_3) to produce excited nitrogen dioxide (NO_2), which emits light when it decays and can be quantified with a chemiluminescence detector. A protein reference material or reference standard that is relatively pure and is similar in composition to the test proteins is used to optimize the injection and pyrolysis parameters and to evaluate consistency in the analysis.

Calculations—The protein concentration is calculated by dividing the nitrogen content of the sample by the known nitrogen content of the protein. The known nitrogen content of the protein can be determined from the chemical composition of the protein or by comparison with the nitrogen content of the USP Reference Standard or reference material. ■1S (*USP30*)

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BRIEFING

⟨1052⟩ Biotechnology-Derived Articles—Amino Acid Analysis—See briefing under *Biotechnology-Derived Articles—Tests* ⟨1047⟩.

(BB PP: I. DeVeau) RTS—43939-1

Add the following:

■⟨1052⟩ BIOTECHNOLOGY-DERIVED ARTICLES—AMINO ACID ANALYSIS

This chapter provides guidance and procedures used for characterization of biotechnology-derived articles by amino acid analysis. This chapter is harmonized with the corresponding chapter in *JP* and *EP*. Other characterization tests, also harmonized, are shown in *Biotechnology-Derived Articles—Capillary Electrophoresis* ⟨1053⟩, *Biotechnology-Derived Articles—Isoelectric Focusing* ⟨1054⟩, *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩, *Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis* ⟨1056⟩, and *Biotechnology-Derived Articles—Total Protein Assay* ⟨1057⟩.

INTRODUCTION

Amino acid analysis refers to the methodology used to determine the amino acid composition or content of proteins, peptides, and other pharmaceutical preparations. Proteins and peptides are macromolecules consisting of covalently bonded amino acid residues organized as a linear polymer. The sequence of the amino acids in a protein or peptide determines the properties of the molecule. Proteins are considered large molecules that commonly exist as folded structures with a specific conformation, while peptides are smaller and may consist of only a few amino acids. Amino acid analysis can be used to quantify protein and peptides, to determine the identity of proteins or peptides based on their amino acid composition, to support protein and peptide structure analysis, to evaluate fragmentation strategies for peptide mapping, and to detect atypical amino acids that might be present in a protein or peptide. It is necessary to hydrolyze a protein/peptide to its individual amino acid constituents before amino acid analysis. Following protein/peptide hydrolysis, the amino acid analysis procedure can be the same as that practiced for free amino acids in other pharmaceutical preparations. The amino acid constituents of the test sample are typically derivatized for analysis.

APPARATUS

Methods used for amino acid analysis are usually based on a chromatographic separation of the amino acids present in the test sample. Current techniques take advantage of the automated chromatographic instrumentation designed for analytical methodologies. An amino acid analysis instrument will typically be a low-pressure or high-pressure liquid chromatograph capable of generating mobile phase gradients that separate the amino acid analytes on a chromatographic column. The instrument must have postcolumn derivatization capability, unless the sample is analyzed using precolumn derivatization. The detector is usually a UV-visible or fluorescence detector depending on the derivatization method used. A recording device (e.g., integrator) is used for transforming the analog signal from the detector and for quantitation. It is preferred that instrumentation be dedicated particularly for amino acid analysis.

GENERAL PRECAUTIONS

Background contamination is always a concern for the analyst in performing amino acid analysis. High-purity reagents are necessary (e.g., low-purity hydrochloric acid can contribute to glycine contamination). Analytical reagents are changed routinely every few weeks using only high-pressure liquid chromatography (HPLC) grade solvents. Potential microbial contamination and foreign material that might be present in

the solvents are reduced by filtering solvents before use, keeping solvent reservoirs covered, and not placing amino acid analysis instrumentation in direct sunlight.

Laboratory practices can determine the quality of the amino acid analysis. Place the instrumentation in a low traffic area of the laboratory. Keep the laboratory clean. Clean and calibrate pipets according to a maintenance schedule. Keep pipet tips in a covered box; the analysts may not handle pipet tips with their hands. The analysts may wear powder-free latex or equivalent gloves. Limit the number of times a test sample vial is opened and closed because dust can contribute to elevated levels of glycine, serine, and alanine.

A well-maintained instrument is necessary for acceptable amino acid analysis results. If the instrument is used on a routine basis, it is to be checked daily for leaks, detector and lamp stability, and the ability of the column to maintain resolution of the individual amino acids. Clean or replace all instrument filters and other maintenance items on a routine schedule.

REFERENCE STANDARD MATERIAL

Acceptable amino acid standards are commercially available* for amino acid analysis and typically consist of an aqueous mixture of amino acids. When determining amino acid composition, protein or peptide standards are analyzed with the test material as a control to demonstrate the integrity of the entire procedure. Highly purified bovine serum albumin has been used as a protein standard for this purpose.

CALIBRATION OF INSTRUMENTATION

Calibration of amino acid analysis instrumentation typically involves analyzing the amino acid standard, which consists of a mixture of amino acids at a number of concentrations, to determine the response factor and range of analysis for each amino acid. The concentration of each amino acid in the standard is known. In the calibration procedure, the analyst dilutes the amino acid standard to several different analyte levels within the expected linear range of the amino acid analysis technique. Then, replicates at each of the different analyte levels can be analyzed. Peak areas obtained for each amino acid are plotted versus the known concentration for each of the amino acids in the standard dilution. These results will allow the analyst to determine the range of amino acid concentrations where the peak area of a given amino acid is an approximately linear function of the amino acid concentration. It is important that the analyst prepare the samples for amino acid analysis so that they are within the analytical limits (e.g., linear working range) of the technique employed in order to obtain accurate and repeatable results.

Four to six amino acid standard levels are analyzed to determine a response factor for each amino acid. The response factor is calculated as the average peak area or peak height per nmol of amino acid present in the standard. A calibration file consisting of the response factor for each amino acid is prepared and is used to calculate the concentration of each amino acid present in the test sample. This calculation involves dividing the peak area corresponding to a given amino acid by the response factor for that amino acid to give the nmol of the amino acid. For routine analysis, a single-point calibration may be sufficient; however, the calibration file is updated frequently and tested by the analysis of analytical controls to ensure its integrity.

REPEATABILITY

Consistent high quality amino acid analysis results from an analytical laboratory require attention to the repeatability of the assay. During analysis of the chromatographic separation of the amino acids or their derivatives, numerous peaks can be observed on the chromatogram that corresponds to the amino acids. The large number of peaks makes it necessary to have an amino acid analysis system that can repeatedly identify the peaks based on retention time and integrate the peak areas for quantitation. A typical repeatability evaluation involves pre-

* Suitable standards may be obtained from NIST (Gaithersburg, MD), Beckman Instruments (Fullerton, CA), Sigma Chemical (St. Louis, MO), Pierce (Rockford, IL), or Agilent (Palo Alto, CA).

paring a standard amino acid solution and analyzing many replicates (i.e., six analyses or more) of the same standard solution. The relative standard deviation (RSD) is determined for the retention time and integrated peak area of each amino acid. An evaluation of the repeatability is expanded to include multiple assays conducted over several days by different analysts. Multiple assays include the preparation of standard dilutions from starting materials to determine the variation due to sample handling. Often, the amino acid composition of a standard protein (e.g., bovine serum albumin) is analyzed as part of the repeatability evaluation. By evaluating the replicate variation (i.e., RSD), the laboratory can establish analytical limits to ensure that the analyses from the laboratory are under control. It is desirable to establish the lowest practical variation limits to ensure the best results. Areas to focus on to lower the variability of the amino acid analysis include sample preparation, high background spectral interference due to the quality of reagents and/or to laboratory practices, instrument performance and maintenance, data analysis and interpretation, and analyst performance and habits. All parameters involved are fully investigated in the scope of the validation work.

SAMPLE PREPARATION

Accurate results from amino acid analysis require purified protein and peptide samples. Buffer components (e.g., salts, urea, detergents) can interfere with the amino acid analysis and are removed from the sample before analysis. Methods that utilize postcolumn derivatization of the amino acids are generally not affected by buffer components to the extent seen with precolumn derivatization methods. It is desirable to limit the number of sample manipulations to reduce potential background contamination, to improve analyte recovery, and to reduce labor. Common techniques used to remove buffer components from protein samples include the following methods: (1) injecting the protein sample onto a reverse-phase HPLC system, removing the protein with a volatile solvent containing a sufficient organic component, and drying the sample in a vacuum centrifuge; (2) dialysis against a volatile buffer or water; (3) centrifugal ultrafiltration for buffer replacement with a volatile buffer or water; (4) precipitating the protein from the buffer using an organic solvent (e.g., acetone); and (5) gel filtration.

INTERNAL STANDARDS

It is recommended that an internal standard be used to monitor physical and chemical losses and variations during amino acid analysis. An accurately known amount of internal standard can be added to a protein solution prior to hydrolysis. The recovery of the internal standard gives the general recovery of the amino acids from the protein solution. Free amino acids, however, do not behave in the same way as protein-bound amino acids during hydrolysis because their rates of release or destruction are variable. Therefore, the use of an internal standard to correct for losses during hydrolysis may give unreliable results. It will be necessary to take this particular point into consideration when interpreting the results. Internal standards can also be added to the mixture of amino acids after hydrolysis to correct for differences in sample application and changes in reagent stability and flow rates. Ideally, an internal standard is an unnaturally occurring primary amino acid that is commercially available and inexpensive. It should also be stable during hydrolysis, its response factor should be linear with concentration, and it needs to elute with a unique retention time without overlapping other amino acids. Commonly used amino acid standards include norleucine, nitrotyrosine, and α-aminobutyric acid.

PROTEIN HYDROLYSIS

Hydrolysis of protein and peptide samples is necessary for amino acid analysis of these molecules. The glassware used for hydrolysis must be very clean to avoid erroneous results. Glove powders and fingerprints on hydrolysis tubes may cause contamination. To clean glass hydrolysis tubes, boil tubes for

1 hour in 1 N hydrochloric acid or soak tubes in concentrated nitric acid or in a mixture of concentrated hydrochloric acid and concentrated nitric acid (1 : 1). Clean hydrolysis tubes are rinsed with high-purity water followed by a rinse with HPLC grade methanol, dried overnight in an oven, and stored covered until use. Alternatively, pyrolysis of clean glassware at 500° for 4 hours may be used to eliminate contamination from hydrolysis tubes. Adequate disposable laboratory material can also be used.

Acid hydrolysis is the most common method for hydrolyzing a protein sample before amino acid analysis. The acid hydrolysis technique can contribute to the variation of the analysis due to complete or partial destruction of several amino acids. Tryptophan is destroyed; serine and threonine are partially destroyed; methionine might undergo oxidation; and cysteine is typically recovered as cystine (but cystine recovery is usually poor because of partial destruction or reduction to cysteine). Application of adequate vacuum (less than 200 µm of mercury or 26.7 Pa) or introduction of an inert gas (argon) in the headspace of the reaction vessel can reduce the level of oxidative destruction. In peptide bonds involving isoleucine and valine, the amido bonds of Ile-Ile, Val-Val, Ile-Val, and Val-Ile are partially cleaved; and asparagine and glutamine are deamidated, resulting in aspartic acid and glutamic acid, respectively. The loss of tryptophan, asparagine, and glutamine during an acid hydrolysis limits quantitation to 17 amino acids. Some of the hydrolysis techniques described are used to address these concerns. Some of the hydrolysis techniques described (i.e., *Methods 4–11*) may cause modifications to other amino acids. Therefore, the benefits of using a given hydrolysis technique are weighed against the concerns with the technique and are tested adequately before employing a method other than acid hydrolysis.

A time-course study (i.e., amino acid analysis at acid hydrolysis times of 24, 48, and 72 hours) is often employed to analyze the starting concentration of amino acids that are partially destroyed or slow to cleave. By plotting the observed concentration of labile amino acids (i.e., serine and threonine) versus hydrolysis time, the line can be extrapolated to the origin to determine the starting concentration of these amino acids. Time-course hydrolysis studies are also used with amino acids that are slow to cleave (e.g., isoleucine and valine). During the hydrolysis time course, the analyst will observe a plateau in these residues. The level of this plateau is taken as the residue concentration. If the hydrolysis time is too long, the residue concentration of the sample will begin to decrease, indicating destruction by the hydrolysis conditions.

An acceptable alternative to the time-course study is to subject an amino acid calibration standard to the same hydrolysis conditions as the test sample. The amino acid in free form may not completely represent the rate of destruction of labile amino acids within a peptide or protein during the hydrolysis. This is especially true for peptide bonds that are slow to cleave (e.g., Ile-Val bonds). However, this technique will allow the analyst to account for some residue destruction. Microwave acid hydrolysis has been used and is rapid but it requires special equipment as well as special precautions. The optimal conditions for microwave hydrolysis must be investigated for each individual protein/peptide sample. The microwave hydrolysis technique typically requires only a few minutes, but even a deviation of 1 minute may give inadequate results (e.g., incomplete hydrolysis or destruction of labile amino acids). Complete proteolysis, using a mixture of proteases, has been used but can be complicated, requires the proper controls, and is typically more applicable to peptides than proteins. [NOTE—During initial analyses of an unknown protein, experiments with various hydrolysis time and temperature conditions are conducted to determine the optimal conditions.]

Method 1

Acid hydrolysis using hydrochloric acid containing phenol is the most common procedure used for protein/peptide hydrolysis preceding amino acid analysis. The addition of phenol to the reaction prevents the halogenation of tyrosine.

Hydrolysis Solution: 6 N hydrochloric acid containing 0.1% to 1.0% of phenol.

Procedure—

Liquid Phase Hydrolysis—Place the protein or peptide sample in a hydrolysis tube, and dry. [NOTE—The sample is dried so that water in the sample will not dilute the acid used for the hydrolysis.] Add 200 µL of *Hydrolysis Solution* per 500 µg of lyophilized protein. Freeze the sample tube in a dry ice–acetone bath, and flame seal in vacuum. Samples are typically hydrolyzed at 110° for 24 hours in vacuum or inert atmosphere to prevent oxidation. Longer hydrolysis times (e.g., 48 and 72 hours) are investigated if there is a concern that the protein is not completely hydrolyzed.

Vapor Phase Hydrolysis—This is one of the most common acid hydrolysis procedures, and it is preferred for microanalysis when only small amounts of the sample are available. Contamination of the sample from the acid reagent is also minimized by using vapor phase hydrolysis. Place vials containing the dried samples in a vessel that contains an appropriate amount of *Hydrolysis Solution.* The *Hydrolysis Solution* does not come in contact with the test sample. Apply an inert atmosphere or vacuum (less than 200 µm of mercury or 26.7 Pa) to the headspace of the vessel, and heat to about 110° for a 24-hour hydrolysis time. Acid vapor hydrolyzes the dried sample. Any condensation of the acid in the sample vials is minimized. After hydrolysis, dry the test sample in vacuum to remove any residual acid.

Method 2

Tryptophan oxidation during hydrolysis is decreased by using mercaptoethanesulfonic acid (MESA) as the reducing acid.

Hydrolysis Solution: 2.5 M MESA solution.

Vapor Phase Hydrolysis—About 1 to 100 µg of the protein/peptide under test is dried in a hydrolysis tube. The hydrolysis tube is placed in a larger tube with about 200 µL of the *Hydrolysis Solution.* The larger tube is sealed in vacuum (about 50 µm of mercury or 6.7 Pa) to vaporize the *Hydrolysis Solution*. The hydrolysis tube is heated to between 170° to 185° for about 12.5 minutes. After hydrolysis, the hydrolysis tube is dried in vacuum for 15 minutes to remove the residual acid.

Method 3

Tryptophan oxidation during hydrolysis is prevented by using thioglycolic acid (TGA) as the reducing acid.

Hydrolysis Solution: a solution containing 7 M hydrochloric acid, 10% of trifluoroacetic acid, 20% of thioglycolic acid, and 1% of phenol.

Vapor Phase Hydrolysis—About 10 to 50 µg of the protein/peptide under test is dried in a sample tube. The sample tube is placed in a larger tube with about 200 µL of the *Hydrolysis Solution*. The larger tube is sealed in vacuum (about 50 µm of mercury or 6.7 Pa) to vaporize the TGA. The sample tube is heated to 166° for about 15 to 30 minutes. After hydrolysis, the sample tube is dried in vacuum for 5 minutes to remove the residual acid. Recovery of tryptophan by this method may be dependent on the amount of sample present.

Method 4

Cysteine-cystine and methionine oxidation is performed with performic acid before the protein hydrolysis.

Oxidation Solution—The performic acid is prepared fresh by mixing formic acid and 30 percent hydrogen peroxide (9 : 1), and incubating at room temperature for 1 hour.

Procedure—The protein/peptide sample is dissolved in 20 µL of formic acid, and heated at 50° for 5 minutes; then 100 µL of the *Oxidation Solution* is added. In this reaction, cysteine is converted to cysteic acid and methionine is converted to methionine sulfone. The oxidation is allowed to proceed for 10 to 30 minutes. The excess reagent is removed from the sample in a vacuum centrifuge. This technique may cause modifications to tyrosine residues in the presence of halides. The oxidized protein can then be acid hydrolyzed using *Method 1* or *Method 2*.

Method 5

Cysteine-cystine oxidation is accomplished during the liquid phase hydrolysis with sodium azide.

Hydrolysis Solution: 6 N hydrochloric acid containing 0.2% of phenol, to which sodium azide is added to obtain a final concentration of 0.2% (w/v). The added phenol prevents halogenation of tyrosine.

Liquid Phase Hydrolysis—The protein/peptide hydrolysis is conducted at about 110° for 24 hours. During the hydrolysis, the cysteine-cystine present in the sample is converted to cysteic acid by the sodium azide present in the *Hydrolysis Solution*. This technique allows better tyrosine recovery than *Method 4,* but it is not quantitative for methionine. Methionine is converted to a mixture of the parent methionine and its two oxidative products, methionine sulfoxide and methionine sulfone.

Method 6

Cysteine-cystine oxidation is accomplished with dimethyl sulfoxide (DMSO).

Hydrolysis Solution: 6 N hydrochloric acid containing 0.1% to 1.0% of phenol, to which DMSO is added to obtain a final concentration of 2% (v/v).

Vapor Phase Hydrolysis—The protein/peptide hydrolysis is conducted at about 110° for 24 hours. During the hydrolysis, the cysteine-cystine present in the sample is converted to cysteic acid by the DMSO present in the *Hydrolysis Solution*. As an approach to limit variability and to compensate for partial destruction, it is recommended to evaluate the cysteic acid recovery from oxidative hydrolyses of standard proteins containing 1 to 8 mol of cysteine. The response factors from protein/peptide hydrolysates are typically about 30% lower than those for nonhydrolyzed cysteic acid standards. Because histidine, methionine, tyrosine, and tryptophan are also modified, a complete compositional analysis is not obtained with this technique.

Method 7

Cysteine-cystine reduction and alkylation is accomplished by a vapor phase pyridylethylation reaction.

Reducing Solution—Transfer 83.3 µL of pyridine, 16.7 µL of 4-vinylpyridine, 16.7 µL of tributylphosphine, and 83.3 µL of water to a suitable container, and mix.

Procedure—Add the protein/peptide (between 1 and 100 µg) to a hydrolysis tube, and place in a larger tube. Transfer the *Reducing Solution* to the large tube, seal in vacuum (about 50 µm of mercury or 6.7 Pa), and incubate at about 100° for 5 minutes. Then remove the inner hydrolysis tube, and dry it in a vacuum desiccator for 15 minutes to remove residual reagents. The pyridylethylated protein/peptide can then be acid hydrolyzed using previously described procedures. The pyridylethylation reaction is performed simultaneously with a protein standard sample containing 1 to 8 mol of cysteine to improve accuracy in the pyridylethyl-cysteine recovery. Longer incubation times for the pyridylethylation reaction can cause modifications to the α-amino terminal group and the ϵ-amino group of lysine in the protein.

Method 8

Cysteine-cystine reduction and alkylation is accomplished by a liquid phase pyridylethylation reaction.

Stock Solutions—Prepare and filter three solutions: 1 M Tris hydrochloride (pH 8.5) containing 4 mM edetate disodium (*Stock Solution 1*), 8 M guanidine hydrochloride (*Stock Solution 2*), and 10% of 2-mercaptoethanol in water (*Stock Solution 3*).

Reducing Solution—Prepare a mixture of *Stock Solution 2* and *Stock Solution 1* (3 : 1) to obtain a buffered solution of 6 M guanidine hydrochloride in 0.25 M Tris hydrochloride.

Procedure—Dissolve about 10 µg of the test sample in 50 µL of the *Reducing Solution*, and add about 2.5 µL of *Stock Solution 3*. Store under nitrogen or argon for 2 hours at room temperature in the dark. To achieve the pyridylethylation reac-

tion, add about 2 µL of 4-vinylpyridine to the protein solution, and incubate for an additional 2 hours at room temperature in the dark. The protein/peptide is desalted by collecting the protein/peptide fraction from a reverse-phase HPLC separation. The collected sample can be dried in a vacuum centrifuge before acid hydrolysis.

Method 9

Cysteine-cystine reduction and alkylation is accomplished by a liquid phase carboxymethylation reaction.

Stock Solutions—Prepare as directed for *Method 8*.

Carboxymethylation Solution—Prepare a solution containing 100 mg of iodoacetamide per mL of alcohol.

Buffer Solution—Use the *Reducing Solution,* prepared as directed for *Method 8*.

Procedure—Dissolve the test sample in 50 µL of the *Buffer Solution*, and add about 2.5 µL of *Stock Solution 3*. Store under nitrogen or argon for 2 hours at room temperature in the dark. Add the *Carboxymethylation Solution* in a 1.5 fold ratio per total theoretical content of thiols, and incubate for an additional 30 minutes at room temperature in the dark. [NOTE—If the thiol content of the protein is unknown, then add 5 µL of 100 mM iodoacetamide for every 20 nmol of protein present.] The reaction is stopped by adding excess of 2-mercaptoethanol. The protein/peptide is desalted by collecting the protein/peptide fraction from a reverse-phase HPLC separation. The collected sample can be dried in a vacuum centrifuge before acid hydrolysis. The *S*-carboxyamidomethylcysteine formed will be converted to *S*-carboxymethyl-cysteine during acid hydrolysis.

Method 10

Cysteine-cystine is reacted with dithiodiglycolic acid or dithiodipropionic acid to produce a mixed disulfide. [NOTE—The choice of dithiodiglycolic acid or dithiodipropionic acid depends on the required resolution of the amino acid analysis method.]

Reducing Solution: a solution containing 10 mg of dithiodiglycolic acid (or dithiodipropionic acid) per mL of 0.2 M sodium hydroxide.

Procedure—Transfer about 20 µg of the test sample to a hydrolysis tube, and add 5 µL of the *Reducing Solution*. Add 10 µL of isopropyl alcohol, and then remove all of the sample liquid by vacuum centrifugation. The sample is then hydrolyzed using *Method 1*. This method has the advantage that other amino acid residues are not derivatized by side reactions, and the sample does not need to be desalted prior to hydrolysis.

Method 11

Asparagine and glutamine are converted to aspartic acid and glutamic acid, respectively, during acid hydrolysis. Asparagine and aspartic acid residues are added and represented by *Asx,* while glutamine and glutamic acid residues are added and represented by *Glx*. Proteins/peptides can be reacted with bis(1,1-trifluoroacetoxy)iodobenzene (BTI) to convert the asparagine and glutamine residues to diaminopropionic acid and diaminobutyric acid residues, respectively, upon acid hydrolysis. These conversions allow the analyst to determine the asparagine and glutamine content of a protein/peptide in the presence of aspartic acid and glutamic acid residues.

Reducing Solutions—Prepare and filter three solutions: a solution of 10 mM trifluoroacetic acid (*Solution 1*), a solution of 5 M guanidine hydrochloride and 10 mM trifluoroacetic acid (*Solution 2*), and a freshly prepared solution of dimethylformamide containing 36 mg of BTI per mL (*Solution 3*).

Procedure—In a clean hydrolysis tube, transfer about 200 µg of the test sample, and add 2 mL of *Solution 1* or *Solution 2* and 2 mL of *Solution 3*. Seal the hydrolysis tube in vacuum. Heat the sample at 60° for 4 hours in the dark. The sample is then dialyzed with water to remove the excess reagents. Extract the dialyzed sample three times with equal volumes of *n*-butyl acetate, and then lyophilize. The protein can then be acid hydrolyzed using previously described procedures. The

α-, β-diaminopropionic and α-, γ-diaminobutyric acid residues do not typically resolve from the lysine residues upon ion-exchange chromatography based on amino acid analysis. Therefore, when using ion-exchange as the mode of amino acid separation, the asparagine and glutamine contents are the quantitative difference in the aspartic acid and glutamic acid assayed contents with un-derivatized and BTI-derivatized acid hydrolysis. [NOTE—The threonine, methionine, cysteine, tyrosine, and histidine assayed content can be altered by BTI derivatization; a hydrolysis without BTI will have to be performed if the analyst is interested in the protein/peptide content of these other amino acid residues.]

METHODOLOGIES OF AMINO ACID ANALYSIS

Many amino acid analysis techniques exist, and the choice of any one technique often depends on the sensitivity required from the assay. In general, about one-half of the amino acid analysis techniques employed rely on the separation of the free amino acids by ion-exchange chromatography followed by postcolumn derivatization (e.g., with ninhydrin or *o*-phthalaldehyde). Postcolumn detection techniques can be used with samples that contain small amounts of buffer components, such as salts and urea, and generally require between 5 and 10 µg of protein sample per analysis. The remaining amino acid techniques typically involve precolumn derivatization of the free amino acids (e.g., phenyl isothiocyanate; 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbonate; (dimethylamino)azobenzenesulfonyl chloride; 9-fluorenyl-methylchloroformate; and 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole) followed by reverse-phase HPLC. Precolumn derivatization techniques are very sensitive and usually require between 0.5 and 1.0 µg of protein sample per analysis but may be influenced by buffer salts in the samples. Precolumn derivatization techniques may also result in multiple derivatives of a given amino acid, which complicates the result interpretation. Postcolumn derivatization techniques are generally influenced less by performance variation of the assay than precolumn derivatization techniques.

The following *Methods* may be used for quantitative amino acid analysis. Instruments and reagents for these procedures are available commercially. Furthermore, many modifications of these methodologies exist with different reagent preparations, reaction procedures, chromatographic systems, etc. Specific parameters may vary according to the exact equipment and procedure used. Many laboratories will utilize more than one amino acid analysis technique to exploit the advantages offered by each. In each of these *Methods*, the analog signal is visualized by means of a data acquisition system, and the peak areas are integrated for quantification purposes.

Method 1—Postcolumn Ninhydrin Detection

Ion-exchange chromatography with postcolumn ninhydrin detection is one of the most common methods employed for quantitative amino acid analysis. As a rule, a Li-based cation-exchange system is employed for the analysis of the more complex physiological samples, and the faster Na-based cation-exchange system is used for the more simplistic amino acid mixtures obtained with protein hydrolysates (typically containing 17 amino acid components). Separation of the amino acids on an ion-exchange column is accomplished through a combination of changes in pH and cation strength. A temperature gradient is often employed to enhance separation.

When the amino acid reacts with ninhydrin, the reactant has characteristic purple or yellow color. Amino acids, except imino acids, give a purple color, and show maximum absorption at 570 nm. The imino acids, such as proline, give a yellow color, and show maximum absorption at 440 nm. The postcolumn reaction between ninhydrin and amino acid eluted from the column is monitored at 440 nm and 570 nm, and the chromatogram obtained is used for the determination of amino acid composition.

The detection limit is considered to be 10 pmol for most of the amino acid derivatives, but 50 pmol for proline. Response linearity is obtained in the range of 20 to 500 pmol with correlation coefficients exceeding 0.999. To obtain good compositional data, samples larger than 1 µg before hydrolysis are best suited for this amino acid analysis of protein/peptide.

One method for postcolumn ninhydrin detection is shown below. Many other methods are also available, with instruments and reagents available commercially.

Mobile Phase Preparation—

Solution A—Transfer about 1.7 g of anhydrous sodium citrate and 1.5 mL of hydrochloric acid to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust, if necessary, with hydrochloric acid to a pH of 3.0.

Solution B—Transfer about 1.7 g of anhydrous sodium citrate and 0.7 mL of hydrochloric acid to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust, if necessary, with hydrochloric acid to a pH of 4.3.

Solution C—Prepare a solution containing 5% of sodium chloride, 1.9% of anhydrous sodium citrate, and 0.1% of phenol in water, and adjust to a pH of 6.

Column Regeneration Solution—Prepare a solution containing 0.8% of sodium hydroxide in water, and adjust to a pH of 13.

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

Postcolumn Reagent—Transfer about 18 g of ninhydrin and 0.7 g of hydrindantin to 900 mL of a solution containing 76.7% of dimethyl sulfoxide, 0.7% of dihydrate lithium acetate, and 0.1% of acetic acid, and mix for at least 3 hours under inert gas, such as nitrogen. [NOTE—This reagent is stable for 30 days if kept between 2° and 8° under inert gas.]

Buffer Solution—Prepare a solution containing 2% of anhydrous sodium citrate, 1% of hydrochloric acid, 0.5% of thiodiglycol, and 0.1% of benzoic acid in water, and adjust to a pH of 2.

Chromatographic System—The liquid chromatograph is equipped with a detector with appropriate interference filters at 440, 570, or 690 nm and a 4.0-mm × 120-mm column that contains 7.5-µm sulfonated styrene-divinylbenzene copolymer packing. The flow rate is about 14 mL per hour. The system is programmed as follows. Initially equilibrate the column with *Solution A;* at 25 minutes, the composition of the *Mobile Phase* is changed to 100% *Solution B;* and at 37 minutes, the composition is changed to 100% *Solution C.* At 75 minutes into the run, the last amino acid has been eluted from the column, and the column is regenerated with *Column Regeneration Solution* for 1 minute. The column is then equilibrated with *Solution A* for 11 minutes before the next injection. The column temperature is programmed as follows. The initial temperature is 48°; after 11.5 minutes, the temperature is increased to 65° at a rate of 3° per minute; at about 35 minutes, the temperature is increased to 77° at a rate of 3° per minute; and finally at about 52 minutes, the temperature is decreased to 48° at a rate of 3° per minute.

Procedure and Postcolumn Reaction—Reconstitute the lyophilized protein/peptide hydrolysate in the *Buffer Solution,* inject an appropriate amount into the chromatograph, and proceed as directed for *Chromatographic System.* As the amino acids are eluted from the column, they are mixed with the *Postcolumn Reagent*, which is delivered at a flow rate of 7 mL per hour, through a tee. After mixing, the column effluent and the *Postcolumn Reagent* pass through a tubular reactor at a temperature of 135°, where a characteristic purple or yellow color is developed. From the reactor, the liquid passes through a colorimeter with a 12-mm flow-through cuvette. The light emerging from the cuvette is split into three beams for analysis by the detector with interference filters at 440, 570, or 690 nm. The 690-nm signal may be electronically subtracted from the other signals for improved signal-to-noise ratios. The 440-nm (imino acids) and the 570-nm (amino acids) signals may be added in order to simplify data handling.

Method 2—Postcolumn OPA Fluorometric Derivatization

Ion-exchange chromatography with postcolumn *o*-phthalaldehyde (OPA) fluorometric detection is used. The procedure employs an ion-exchange column for separation of free amino acids followed by postcolumn oxidation with sodium hypochlorite and derivatization using OPA and *N*-acetyl-L-cysteine. The sodium hypochlorite oxidation step allows secondary amines, such as proline, to react with the OPA reagent.

OPA reacts with primary amines in the presence of thiol compound to form highly fluorescent isoindole products. This reaction is utilized for the postcolumn derivatization in analysis of amino acids by ion-exchange chromatography. The rule of the separation is the same as *Method I.* Instruments and reagents for this form of amino acid analysis are available commercially. Many modifications of this method exist.

Although OPA does not react with secondary amines (imino acids, such as proline) to form fluorescent substances, the oxidation with sodium hypochlorite allows secondary amines to react with OPA. The procedure employs a strongly acidic cation-exchange column for separation of free amino acids followed by postcolumn oxidation with sodium hypochlorite and postcolumn derivatization using OPA and thiol compound, such as *N*-acetyl-L-cysteine and 2-mercaptoethanol. The derivatization of primary amino acids are not noticeably affected by the continuous supply of sodium hypochlorite.

Separation of the amino acids on an ion-exchange column is accomplished through a combination of changes of pH and cation strength. After postcolumn derivatization of eluted amino acids with OPA, the reactant passes through the fluorometric detector. Fluorescence intensity of OPA-derivatized amino acids are monitored with an excitation wavelength of 348 nm and an emission wavelength of 450 nm.

The detection limit is considered to be a few tens of pmol level for most of the amino acid derivatives. Response linearity is obtained in the range of a few pmol level to a few tens of nmol level. To obtain good compositional data, a sample greater than 500 ng before hydrolysis is best suited for the amino acid analysis of protein/peptide.

One method of postcolumn OPA fluorometric detection is shown below.

Mobile Phase Preparation—

Solution A—Prepare a solution of sodium hydroxide, citric acid, and alcohol in HPLC grade water having a 0.2 N sodium concentration and containing 7% of alcohol (w/v), adjusted to a pH of 3.2.

Solution B—Prepare a solution of sodium hydroxide and citric acid in HPLC grade water having a 0.6 N sodium concentration, adjusted to a pH of 10.0.

Solution C: 0.2 N sodium hydroxide.

Mobile Phase—Use variable mixtures of *Solution A,* Solution B, and *Solution C* as directed for *Chromatographic System*.

Postcolumn Reagent Preparation—

Alkaline Buffer—Prepare a solution containing 384 mM sodium carbonate, 216 mM boric acid, and 108 mM potassium sulfate, and adjust to a pH of 10.0.

Hypochlorite Reagent—To 1 L of *Alkaline Buffer,* add 0.4 mL of sodium hypochlorite solution (10% chlorine concentration). [NOTE—The hypochlorite solution is stable for 2 weeks.]

OPA Reagent—Transfer 2 g of *N*-acetyl-L-cysteine and 1.6 g of OPA to a 15-mL volumetric flask, dissolve in and dilute with alcohol to volume, and mix. Transfer this solution and 4 mL of 10% aqueous polyethylene (23) lauryl ether to a 1-L volumetric flask, dilute with 980 mL of *Alkaline Buffer*, and mix.

Chromatographic System—The liquid chromatograph is equipped with a fluorometric detector set to an excitation wavelength of 348 nm and an emission wavelength of 450 nm and a 4.0-mm × 150-mm column that contains 7.5-µm packing L17. The flow rate is about 0.3 mL per minute, and the column temperature is set at 50°. The system is programmed as follows. The column is equilibrated with *Solution A;* over the next 20 minutes, the composition of the *Mobile Phase* is changed linearly to 85% *Solution A* and 15% *Solution B;* then there is a step change to 40% *Solution A* and 60% *So-*

lution B; over the next 18 minutes, the composition is changed linearly to 100% *Solution B* and held for 7 minutes; then there is a step change to 100% *Solution C,* and this is held for 6 minutes; then there is a step change to *Solution A,* and this composition is maintained for the next 8 minutes.

Procedure and Postcolumn Reaction—Inject about 1.0 nmol of each amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System*. As the effluent leaves the column, it is mixed with the *Hypochlorite Reagent*. The mixture passes through the first postcolumn reactor which consists of stainless steel 0.5-mm × 2-m tubing. A second postcolumn reactor of similar design is placed immediately downstream from the first postcolumn reactor and is used for the OPA postcolumn reaction. The flow rates for both the *Hypochlorite Reagent* and the *OPA Reagent* are 0.2 mL per minute, resulting in a total flow rate (i.e., *Hypochlorite Reagent*, *OPA Reagent,* and column effluent) of 0.7 mL per minute exiting from the postcolumn reactors. Postcolumn reactions are conducted at 55°. This results in a residence time of about 33 seconds in the OPA postcolumn reactor. After postcolumn derivatization, the column effluent passes through the fluorometric detector.

Method 3—Precolumn Determination

Precolumn derivatization of amino acids with phenylisothiocyanate (PITC) followed by reverse-phase HPLC separation with UV detection is used.

PITC reacts with amino acids to form phenylthiocarbamyl (PTC) derivatives, which can be detected with high sensitivity at 254 nm. Therefore, precolumn derivatization of amino acids with PITC followed by a reverse-phase HPLC separation with UV detection is used to analyze the amino acid composition.

After the reagent is removed under vacuum, the derivatized amino acids can be stored dry and frozen for several weeks with no significant degradation. If the solution for injection is kept cold, no noticeable loss in chromatographic response occurs after three days.

Separation of the PTC-amino acids on a reverse-phase HPLC with ODS column is accomplished through a combination of changes in concentrations of acetonitrile and buffer ionic strength. PTC-amino acids eluted from the column are monitored at 254 nm.

The detection limit is considered to be 1 pmol for most of the amino acid derivatives. Response linearity is obtained in the range of 20 to 500 pmol with correlation coefficients exceeding 0.999. To obtain good compositional data, a sample larger than 500 ng of protein/peptide before hydrolysis is best suited for this amino analysis of proteins/peptides.

One method of precolumn PITC derivatization is described below.

Mobile Phase Preparation—

Solution A: 0.05 M ammonium acetate, adjusted with phosphoric acid to a pH of 6.8.

Solution B—Prepare 0.1 M ammonium acetate, adjust with phosphoric acid to a pH of 6.8, and then prepare a mixture of this solution and acetonitrile (1 : 1).

Solution C: a mixture of acetonitrile and water (70 : 30).

Mobile Phase—Use variable mixtures of *Solution A, Solution B,* and *Solution C* as directed for *Chromatographic System*.

Derivatization Reagent Preparation—

Coupling Buffer: a mixture of acetonitrile, pyridine, triethylamine, and water (10 : 5 : 2 : 3).

Sample Solvent: a mixture of water and acetonitrile (7 : 2).

Sample Derivatization Procedure—Dissolve the lyophilized test sample in 100 µL of the *Coupling Buffer,* and then dry in a vacuum centrifuge to remove any hydrochloride if a protein hydrolysis step was used. Dissolve the test sample in 100 µL of *Coupling Buffer,* add 5 µL of PITC, and incubate at room temperature for 5 minutes. The test sample is again dried in a vacuum centrifuge, and is dissolved in 250 µL of *Sample Solvent*.

Chromatographic System—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 250-mm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 52°. The system is programmed as follows. The column is equilibrated with *Solution A;* over the next 15 minutes, the composition of the *Mobile Phase* is changed linearly to 85% *Solution A* and 15% *Solution B;* over the next 15 minutes, the composition is changed linearly to 50% *Solution A* and 50% *Solution B;* then there is a step change to 100% *Solution C,* and this is held for 10 minutes; then there is a step change to 100% *Solution A,* and the column is allowed to equilibrate before the next injection.

Procedure—Inject about 1.0 nmol of each PITC-amino acid under test (10-µL sample in *Sample Solvent*) into the chromatograph, and proceed as directed for *Chromatographic System*.

Method 4—Precolumn AQC Derivatization

Precolumn derivatization of amino acids with 6-aminoquinolyl-*N*-hydroxysuccinimidyl carbamate (AQC) followed by reverse-phase HPLC separation with fluorometric detection is used.

AQC reacts with amino acids to form stable, fluorescent unsymmetric urea derivatives (AQC-amino acids) which are readily amenable to analysis by reverse-phase HPLC. Therefore, precolumn derivatization of amino acids with AQC followed by reverse-phase HPLC separation is used to analyze the amino acid composition.

Separation of the AQC-amino acids on an ODS column is accomplished through a combination of changes in the concentrations of acetonitrile and salt. Selective fluorescence detection of the derivatives with an excitation wavelength at 250 nm and an emission wavelength at 395 nm allows for the direct injection of the reaction mixture with no significant interference from the only major fluorescent reagent byproduct, 6-aminoquinoline. Excess reagent is rapidly hydrolyzed ($t_{1/2} < 15$ seconds) to yield 6-aminoquinoline-*N*-hydroxysuccinimide and carbon dioxide, and after 1 minute no further derivatization can take place.

Peak areas for AQC-amino acids are essentially unchanged for at least 1 week at room temperature, and the derivatives have more than sufficient stability to allow for overnight automated chromatographic analysis.

The detection limit is considered to be ranging from about 40 fmol to 320 fmol for each amino acid, except for Cys. The detection limit for Cys is approximately 800 fmol. Response linearity is obtained in the range of 2.5 µM to 200 µM with correlation coefficients exceeding 0.999. Good compositional data can be obtained from the analysis of derivatized protein hydrolysates containing as little as 30 ng of protein/peptide.

One method of precolumn AQC derivatization is shown below.

Mobile Phase Preparation—

Solution A—Prepare a solution having a composition of 140 mM sodium acetate and 17 mM triethylamine, and adjust with phosphoric acid to a pH of 5.02.

Solution B: a mixture of acetonitrile and water (60 : 40).

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

Sample Derivatization Procedure—Dissolve about 2 µg of the test sample in 20 µL of 15 mM hydrochloric acid, and dilute with 0.2 M borate buffer (pH 8.8) to 80 µL. The derivatization is initiated by the addition of 20 µL of 10 mM AQC in acetonitrile, and allowed to proceed for 10 minutes at room temperature.

Chromatographic System—The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 250 nm and an emission wavelength of 395 nm and a 3.9-mm × 150-mm column that contains 4-µm packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 37°. The system is programmed as follows. The column is equilibrated with *Solution A;* over the next 0.5 minute, the composition of the *Mobile Phase* is changed linearly to 98% *Solution A* and 2% *Solution*

B; then over the next 14.5 minutes to 93% *Solution A* and 7% *Solution B;* then over the next 4 minutes to 87% *Solution A* and 13% *Solution B;* over the next 14 minutes to 68% *Solution A* and 32% *Solution B;* then there is a step change to 100% *Solution B* for a 5-minute wash; over the next 10 minutes, there is a step change to 100% *Solution A;* and the column is allowed to equilibrate before the next injection.

Procedure—Inject about 0.05 nmol of each AQC-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System.*

Method 5—Precolumn OPA Derivatization

Precolumn derivatization of amino acids with OPA followed by reverse-phase HPLC separation with fluorometric detection is used. This technique does not detect amino acids that exist as secondary amines (e.g., proline).

OPA in conjunction with a thiol reagent reacts with primary amine groups to form highly fluorescent isoindole products. 2-Mercaptoethanol and 3-mercaptopropionic acid can be used as thiol. OPA itself does not fluoresce and consequently produces no interfering peaks. In addition, its solubility and stability in aqueous solution, along with the rapid kinetics for the reactions, make it amenable to automated derivatization and analysis using an autosampler to mix the sample with the reagent. However, lack of reactivity with secondary amino acids has been a predominant drawback. This method does not detect amino acids that exist as secondary amines (e.g., proline). To compensate for this drawback, this technique may be combined with another technique described in *Method 7* or *Method 8.*

Precolumn derivatization of amino acids with OPA is followed by reverse-phase HPLC separation. Because of the instability of the OPA-amino acid derivative, HPLC separation and analysis are performed immediately following derivatization. The liquid chromatograph is equipped with a fluorometric detector for the detection of derivatized amino acids. Fluorescence intensity of the OPA-derivatized amino acids are monitored with an excitation wavelength of 348 nm and an emission wavelength of 450 nm.

The detection limits as low as 50 fmol via fluorescence have been reported, although the practical limit of analysis remains at 1 pmol. One method of precolumn OPA derivatization is shown below.

Mobile Phase Preparation—

Solution A: a mixture of 100 mM sodium acetate (pH 7.2), methanol, and tetrahydrofuran (900 : 95 : 5).

Solution B: methanol.

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

Derivatization Reagent—Dissolve 50 mg of OPA in 1.25 mL of methanol (protein sequencing grade). Add 50 µL of 2-mercaptoethanol and 11.2 mL of 0.4 M sodium borate (pH 9.5), and mix. [NOTE—This reagent is stable for 1 week.]

Sample Derivatization Procedure—Transfer about 5 µL of the test sample to an appropriate container, add 5 µL of the *Derivatization Reagent,* and mix. After 1 minute, add not less than 20 µL of 0.1 M sodium acetate (pH 7.0). Use 20 µL of this solution for analysis. [NOTE—Use of an internal standard (e.g., norleucine) is recommended for quantitative analysis because of potential reagent volume variations in the sample derivatization. The sample derivatization is performed in an automated on-line fashion. Because of the instability of the OPA-amino acid derivative, HPLC separation and analysis are performed immediately following derivatization.]

Chromatographic System—The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 348 nm and an emission wavelength of 450 nm and a 4.6-mm × 75-mm column that contains 3-µm packing L3. The flow rate is about 1.7 mL per minute, and the column temperature is maintained at 37°. The system is programmed as follows. The column is equilibrated with 92% *Solution A* and 8% *Solution B;* over the next 2 minutes, the composition of the *Mobile Phase* is changed to 83% *Solu-*

tion A and 17% *Solution B,* and held for an additional 3 minutes; then changed to 54% *Solution A* and 46% *Solution B* over the next 5 minutes, and held for an additional 2 minutes; then changed to 34% *Solution A* and 66% *Solution B* over the next 2 minutes, and held for 1 minute; then over the next 0.3 minute changed to 20% *Solution A* and 80% *Solution B,* and held for an additional 2.6 minutes; and then finally over 0.6 minute changed to 92% *Solution A* and 8% *Solution B,* and held for an additional 0.6 minute.

Procedure—Inject about 0.02 nmol of each OPA-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System.*

Method 6—Postcolumn DABS-Cl Derivatization

Precolumn derivatization of amino acids with (dimethylamino)azobenzenesulfonyl chloride (DABS-Cl) followed by reverse-phase HPLC separation with visible light detection is used.

DABS-Cl is a chromophoric reagent employed for the labeling of amino acids. Amino acids labeled with DABS-Cl (DABS-amino acids) are highly stable and show the maximum absorption at 436 nm.

DABS-amino acids, all 19 naturally occurring amino acids derivatives, can be separated on an ODS column of a reverse-phase HPLC by employing gradient systems consisting of acetonitrile and aqueous buffer mixture. Separated DABS-amino acids eluted from the column are detected at 436 nm in the visible region.

This method can analyze the imino acids, such as proline, together with the amino acids, at the same degree of sensitivity. DABS-Cl derivatization method permits the simultaneous quantification of tryptophan residues by previous hydrolysis of the protein/peptide with sulfonic acids, such as mercaptoethanesulfonic acid, *p*-toluenesulfonic acid, or methanesulfonic acid, described for *Method 2* in *Protein Hydrolysis* under *Amino Acid Analysis.* The other acid-labile residues, asparagine and glutamine, can also be analyzed by previous conversion into diaminopropionic acid and diaminobutyric acid, respectively, by treatment of protein/peptide with BTI, described for *Method 11* in *Protein Hydrolysis* under *Amino Acid Analysis.*

The nonproteinogenic amino acid, norleucine, cannot be used as an internal standard in this method as this compound is eluted in a chromatographic region crowded with peaks of primary amino acids. Nitrotyrosine can be used as an internal standard because it is eluted in a clean region.

The detection limit of DABS-amino acid is about 1 pmol. As little as 2 to 5 pmol of an individual DABS-amino acid can be quantitatively analyzed with reliability, and only 10 ng to 30 ng of the dabsylated protein hydrolysate is required for each analysis.

One method for precolumn DABS-Cl derivatization is shown below.

Mobile Phase Preparation—

Solution A: 25 mM sodium acetate (pH 6.5) containing 4% of dimethylformamide.

Solution B: acetonitrile.

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

Derivatization Reagent Preparation—

Sample Buffer: 50 mM sodium bicarbonate, adjusted to a pH of 8.1.

Derivatization Reagent—Dissolve 1.3 mg of DABS-Cl in 1 mL of acetonitrile. [NOTE—This reagent is prepared fresh shortly before the derivatization step.]

Sample Dilution Buffer—Prepare a mixture of 50 mM sodium phosphate (pH 7.0) and alcohol (1 : 1).

Sample Derivatization Procedure—Dissolve the test sample in 20 µL of *Sample Buffer*, add 40 µL of *Derivatization Reagent*, and mix. The sample container is sealed with a silicon-rubber stopper, and heated to 70° for 10 minutes. During the sample heating, the mixture will become completely soluble. After the derivatization, dilute the test sample with an appropriate quantity of the *Sample Dilution Buffer.*

Chromatographic System—The liquid chromatograph is equipped with a 436-nm detector and a 4.6-mm × 250-mm column that contains packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 40°. The system is programmed as follows. The column is equilibrated with 85% *Solution A* and 15% *Solution B;* over the next 20 minutes, the composition of the *Mobile Phase* is changed to 60% *Solution A* and 40% *Solution B;* over the next 12 minutes, the composition is changed to 30% *Solution A* and 70% *Solution B*, and held for an additional 2 minutes.

Procedure—Inject about 0.05 nmol of the DABS-amino acids into the chromatograph, and proceed as directed for *Chromatographic System.*

Method 7—Precolumn FMOC-Cl Derivatization

Precolumn derivatization of amino acids with 9-fluorenylmethyl chloroformate (FMOC-Cl) followed by reverse-phase HPLC separation with fluorometric detection is used.

FMOC-Cl reacts with both primary and secondary amino acids to form highly fluorescent products. The reaction of FMOC-Cl with amino acid proceeds under mild conditions, in aqueous solution, and is completed in 30 seconds. The derivatives are stable, with only the histidine derivative showing any breakdown. Although FMOC-Cl is fluorescent itself, the reagent excess and fluorescent side-products can be eliminated without loss of FMOC-amino acids.

FMOC-amino acids are separated by reverse-phase HPLC using an ODS column. The separation is carried out by gradient elution varied linearly from a mixture of acetic acid buffer, methanol, and acetonitrile (50 : 40 : 10) to a mixture of acetonitrile and acetic acid buffer (50 : 50), and 20 amino acid derivatives that are separated in 20 minutes. Each derivative eluted from the column is monitored by a fluorometric detector set at an excitation wavelength of 260 nm and an emission wavelength of 313 nm.

The detection limit is in the low fmol range. A linearity range of 0.1 μM to 50 μM is obtained for most amino acids.

One method for precolumn FMOC-Cl derivatization is shown below.

Mobile Phase Preparation—

Acetic Acid Buffer—Transfer 3 mL of glacial acetic acid and 1 mL of triethylamine to a 1-L volumetric flask, and dilute with HPLC grade water to volume. Adjust with sodium hydroxide to a pH of 4.20.

Solution A: a mixture of *Acetic Acid Buffer,* methanol, and acetonitrile (50 : 40 : 10).

Solution B: a mixture of acetonitrile and *Acetic Acid Buffer* (50 : 50).

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

Derivatization Reagent Preparation—

Borate Buffer—Prepare a 1 M boric acid solution, and adjust with sodium hydroxide to a pH of 6.2.

FMOC-Cl Reagent—Dissolve 155 mg of 9-fluorenylmethyl chloroformate in 40 mL of acetone, and mix.

Sample Derivatization Procedure—To 0.4 mL of the test sample add 0.1 mL of *Borate Buffer* and 0.5 mL of *FMOC-Cl Reagent*. After about 40 seconds, extract the mixture with 2 mL of pentane, and then extract again with fresh pentane. The aqueous solution with amino acid derivatives is then ready for injection.

Chromatographic System—The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 260 nm and an emission wavelength of 313 nm and a 4.6-mm × 125-mm column that contains 3-μm packing L1. The flow rate is about 1.3 mL per minute. The system is programmed as follows. The column is equilibrated with *Solution A,* and this composition is maintained for 3 minutes; over the next 9 minutes, it is changed to 100% *Solution B;* then over the next 0.5 minute, the flow rate is increased to 2 mL per minute, and held until the final FMOC-amino acid is eluted from the column. The total run time is about 20 minutes.

Procedure—Inject not less than 0.01 nmol of each FMOC-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System*. The FMOC-histidine derivative will generally give a lower response than the other derivatives.

Method 8—Precolumn NBD-F Derivatization

Precolumn derivatization of amino acids with 7-fluoro-4-nitrobenzo-2-oxa-1,3-diazole (NBD-F) followed by reverse-phase HPLC separation with fluorometric detection is used.

7-Fluoro-4-nitrobenzo-2-oxa-1,3-diazole (NBD-F) reacts with both primary and secondary amino acids to form highly fluorescent products. Amino acids are derivatized with NBD-F by heating to 60° for 5 minutes.

NBD-amino acid derivatives are separated on an ODS column of reverse-phase HPLC by employing a gradient elution system consisting of acetonitrile and aqueous buffer mixture, and 17 amino acid derivatives that are separated in 35 minutes. *E*-aminocaproic acid can be used as an internal standard because it is eluted in a clean chromatographic region. Each derivative eluted from the column is monitored by a fluorometric detector set at an excitation wavelength of 480 nm and an emission wavelength of 530 nm.

The sensitivity of this method is almost the same as that for the precolumn OPA derivatization method (*Method 5*), excluding proline to which OPA is not reactive and might be advantageous for NBD-F against OPA.

The detection limit for each amino acid is about 10 fmol. Profile analysis was achieved for about 1.5 mg of protein hydrolysates in the final precolumn labeling reaction mixture for HPLC.

One method for precolumn NBD-F derivatization is shown below.

Mobile Phase Preparation—

Solution A: a solution of 10mM sodium citrate containing 75 mM sodium perchlorate, adjusted with hydrochloric acid to a pH of 6.2.

Solution B: a mixture of acetonitrile and water (50 : 50).

Derivatization Reagent Preparation—

Sample Buffer: a 0.1 M boric acid solution, adjusted with sodium hydroxide to a pH of 9.2.

Derivatization Reagent—Dissolve 5 mg of NBD-F in 1.0 mL of alcohol, and mix.

Sample Derivatization Procedure—Dissolve the test sample in 20 µL of *Sample buffer,* add 10 µL of *Derivatization Reagent,* and mix. The sample container is heated at 60° for 5 minutes. After the derivatization, dilute the test sample with 300 µL of *Solution A.*

Chromatographic System—The liquid chromatograph is equipped with a fluorometric detector set at an excitation wavelength of 480 nm and an emission wavelength of 530 nm and a 4.6-mm × 150-mm column that contains 5-µm particle size ODS silica packing. The flow rate is about 1.0 mL per minute, and the column temperature is maintained at 40°. The system is programmed as follows. The column is equilibrated with 94% *Solution A* and 6% *Solution B;* over the next 16 minutes, the composition is changed linearly to 63% *Solution A* and 37% *Solution B;* over the next 5 minutes, the composition is changed linearly to 62% *Solution A* and 38% *Solution B;* over the next 9 minutes, the composition is changed linearly to 100% *Solution B*, and held for an additional 5 minutes; then finally over 2 minutes, the composition is changed linearly to 94% *Solution A* and 6% *Solution B;* and then the column is allowed to equilibrate before the next injection.

Procedure—Inject about 15 pmol of each NBD-amino acid under test into the chromatograph, and proceed as directed for *Chromatographic System.*

DATA CALCULATION AND ANALYSIS

When determining the amino acid content of a protein/peptide hydrolysate, it should be noted that the acid hydrolysis step destroys tryptophan and cysteine. Serine and threonine are partially destroyed by acid hydrolysis, while isoleucine and valine residues may be only partially cleaved. Methionine can undergo oxidation during acid hydrolysis, and some amino acids (e.g., glycine and serine) are common contaminants. Application of adequate vacuum (less than 200 um µm of mercury or 26.7 Pa) or introduction of inert gas (argon) in the headspace of the reaction vessel during vapor phase hydrolysis can reduce the level of oxidative destruction. Therefore, the quantitative results obtained for cysteine, tryptophan, threonine, isoleucine, valine, methionine, glycine, and serine from a protein/peptide hydrolysate may be variable and may warrant further investigation and consideration.

Calculations

Amino Acid Mole Percent—This is the number of specific amino acid residues per 100 residues in a protein. This result may be useful for evaluating amino acid analysis data when the molecular weight of the protein/peptide under investigation is unknown. This information can be used to corroborate the identity of a protein and has other applications. Carefully identify and integrate the peaks obtained as directed for each *Procedure*. Calculate the mole percent for each amino acid present in the test sample by the formula:

$$100r_U / r$$

in which r_U is the peak response, in nmol, of the amino acid under test; and r is the sum of peak responses, in nmol, for all amino acids present in the test sample. Comparison of the mole percent of the amino acids under test to data from known proteins can help establish or corroborate the identity of the sample protein.

Unknown Protein Samples—This data analysis technique can be used to estimate the protein concentration of an unknown protein sample using the amino acid analysis data. Calculate the mass, in µg, of each recovered amino acid by the formula:

$$mM_W/1000$$

in which m is the recovered quantity, in nmol, of the amino acid under test; and M_W is the average molecular weight, in mg, for that amino acid, corrected for the weight of the water molecule that was eliminated during peptide bond formation. The sum of the masses of the recovered amino acids will give an estimate of the total mass of the protein analyzed after appropriate correction for partially and completely destroyed amino acids. If the molecular weight of the unknown protein is available (i.e., by SDS-PAGE analysis or mass spectroscopy), the amino acid composition of the unknown protein can be predicted. Calculate the number of residues of each amino acid by the formula:

$$m/(1000M/M_{WT})$$

in which m is the recovered quantity, in nmol, of the amino acid under test; M is the total mass, in µg, of the protein; and M_{WT} is the molecular weight, in mg, of the unknown protein.

Known Protein Samples—This data analysis technique can be used to investigate the amino acid composition and protein concentration of a protein sample of known molecular weight and amino acid composition using the amino acid analysis data. When the composition of the protein being analyzed is known, one can exploit the fact that some amino acids are recovered well, while other amino acid recoveries may be compromised because of complete or partial destruction (e.g., tryptophan, cysteine, threonine, serine, methionine), incomplete bond cleavage (i.e., for isoleucine and valine), and free amino acid contamination (i.e., by glycine and serine).

Because those amino acids that are recovered best represent the protein, these amino acids are chosen to quantify the amount of protein. Well-recovered amino acids are, typically, aspartate-asparagine, glutamate-glutamine, alanine, leucine, phenylalanine, lysine, and arginine. This list can be modified based on experience with one's own analysis system. Divide the quantity, in nmol, of each of the well-recovered amino acids by the expected number of residues for that amino acid to obtain the protein content based on each well-recovered amino acid. Average the protein content results calculated. The protein content determined for each of the well-recovered amino acids should be evenly distributed about the mean. Discard protein content values for those amino acids that have an unacceptable deviation from the mean. Typically, a greater than 5% variation from the mean is considered unacceptable, but this is arbitrary. Recalculate the mean protein content from the remaining values to obtain the protein content of the sample. Divide the content of each amino acid by the calculated mean protein content to determine the amino acid composition of the sample by analysis.

Calculate the relative compositional error, in percentage, by the formula:

$$100m / m_S$$

in which m is the experimentally determined quantity, in nmol per amino acid residue, of the amino acid under test; and m_S is the known residue value for that amino acid. The average relative compositional error is the average of the absolute values of the relative compositional errors of the individual amino acids, typically excluding tryptophan and cysteine from this calculation. The average relative compositional error can provide important information on the stability of analysis run over time. The agreement in the amino acid composition between the protein sample and the known composition can be used to corroborate the identity and purity of the protein in the sample.■ IS (*USP30*)

BRIEFING

⟨1053⟩ Biotechnology-Derived Articles—Capillary Electrophoresis—See briefing under *Biotechnology-Derived Articles—Tests* ⟨1047⟩. In addition, the resolution equation cited in the section *Micellar Electrokinetic Chromatography (MEKC)* has been corrected.

(BB PP: I. DeVeau) RTS—43939-2

Add the following:

■⟨1053⟩ BIOTECHNOLOGY-DERIVED ARTICLES—CAPILLARY ELECTROPHORESIS

This chapter provides guidance and procedures used for characterization of biotechnology-derived articles by capillary electrophoresis. This chapter is harmonized with the corresponding chapter in *JP* and *EP*. Other characterization tests, also harmonized, are shown in *Biotechnology-Derived Articles—Amino Acid Analysis* ⟨1052⟩, *Biotechnology-Derived Articles—Isoelectric Focusing* ⟨1054⟩, *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩, *Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis* ⟨1056⟩, and *Biotechnology-Derived Articles—Total Protein Assay* ⟨1057⟩.

INTRODUCTION

Capillary electrophoresis is a physical method of analysis based on the migration, inside a capillary, of charged analytes dissolved in an electrolyte solution under the influence of a direct-current electric field. In this section we are describing four capillary electrophoresis methods: *Free Solution Capillary Electrophoresis, Capillary Gel Electrophoresis, Capillary Isoelectric Focusing,* and *Micellar Electrokinetic Chromatography.*

In-Process Revision

GENERAL PRINCIPLE

The migration velocity of the analyte under an electric field of intensity *(E)* is determined by the electrophoretic mobility of the analyte and the electroosmotic mobility of the buffer inside the capillary. The electrophoretic mobility of a solute *(μ_{ep})* depends on the characteristics of the solute (electrical charge, molecular size, and shape) and the characteristics of the buffer in which the migration takes place (type and ionic strength of the electrolyte, pH, viscosity, and additives). The electrophoretic velocity *(V_{ep})* of a solute, assuming a spherical shape, is as follows:

$$V_{ep} = \mu_{ep}E = \left(\frac{q}{6\pi\eta r}\right)\left(\frac{V}{L}\right)$$

in which q is the effective charge of the particle; η is the viscosity of the buffer; r is the size of the solute ion; V is the applied voltage; and L is the total length of the capillary.

When an electric field is applied through the capillary filled with buffer, a flow of solvent, called electroosmotic flow, is generated inside the capillary. Its velocity depends on the electroosmotic mobility *(μ_{eo}),* which in turn depends on the charge density on the capillary internal wall and the buffer characteristics. The electroosmotic velocity *(V_{eo})* is as follows:

$$V_{eo} = \mu_{eo}E = \left(\frac{\varepsilon\zeta}{\eta}\right)\left(\frac{V}{L}\right)$$

in which ϵ is the dielectric constant of the buffer; ζ is the zeta potential of the capillary surface; and the other terms are as defined above.

The electrophoretic and electroosmotic mobilities of the analyte may act in the same direction or in opposite directions, depending on the charge (positive or negative) of the solute, and the velocity of the solute *(v)* is as follows:

$$V = V_{ep} \pm V_{eo}$$

The sum or the difference between the two velocities (V_{ep} and V_{eo}) is used depending on whether the mobilities act in the same or opposite directions. Under conditions with a fast V_{eo}, with respect to the V_{ep} of the solutes, both negative and positive charged analytes can be separated in the same run. The time *(t)* taken by the solute to migrate the distance *(l)* from the injection end of the capillary to the detection point (capillary effective length) is as follows:

$$t = \frac{l}{V_{ep} \pm V_{eo}} = \frac{l(L)}{V(\mu_{ep} \pm \mu_{eo})}$$

in which the other terms are as defined above.

In general, the fused-silica capillaries used in electrophoresis bear negative charges on the inner wall, producing electroosmotic flow towards the cathode. The electroosmotic flow has to remain constant from run to run to obtain good reproducibility in the migration velocity of the solutes. For some applications, it might be necessary to reduce or suppress the electroosmotic flow by modifying the inner wall of the capillary or by changing the pH of the buffer solution.

When the sample is introduced in the capillary, each analyte ion of the sample migrates within the background electrolyte as an independent zone according to its electrophoretic mobility. The spreading of each solute band (zone dispersion) results from a different phenomena. Under ideal conditions, the sole contribution to the solute-zone broadening is molecular diffu-

sion of the solute along the capillary (longitudinal diffusion). In this case, the efficiency of the zone is expressed as the number of theoretical plates *(N),* as follows:

$$N = \frac{(\mu_{ep} \pm \mu_{eo})(Vl)}{2DL}$$

in which D is the molecular diffusion of the solute in the buffer; and the other terms are as defined above.

From a practical point of view, other phenomena, such as heat dissipation, sample adsorption onto the capillary wall, mismatched conductivity between sample and buffer, length of the injection plug, detector cell size, and unleveled buffer reservoirs, can also significantly contribute to band dispersion. Separation between two bands (expressed by the resolution, R_S) can be achieved by modification of the electrophoretic mobility of the analytes, by the electroosmotic mobility induced by capillary, and by increasing the efficiency for the band of each analyte as follows:

$$R_S = \frac{\sqrt{N}(\mu_{epb} - \mu_{epa})}{4(\mu_{ep} \pm \mu_{eo})}$$

in which μ_{epa} and μ_{epb} are the electrophoretic mobilities of the two compounds to be separated; $\overline{\mu}_{ep}$ is the average electrophoretic mobility of the two solutes calculated as:

$$\overline{\mu}_{ep} = ½ (\mu_{epb} + \mu_{epa})$$

and the other terms are as defined above.

APPARATUS

An apparatus for capillary electrophoresis is composed of a high voltage controllable power supply; two buffer reservoirs held at the same level and containing specified anodic and cathodic solutions; two electrodes assemblies (cathode and anode) immersed in the buffer reservoirs and connected to the power supply; a separation capillary usually made of fused-silica, sometimes with an optical viewing window aligned with the detector, depending on the detector, with the ends of the capillary placed in the buffer reservoirs and the capillary being filled with a solution specified in a given monograph; a suitable injection system; a detector capable of monitoring the amount of substance of interest passing through a segment of the separation capillary at a given time, generally based on absorption spectrophotometry (UV and visible), fluorimetry, conductimetric, amperometric, or mass spectrometric detection, depending on the specific applications, or even indirect detection to detect non-UV-absorbing and nonfluorescent compounds; and a thermostatic system capable of maintaining the temperature inside the capillary.

The method of injection of samples and its automation is critical for precise quantitative analysis. Methods of injection include gravity, pressure or vacuum, or electrokinetic injection. The amount of each sample component introduced electrokinetically depends on its electrophoretic mobility, thus possibly biasing the results.

It is expected that the capillary, the buffer solutions, the preconditioning method, the sample solution, and the migration conditions will be specified in the individual monograph. The electrolytic solution employed may be filtered to remove particles and degassed to avoid bubble formation that could interfere with the detection system. To achieve reproducible migration time of the solutes, it would be necessary to develop, for each analytical method, a rigorous rinsing routine after each injection.

FREE SOLUTION CAPILLARY ELECTROPHORESIS

In free solution capillary electrophoresis, analytes are separated in a capillary containing only buffer without any anticonvective medium. In this technique, separation takes place because the different components of the sample migrate as discrete bands with different velocities. The velocity of each band depends on the electrophoretic mobility of the solute and the

electroosmotic flow on the capillary. Coated capillaries, with reduced electroosmotic flow, can be used to increase the separation capacity of those substances absorbing on fused-silica surfaces.

This mode of capillary electrophoresis is appropriate for the analysis of small (MW < 2000) and large (2000 < MW < 100,000) molecules. Due to the high efficiency achieved, molecules having only minute differences in their charge-to-mass ratio can be separated. This method also allows the separation of chiral compounds by adding chiral selectors to the separation buffer. The optimization of the separations requires consideration of a number of instrumental and electrolytic solution parameters.

Instrumental Parameters

Voltage—The separation time is universally proportional to applied voltage. However, an increase in the voltage used can cause excessive heat production, giving rise to temperature and viscosity gradients in the buffer inside the capillary, which causes band broadening and decreases resolution.

Temperature—The main effect of temperature is observed on buffer viscosity and electrical conductivity, thus affecting migration velocity. In some cases, an increase in capillary temperature can cause a conformational change of some proteins, modifying their migration time and the efficiency of the separation.

Capillary—The length and internal diameter of the capillary affects the analysis time, the efficiency of separations, and the load capacity. Increasing both effective length and total length can decrease the electric fields, at a constant voltage, which will increase migration time. For a given buffer and electric field, heat dissipation (thus, sample band broadening) depends on the internal diameter of the capillary. The latter also affects the detection limit, depending on the sample volume injected into the capillary and the detection system used.

The adsorption of sample components on the capillary wall limits efficiency; therefore, methods to avoid these interactions should be considered in the development of a separation method. This is critical in samples containing proteins. Strategies have been devised to avoid adsorption of proteins on the capillary wall. These strategies include both the use of extreme pH and the absorption of positively charged buffer additives that only require modification of the buffer composition. Other strategies include the coating of the internal wall of the capillary with a polymer covalently bonded to the silica that prevents interaction between the proteins and the negatively charged silica surface. Capillaries with coatings consisting of neutral-hydrophilic, cationic, and anionic polymers are commercially available.

Electrolytic Solution Parameters

Buffer Type and Concentrations—Suitable buffers for capillary electrophoresis have an appropriate buffer capacity in the pH range of choice and low mobility to minimize current generation.

To minimize peak shape distortion, it is important to match buffer–ion mobility to solute mobility whenever possible. The type of sample solvent used is important to achieve on-column sample focusing, which increases separation efficiency and improves detection. Also, an increase in buffer concentration at a given pH will decrease electroosmotic flow and solute velocity.

Buffer pH—The pH of the buffer can affect separation by modifying the charge of the analyte or other additives and by changing the electroosmotic flow. For protein and peptide separation, a change in the pH of the buffer from above the isoelectric point to below the isoelectric point changes the net charge of the solute from negative to positive. An increase in the buffer pH generally increases the electroosmotic flow.

Organic Solvents—Organic modifiers, such as methanol, acetonitrile, and others, are added to the aqueous buffer to increase the solubility of the solute or other additives and/or to

affect the ionization degree of the sample components. The addition of these organic modifiers to the buffer generally causes a decrease in the electroosmotic flow.

Additives for Chiral Separations—To separate optical isomers, a chiral selector is added to the separation buffer. The most commonly used chiral selectors are cyclodextrins, although in some cases crown ethers, certain polysaccharides, or even proteins can be used. Because chiral recognition is governed by the different interactions between the chiral selector and each of the enantiomers, the resolution achieved for the chiral compounds depends largely on the type of chiral selector used. While developing a given separation it may be useful to test cyclodextrins having a different cavity size (α-, *β*-, or Γ-cyclodextrin) or modified cyclodextrins with neutral (methyl, ethyl, hydroxyalkyl, etc.) or ionizable (aminomethyl, carboxymethyl, sulfobutylether, etc.) moities. The resolution of chiral separations is also controlled by the concentration of the chiral selector, the composition and pH of the buffer, and the separation temperature. Organic additives, such as methanol or urea, can also affect the resolution of separation.

CAPILLARY GEL ELECTROPHORESIS

Separation takes place inside a capillary filled with a polymer acting as a molecular sieve. The smaller components in the sample move faster along the capillary than the larger ones. This method can be used for separation of biopolymers-proteins and DNA fragments, according to their molecular mass.

Characteristics of Chemical and Physical Gels

Chemical Gels—Chemical gels are prepared inside the capillary by reaction of monomers. One example of such a gel is a cross-linked polyacrylamide. This type of gel is bonded to the fused-silica wall and cannot be removed without destroying the capillary. For protein analysis, the separation buffer usually contains sodium dodecyl sulfate, and the sample is denatured by heating in a mixture of sodium dodecyl sulfate and 2-mercaptoethanol or dithiothreitol before injection. Optimization of separation in a cross-linked gel is obtained by modifying the separation buffer (see *Free Solution Capillary Electrophoresis*) and by controlling the gel porosity during the gel preparation. For a cross-linked polyacrylamide gel, the porosity can be modified by changing the concentration of acrylamide and/or the ratio of the cross-linker. As a rule, a decrease in the porosity of the gel leads to a decrease in the mobility of the solutes. Due to the rigidity of this type of gel, only electrokinetic injection can be used.

Physical Gels—Physical gels are hydrophilic polymers (i.e., linear polyacrylamide, cellulose derivatives, dextran, etc.) which can be dissolved in aqueous separation buffers, giving rise to a separation medium that also acts as a molecular sieve. These polymeric separation media are easier to prepare than cross-linked polymers. They can be prepared in a vial and filled by pressure in a wall-coated capillary with no electroosmotic flow. Replacing the gel before every injection generally improves the separation reproducibility. The porosity of the physical gels can be increased by using polymers of higher molecular weight (at a given polymer concentration) or by decreasing the polymer concentration (for a given polymer molecular weight). A decrease in gel porosity leads to a decrease in the mobility of the solute for the same buffer. Both hydrodynamic and electromigration injection techniques can be used because the dissolution of these polymers in the buffer gives low viscosity solutions.

CAPILLARY ISOELECTRIC FOCUSING

The molecules migrate under the influence of the electric field, so long as they are charged, in a pH gradient generated by ampholytes having *pI* values in a wide range (poly-amino-carboxylic acids) dissolved in the separation buffer. The three basic steps in capillary isoelectric focusing are loading, focusing, and mobilization.

Loading—

Loading in One Step—The sample is mixed with ampholytes and introduced into the capillary by pressure or vacuum.

Sequential Loading—A leading buffer, then the ampholytes, then the sample mixed with ampholytes, again ampholytes alone, and finally the terminating buffer are introduced into the capillary. The volume of the sample must be small enough so as to not modify the pH gradient.

Focusing—When the voltage is applied, ampholytes migrate toward the cathode or the anode according to their net charge, creating the pH gradient from anode (lower pH) to cathode (higher pH). The components to be separated migrate until they reach a pH corresponding to their isoelectric point, and the current drops to very low values.

Mobilization—The bands of separated components migrate past the detector by one of the three following methods.

Method 1—During *Focusing,* under the influence of the electroosmotic flow when this flow is small enough to allow the focusing of the components.

Method 2—By application of positive pressure after *Focusing.*

Method 3—After *Focusing,* by adding salts in the cathode reservoir or the anode reservoir, depending on the direction chosen for mobilization, in order to alter the pH in the capillary when the voltage is applied. As the pH is changed, the proteins and ampholytes are mobilized in the direction of the reservoir, which contains added salts and pass the detector.

The separation achieved is expressed as ΔpI and depends on the pH gradient *(dpH),* the number of ampholytes having different *pI* values, the diffusion coefficient *(D),* the intensity of the electric field *(E),* and the variation of the electrophoretic mobility of the analyte with the pH, and is as follows:

$$\Delta pI = 3\sqrt{\frac{D(dpH/dx)}{E(-d\mu/dpH)}}$$

in which dpH/dx is the pH gradient; and $-d\mu/dpH$ is the variation of the solution mobility with the pH in the region close to the *pI.*

Optimization Parameters—The major parameters that need to be considered in the development of separations are voltage, capillary, and solutes.

Voltage: use of high fields from 300 V/cm to 1,000 V/cm during *Focusing.*

Capillary—Depending on the *Mobilization* strategy selected (see above), the electroosmotic flow must be reduced or suppressed. Coated capillaries tend to reduce the electroosmotic flow.

Solutions—The anode buffer reservoir is filled with a solution of a lower pH than the *pI* of the most acidic ampholyte, and the cathode reservoir is filled with a solution with a higher pH than the *pI* of the most basic ampholyte. Phosphoric acid for the anode and sodium hydroxide for the cathode are frequently used.

Addition of a polymer, like methylcellulose, in the ampholyte solution tends to suppress convective forces (if any) and electroosmotic flow by increasing the viscosity. Commercial ampholytes covering many pH ranges are available and may also be mixed to obtain an expanded pH range. Broad pH ranges are used to estimate the isoelectric point, whereas narrower ranges are employed to improve accuracy. Calibration can be made by correlating migration time with the isoelectric point of a series of standard protein markers. During *Focusing,* precipitation of proteins at their isoelectric point can be prevented, if necessary, using buffer additives such as glycerol, surfactants, urea, or Zwitterionic buffers. However, depending on the concentration, urea can denature proteins.

MICELLAR ELECTROKINETIC CHROMATOGRAPHY (MEKC)

Separation takes place in an electrolytic solution that contains a surfactant, generally ionic, at a concentration above the critical micellar concentration. The solute molecules are distributed between the aqueous buffer and the pseudo-stationary phase composed by the micelles according to the solute's partition coefficient. The technique can be considered as a hy-

brid of electrophoresis and chromatography. It is an electrophoretic technique that can be used for the separation of both neutral and charged solutes maintaining the efficiency, speed, and instrumental suitability of capillary electrophoresis. One of the most widely used surfactants is sodium dodecyl sulfate, although other anionic and cationic surfactants, such as cetyl trimethyl ammonium salts, have also been used.

At neutral and alkaline pH, a strong electroosmotic flow is generated and moves the separation buffer ions in the direction of the cathode. If sodium dodecyl sulfate is used as surfactant, the electrophoretic migration of the anionic micelle is in the opposite direction, toward the anode. As a result, the overall micelle migration velocity is slowed compared to the bulk flow of the electrolytic solution. In the case of neutral solutes, because the analyte can partition between the micelle and the aqueous buffer and has no electrophoretic mobility, the analyte migration velocity will only depend on the partition coefficient between the micelle and the aqueous buffer. In the electropho-retogram, the peak corresponding to each uncharged solute is always between that of the electroosmotic flow marker and that of the micelle; and the time elapsed between these two peaks is called the separation window. For electrically charged solutes, the migration velocity depends on both the partition coefficient of the solute between the micelle and the aqueous buffer and on the electrophoretic mobility of the solute in the absence of micelles.

The separation mechanism is essentially chromatographic, and migration of the solute and resolution can be expressed in terms of the capacity factor of the solute *(K′),* which is the ratio between the total number of moles of solute in the micelle to those in the mobile phase. For a neutral compound, K' is as follows:

$$K' = \frac{t_r - t_0}{t_0(1 - t_r/t_m)} = K\left(\frac{V_S}{V_M}\right)$$

in which t_r is the migration time of the solute; t_0 is the analysis time of the unretained solute obtained by injecting an electroosmotic flow marker that does not enter the micelle (i.e., methanol); t_m is the micelle migration time measured by injecting a micelle marker, such as Sudan III, which migrates continuously associated in the micelle; K is the partition coefficient of the solute; V_S is the volume of the micelles phase; and V_M is the volume of the mobile phase.

The resolution between two closely-migrating compounds *(R_S)* is as follows:

$$R_S = \frac{\sqrt{N}}{4} \times \frac{\alpha - 1}{\alpha} \times \frac{k_b}{k_b + 1} \times \frac{1 - \left(\frac{t_0}{t_m}\right)}{1 + k_a \times \left(\frac{t_0}{t_m}\right)}$$

in which N is the number of theoretical plates for one of the compounds; α is the selectivity obtained; k_a and k_b are retention factors for both components, respectively *($k_b > k_a$);* and the other terms are as defined above.

Similar, but not identical, equations give k and R_S values for electrically charged compounds.

Optimization Parameters

The main parameters to be considered in the development of separations by MEKC are instrumental and electrolytic solution parameters.

Instrumental Parameters—

Voltage—Separation time is inversely proportional to applied voltage. An increase in voltage can cause excessive heat production that gives rise to temperature gradients and viscosity gradients of the buffer in the cross section of the capillary. This effect can be significant with high conductivity buffers, such as those containing micelles. Poor heat dissipation causes band broadening and decreases resolution.

In-Process Revision

Temperature—Variations in capillary temperature affect the partition coefficient of the solute between the buffer and the micelle, the critical micelle concentration, and the viscosity of the buffer. These parameters contribute to the migration time of the solutes.

Capillary—Length and internal diameter contribute to analysis time and efficiency of separations. Increasing both effective length and total length can decrease the electrical fields, working at constant voltage, and will increase migration time and improve the separation efficiency. The internal diameter controls heat dissipation, at a given buffer and electrical field, and provides a broadening of the sample band.

Electrolytic Solution Parameters—

Surfactant Type and Concentration—The type of surfactant, as the stationary phase in chromatography, affects the resolution because it modifies separation selectively. The log K' of a neutral compound increases linearly with the concentration of detergent in the mobile phase. When K' approaches the value of

$$\sqrt{t_m / t_a}$$

resolution in MEKC reaches a maximum. Modifying the concentration of surfactant in the mobile phase changes the resolution.

Buffer pH—pH does not modify the partition coefficient of non-ionized solutes, but it can modify the electroosmotic flow in uncoated capillaries. A decrease in the buffer pH decreases the electroosmotic flow and, therefore, increases the resolution of the neutral solutes, giving rise to longer analysis time.

Organic Solvents—To improve separation of hydrophobic compounds, organic modifiers (methanol, propanol, acetonitrile, etc.) can be added to the separation electrolytic solution. The addition of these modifiers generally decreases migration time and selectivity of the separation. The addition of organic modifiers affects micelle formation, thus, a given surfactant concentration can be used only with a certain percentage of organic modifier before the micellezation equilibrium is eliminated or adversely affected, resulting in the absence of micelles and, therefore, the absence of the partition mechanism of MEKC. The elimination of micelles in the presence of a high content of organic solvent does not always mean that the separation will no longer be possible, because, in some cases, the hydrophobic interaction between the ionic surfactant monomer and the neutral solutes form solvophobic complexes that can be separated electrophoretically.

Additives for Chiral Separations—A chiral selector is included in the micellar system, either covalently bound to the surfactant or added to the micellar separation electrolyte. Micelles that have a moiety with chiral discrimination properties include salts, *N*-dodecanoyl-L-amino acids, bile salts, etc. Chiral resolution can also be achieved using chiral discriminators, such as cyclodextrins, added to the electrolytic solutions that contain micelliced achiral surfactants.

Other Additives—Selectivity can be modified by adding chemicals to the buffer. Addition of several types of cyclodextrins to the buffer is also used to reduce the interaction of hydrophobic solutes with the micelle, increasing the selectivity for this type of compound. The addition of substances able to modify solute-micelle interactions by adsorption on the latter has been used to improve the selectivity of the separations in MEKC. These additives may consist of a second surfactant (ionic or non-ionic), which gives rise to mixed micelles, metallic cations that dissolve in the micelle and give co-ordination complexes with the solutes.

Quantitative Analysis

Peak areas must be divided by the corresponding migration time to give the corrected area in order to compensate for the shift in migration time from run to run, thus reducing the variation of the response. Dividing the peak areas by migration time will also compensate for the different responses of sam-

ple constituents with different migration times. Where an internal standard is used, check that no peak of the substance to be examined is masked by that of the internal standard.

Calculations—From the values obtained, calculate the content of a component or components being determined. When indicated, the percentage of one (or more) components of the sample to be examined is calculated by determining the areas of the peak(s) as a percentage of the total corrected areas of all the peaks, excluding those due to solvents or any added reagents. The use of an automatic integration system (integrator or data acquisition and processing system) is recommended.

CAPILLARY ELECTROPHORESIS SYSTEM SUITABILITY

The choice of suitability parameters to be used will depend on the type of capillary electrophoresis that is performed. These parameters are the capacity factor *(K′)* used only for *Micellar Electrokinetic Chromatography,* the number of theoretical plates *(n),* the symmetry factor *(A_S),* and the resolution *(R_S)*. Note that in previous sections, the theoretical expressions for n and R_s have been described, but more practical equations that allow for the determination of these suitability parameters using the electrophoretograms are described below.

The number of theoretical plates *(n)* may be calculated from the formula:

$$n = 5.54\ (t/b_{0.5})^2$$

in which t is the distance, in mm, along the baseline between the point of injection and the perpendicular dropped from the maximum of the peak in question; and $b_{0.5}$ is the peak width, in mm, at half-height.

The resolution *(R_S)* may be calculated from the formula:

$$R_S = 1.18(t_b - t_a/b_{0.5b}\ \ b_{0.5a})$$

in which t_b and t_a are the distances, in mm, along the baseline between the point of injection and the perpendicular dropped from the maxima of two adjacent peaks *($t_b > t_a$);* and $b_{0.5b}$ and $b_{0.5a}$ are the peak widths, in mm, at half-height.

The resolution *(R_S)* may also be calculated by measuring the height of the valley *(c)* between two partly resolved peaks in a standard preparation, the height of the smaller peak *(d),* and by specifying *$(c/d) \leq x$,* in which x is the limit indicated in the individual monograph.

The symmetry factor of a peak *(A_S)* may be calculated using the formula:

$$A_S = b_{0.05}/2A$$

in which $b_{0.05}$ is the width of the peak at one-twentieth of the peak height; and A is the distance between the perpendicular dropped from the peak maximum and the leading edge of the peak at one-twentieth of the peak height.

Other system suitability parameters include tests for area repeatability (i.e., standard deviation of areas or of area/migration time) and tests for migration time repeatability (i.e., standard deviation of migration time). For migration time repeatability, it will be necessary to provide for a test to measure the suitability of the capillary washing procedures. To avoid the lack of repeatability of the migration time, an alternative practice is to use a migration time relative to an internal standard.

A test for the verification of the signal-to-noise ratio for a standard preparation or the determination of the limit of quantitation is a useful system suitability parameter. The detection limit and quantitation limit correspond to a signal-to-noise ratio greater than 3 and 10, respectively. The signal-to-noise ratio *(S/N)* is calculated as follows:

$$S/N = 2H/h_n$$

in which H is the height of the peak corresponding to the component concerned in the electrophoretogram obtained with the specified reference solution; and h_n is the absolute value of the

largest noise fluctuation from the baseline in an electrophoretogram obtained after injection of a blank and observed over a distance equal to twenty times the width at the half-height of the peak in the electrophoretogram obtained with the reference solution, and situated equally around the place where this peak would be found.■1S *(USP30)*

BRIEFING

⟨1054⟩ Biotechnology-Derived Articles—Isoelectric Focusing—See briefing under *Biotechnology-Derived Articles—Tests* ⟨1047⟩.

(BB PP: I. DeVeau) RTS—43939-3

Add the following:

■⟨1054⟩ BIOTECHNOLOGY-DERIVED ARTICLES—ISOELECTRIC FOCUSING

This chapter provides guidance and procedures used for the characterization of biotechnology-derived articles by isoelectric focusing. This chapter is harmonized with the corresponding chapters in *JP* and *EP*. Other characterization tests, also harmonized, are shown in the USP general information chapters *Biotechnology-Derived Articles—Amino Acid Analysis* ⟨1052⟩, *Biotechnology-Derived Articles—Capillary Electrophoresis* ⟨1053⟩, *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩, *Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis* ⟨1056⟩, and *Biotechnology-Derived Articles—Total Protein Assay* ⟨1057⟩.

INTRODUCTION

Isoelectric focusing (IEF) is a method of electrophoresis that separates proteins according to their isoelectric points. Separation is carried out in a slab of polyacrylamide or agarose gel that contains a mixture of amphoteric electrolytes (ampholytes). When subjected to an electrical field, the ampholytes migrate in the gel to create a pH gradient. In some cases, gels containing an immobilized pH gradient, prepared by incorporating weak acids and bases to specific regions of the gel network during the preparation of the gel, are used. When the applied proteins reach the gel fraction that has a pH that is the same as their isoelectric point, their charge is neutralized and migration ceases. Gradients can be made over various ranges of pH, according to the mixture of ampholytes chosen.

GENERAL PRINCIPLES

When a protein is at the position of its isoelectric point, it has no net charge and cannot be moved in a gel matrix by the electric field. It may, however, move from that position by diffusion. The pH gradient forces a protein to remain in its isoelectric point position, thus concentrating it; this concentration effect is called "focusing". Increasing the applied voltage or reducing the sample load results in improved resolution of bands. The applied voltage is limited by the heat generated because the heat must be dissipated. The use of thin gels and an efficient cooling plate controlled by a thermostatic circulator prevents the burning of the gel while allowing sharp focusing. The separation is estimated by determining the minimum pI difference, which is necessary to separate two neighboring bands, as follows:

$$\Delta pI = 3\sqrt{\frac{D(dpH/dx)}{E(-d\mu/dpH)}}$$

in which D is the diffusion coefficient of the protein; dpH/dx is the pH gradient; E is the intensity of the electric field, in volts per centimeter; and $-d\mu/dpH$ is the variation of the solute mobility with the pH in the region close to the pI. Because D and $-d\mu/dpH$ for a given protein cannot be altered, the separation can be improved by using a narrower pH range and by increasing the intensity of the electric field.

In-Process Revision

From an operational point, special attention must be paid to sample characteristics and/or preparation. Salt in a sample can be problematic, and it is best to prepare the sample, if possible, in deionized water or 2% ampholytes using dialysis or gel filtration if necessary. Potentials of 2500 volts have been used and are considered optimal under a given set of conditions. Up to 30 watts of constant power can be applied and will generally give complete separation in 1.5 to 3.0 hours. The time required for completion of focusing in thin-layer polyacrylamide gels is determined by placing a colored protein (e.g., hemoglobin) at different positions on the gel surface and by applying the electric field: the steady state is reached when all applications give an identical band pattern. In some procedures the completion of the focusing is indicated by the time elapsed after the sample application.

Resolution between protein bands on an IEF gel prepared with carrier ampholytes can be quite good. Better resolution may be achieved by using immobilized pH gradients where the buffering species, which are analogous to carrier ampholytes, are copolymerized within the gel matrix. Proteins exhibiting pI values differing by as little as 0.02 pH units may be resolved using a gel prepared with carrier ampholytes, whereas immobilized pH gradients can resolve protein differing by approximately 0.001 pH units.

The IEF gel can be used as an identity test when migration on the gel is compared to a standard preparation and IEF calibration proteins; the IEF gel can be used as a limit test when the density of a band on IEF is compared subjectively with the density of bands appearing in a standard preparation, or it can be used as a semiquantitative test when the density is measured using a densitometer or similar instrumentation to determine the relative concentration of protein in the bands.

APPARATUS

An apparatus for isoelectric focusing consists of a controllable direct current generator, of stabilized output; a rigid plastic isoelectric focusing chamber that contains a cooled plate of suitable material to support the gel; and a plastic cover with platinum electrodes that are connected to the gel by means of paper wicks of suitable width, length, and thickness, impregnated with solutions of anodic and cathodic electrolytes.

PROCEDURE

Unless otherwise indicated in a given monograph, the following procedure in thick polyacrylamide slab gels is to be used.

Preparation of the Gels

Assembly—Composed of a glass plate (A) on which a polyester film (B) is placed to facilitate handling of the gel, one or more spacers (C), a second glass plate (D), and clamps to hold the structure together (see *Figure 1*).

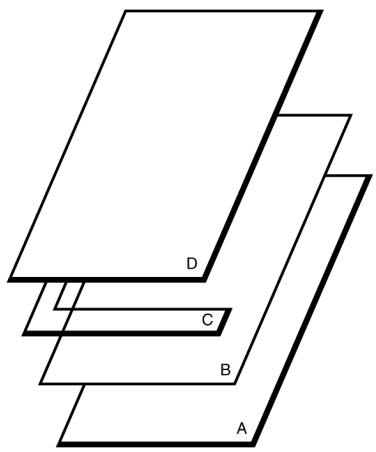

Figure 1. Mould

7.5% Polyacrylamide Gel—Dissolve 29.1 g of acrylamide and 0.9 g of methylenebisacrylamide in 100 mL of water. To 2.5 volumes of this solution, add the mixture of ampholytes specified in the individual monograph, and dilute up to 10 volumes with water. Mix carefully, and degas the solution.

Preparation of the Assembly—Place the polyester film on the lower glass plate, apply the spacer, place the second glass plate, and fit the clamps. Before use, place the mixture on a

magnetic stirrer, and add 0.25 volumes of a 10% solution of ammonium persulfate and 0.25 volumes of tetramethylenediamine. Immediately fill the space between the glass plates of the assembly with the gel.

Fixing Solution for Isoelectric Focusing Polyacrylamide Gel—Mix 35 g of sulfosalicylic acid and 100 g of trichloroacetic acid in 1000 mL of water.

Coomassie Staining Solution and *Destaining Solution*—Use the same solutions indicated in general information chapter *Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis* ⟨1056⟩.

Procedure—Dismantle the assembly, and using the polyester film, transfer the gel onto the cooled support wetted with a few mL of a suitable liquid, taking care to avoid forming air bubbles. Prepare the test solutions and reference solutions as specified in the individual monograph. Place strips of paper for sample application, about 10 mm × 5 mm in size, on the gel, and impregnate each with the prescribed amount of the test and reference solutions. If the protein concentration of the solution is too low, several strips may be superimposed (up to four). Also apply the prescribed quantity of a solution of proteins with known isoelectric points as pH markers to calibrate the gel. In some procedures, the gel has precast slots where a solution of the sample is applied instead of using impregnated paper strips. Cut two strips of paper to the length of the gel, and impregnate them with the electrolyte solutions: acid for the anode and alkaline for the cathode. The compositions of the anode and cathode solutions are given in the individual monograph. Apply these paper wicks to each side of the gel several mm from the edge. Fit the cover so that the electrodes are in contact with the wicks (with respect to the anodic and cathodic poles). Proceed with the isoelectric focusing by applying the electrical parameters described in the individual monograph. Switch off the current when the migration of the mixture of standard proteins has stabilized. Using forceps, remove the sample application strips and the two electrode wicks. Immerse the gel in *Fixing Solution for Isoelectric Focusing Polyacrylamide Gel.* Incubate with gentle shaking at room temperature for 30 minutes. Drain off the solution, and add 200 mL of *Destaining Solution.* Incubate with shaking for 1 hour. Drain the gel, and add *Coomassie Staining Solution.* Incubate for 30 minutes. Destain the gel by passive diffusion with *Destaining Solution* until the bands are well visualized against a clear background. Locate the position and intensity of the bands in the electropherogram, as prescribed in the individual monograph.

Alternative Procedure—When a monograph references the general method for isoelectric focusing above, variations in methodology or procedure may be used, subject to validation. These variations include the use of commercially available precast gels; the use of immobilized pH gradients; the use of rod gels, and the use of cassettes of different dimensions, including ultrathin (0.2 mm) gels; variations in the sample application procedure, including different sample volumes or the use of sample application masks or wicks other than paper; the use of alternate running conditions, including variations in the electric field depending on gel dimensions and equipment, and the use of fixed migration times rather than subjective interpretation of band stability; the inclusion of a prefocusing step; the use of automated instrumentation; and the use of agarose gels.

Validation of Procedure

Where alternative methods to the general method are employed, they must be validated. The following criteria may be used to validate the separation: formation of a stable pH gradient of desired characteristics, evaluated using colored pH markers of known isoelectric points; comparison with the electropherogram provided with the chemical reference substance for the preparation to be examined; and any other validation criteria as prescribed in the individual monograph.

SPECIFIED VARIATIONS TO THE GENERAL METHOD

Variations to the general method required for the analysis of specific substances may be specified in detail in individual monographs. Variations may include the addition of urea in the running gel (a 3 M concentration is often satisfactory to keep the protein in solution, but up to 8 M can be used). Some proteins precipitate at their isoelectric point. In this case, urea is included in the gel formulation to keep the protein in solution. If urea is used, only fresh solutions should be used to prevent carbamylation of the protein. Other variations include the use of alternative staining methods and the use of gel additives such as nonionic detergents (e.g., octylglucoside) or zwitterionic detergents (e.g., CHAPS or CHAPSO) to prevent proteins from aggregating or precipitating.

NOTE—The following are general precautionary items that can be used to improve the method.

- Samples can be applied to any area on the gel, but in general, they should be applied to areas where they are expected to focus. To protect the proteins from extreme pH environments, samples should not be applied close to either electrode. During method development, the analyst can try applying the protein in three positions on the gel (i.e., middle and both ends); the pattern of a protein applied at opposite ends of the gel may not be identical.
- A phenomenon known as cathodic drift, where the pH gradient decays over time, may occur if a gel is focused too long. Although not well understood, electroendoosmosis and absorption of carbon dioxide may be factors that lead to cathodic drift. Cathodic drift is observed as focused protein migrating off the cathode end of the gel. Immobilized pH gradients may be used to address this problem.
- Efficient cooling (approximately 4°) of the bed that the gel lies on during focusing is important. High field strengths used during isoelectric focusing can lead to overheating and affect the quality of the focused gel.■1S (*USP30*)

BRIEFING

⟨1055⟩ Biotechnology-Derived Articles—Peptide Mapping— See briefing under *Biotechnology-Derived Articles—Tests* ⟨1047⟩.

(BB PP: I. DeVeau) RTS—43939-4

Add the following:

■⟨1055⟩ BIOTECHNOLOGY-DERIVED ARTICLES—PEPTIDE MAPPING

This chapter provides guidance and procedures used for characterization of biotechnology-derived articles by peptide mapping. This chapter is harmonized with the corresponding chapter in *JP* and *EP*. Other characterization tests, also harmonized, are shown in *Biotechnology-Derived Articles—Amino Acid Analysis* ⟨1052⟩, *Biotechnology-Derived Articles—Capillary Electrophoresis* ⟨1053⟩, *Biotechnology-Derived Articles—Isoelectric Focusing* ⟨1054⟩, *Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis* ⟨1056⟩, and *Biotechnology-Derived Articles—Total Protein Assay* ⟨1057⟩.

INTRODUCTION

Purpose and Scope

Peptide mapping is an identity test for proteins, especially those obtained by rDNA technology. It involves the chemical or enzymatic treatment of a protein, resulting in the formation of peptide fragments, followed by separation and identification of the resultant fragments in a reproducible manner. It is a powerful test that is capable of identifying single amino acid changes resulting from events such as errors in the reading of complementary DNA (cDNA) sequences or point mutations. Peptide mapping is a comparative procedure because the information obtained, compared to a reference standard or reference material similarly treated, confirms the primary structure of the protein, is capable of detecting whether alterations in

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structure have occurred, and demonstrates process consistency and genetic stability. Each protein presents unique characteristics that must be well understood so that the scientific and analytical approaches permit validated development of a peptide map that provides sufficient specificity.

This section provides detailed assistance in the application of peptide mapping and its validation to characterize the desired protein product, to evaluate the stability of the expression construct of cells used for recombinant DNA products, to evaluate the consistency of the overall process, and to assess product stability, as well as to ensure the identity of the protein product or to detect the presence of protein variant. The validation scheme presented differentiates between qualification of the method at an early stage in the regulatory process, the Investigational New Drug (IND) level, and full validation in support of New Drug Application (NDA), Product License Application (PLA), or Marketing Authorization Application (MAA). The validation concepts described are consistent with the general information chapter *Validation of Compendial Procedures* ⟨1225⟩ and with the International Conference on Harmonization (ICH) document on *Analytical Methods Validation*.

The Peptide Map

Peptide mapping is not a general method, but involves developing specific maps for each unique protein. Although the technology is evolving rapidly, there are certain methods that are generally accepted. Variations of these methods will be indicated, when appropriate, in specific monographs.

A peptide map may be viewed as a fingerprint of a protein and is the end product of several chemical processes that provide a comprehensive understanding of the protein being analyzed. Four major steps are necessary for the development of the procedure: isolation and purification of the protein, if the protein is part of a formulation; selective cleavage of the peptide bonds; chromatographic separation of the peptides; and analysis and identification of the peptides. A test sample is digested and assayed in parallel with a reference standard or reference material. Complete cleavage is more likely to occur when enzymes such as endoproteases (e.g., trypsin) are used instead of chemical cleavage reagents. A map should contain enough peptides to be meaningful. On the other hand, if there are too many fragments, the map might lose its specificity because many proteins will then have the same profiles.

ISOLATION AND PURIFICATION

Isolation and purification are necessary for analysis of bulk drugs or dosage forms containing interfering excipients and carrier proteins and, when required, will be specified in the monograph. Quantitative recovery of protein from the dosage form should be validated.

SELECTIVE CLEAVAGE OF PEPTIDE BONDS

The selection of the approach used for the cleavage of peptide bonds will depend on the protein under test. This selection process involves determination of the type of cleavage to be employed—enzymatic or chemical—and the type of cleavage agent within the chosen category. Several cleavage agents and their specificity are shown in *Table 1*. This list is not all-inclusive and will be expanded as other cleavage agents are identified.

Table 1. Examples of Cleavage Agents

Type	Agent	Specificity
Enzymatic	Trypsin (EC 3.4.21.4)	*C*-terminal side of Arg and Lys
	Chymrotrypsin (EC 3.4.21.1)	*C*-terminal side of hydrophobic residues (e.g., Leu, Met, Ala, aromatics)
	Pepsin (EC 3.4.23.1)	Nonspecific digest
	Lysyl endopeptidase (Lys-C Endopeptidase) (EC 3.4.21.50)	*C*-terminal side of Lys
	Glutamyl endopeptidase (from *S. aureus* stain V8) (EC 3.4.21.19)	*C*-terminal side of Glu and Asp
	Peptidyl-Asp metaplo-endopeptidase (Endoproteinase Asp-N) (EC 3.4.24.33)	*N*-terminal side of Asp
	(Clostripain) (EC 3.4.28.8)	*C*-terminal side of Arg
Chemical	Cyanogen bromide	*C*-terminal side of Met
	2-Nitro-5-thio-cyano- benzoic acid	*N*-terminal side of Cys
	O-Iodosobenzoic acid	*C*-terminal side of Trp and Tyr
	Dilute acid	Asp and Pro
	BNPS-skatole	Trp

Pretreatment of Sample—Depending on the size or the configuration of the protein, different approaches in the pretreatment of samples can be used. For monoclonal antibodies, the heavy and light chains will need to be separated before mapping. If trypsin is used as a cleavage agent for proteins with a molecular mass greater than 100,000 Da, lysine residues must be protected by citraconylation or maleylation; otherwise, too many peptides will be generated.

Pretreatment of the Cleavage Agent—Pretreatment of cleavage agents—especially enzymatic agents—might be necessary for purification purposes to ensure reproducibility of the map. For example, trypsin used as a cleavage agent will have to be treated with tosyl-L-phenylalanine chloromethyl ketone to inactivate chymotrypsin. Other methods, such as purification of trypsin by HPLC or immobilization of enzyme on a gel support, have been successfully used when only a small amount of protein is available.

Pretreatment of the Protein— It might be necessary under certain conditions to concentrate the sample, or to separate the protein from added substances and stabilizers used in the formulation of the product if these interfere with the mapping procedure. Physical procedures used for pretreatment can include ultrafiltration, column chromatography, and lyophilization.

Other pretreatments such as the addition of chaotropic agents (e.g., urea) can be used to unfold the protein prior to mapping. It is often necessary to reduce and alkylate the disulfide bonds prior to digestion in order to allow the enzyme to have full access to cleavage sites and permit some unfolding of the protein.

Digestion with trypsin can introduce ambiguities in the tryptic map as a result of side reactions occurring during the digestion reaction, such as nonspecific cleavage, deamidation, disulfide isomerization, oxidation of methionine residues, or formation of pyroglutamic groups created from the deamidation of glutamine at the *N*-terminal side of a peptide. Furthermore, peaks may be produced by autohydrolysis of trypsin. Their intensities depend on the ratio of trypsin to protein. To avoid autohydrolysis, solutions of proteases may be prepared at a pH that is not optimal (e.g., at pH 5 for trypsin), which would mean that the enzyme would not become active until diluted with the digest buffer.

Establishment of Optimal Digestion Conditions—Factors that affect the completeness and effectiveness of digestion of proteins are those that could affect any chemical or enzymatic reactions.

pH—The digestion mixture pH is empirically determined to ensure the optimal performance of the given cleavage agent. For example, a highly acidic environment (e.g., pH 2, formic acid) is necessary when using cyanogen bromide as a cleavage agent; however, a slightly alkaline environment (pH 8) is optimal when using trypsin as a cleavage agent. As a general rule, the pH of the reaction milieu should not alter the chemical integrity of the protein during the digestion and should not change during the course of the fragmentation reaction.

Temperature—A temperature between 25° and 37° is adequate for most digestions. The temperature used is intended to minimize chemical side reactions. The type of protein under test will dictate the temperature of the reaction milieu because some proteins are more susceptible to denaturation as the temperature of the reaction increases. For example, digestion of recombinant bovine somatropin is conducted at 4° because at higher temperatures it will precipitate during digestion.

Time—If a sufficient amount of sample is available, a time course study is considered in order to determine the optimum time to obtain a reproducible map and avoid incomplete digestion. Time of digestion varies from 2 to 30 hours. The reaction is stopped by the addition of an acid that does not interfere with the tryptic map, or by freezing.

Amount of Cleavage Agent—Although excessive amounts of cleavage agent are used to accomplish a reasonably rapid digestion time (i.e., 6 to 20 hours), the amount of cleavage agent is minimized to avoid its contribution to the chromatographic map pattern. A protein-to-protease ratio between 20 : 1 and 200 : 1 is generally used. It is recommended that the cleavage agent be added in two or more stages to optimize cleavage. Nonetheless, the final reaction volume remains small enough to facilitate the next step in peptide mapping—the separation step. To sort out digestion artifacts that might be interfering with the subsequent analysis, a blank determination is performed using a digestion control with all the reagents except the test protein.

CHROMATOGRAPHIC SEPARATION

Many techniques are used to separate peptides for mapping. The selection of a technique depends on the protein being mapped. Techniques that have been successfully used for the separation of peptides are shown in *Table 2*.

Table 2. Techniques Used for the Separation of Peptides

Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC)
Ion-Exchange Chromatography (IEC)
Hydrophobic Interaction Chromatography (HIC)
Polyacrylamide Gel Electrophoresis (PAGE), nondenaturating
Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE)
Capillary Electrophoresis (CE)
Paper Chromatography
High-Voltage Paper Electrophoresis (HVPE)

In-Process Revision

In this section, a most widely used reverse-phase HPLC (RP-HPLC) method is described as one of the procedures of chromatographic separation.

The purity of solvents and mobile phases is a critical factor in HPLC separation. HPLC-grade solvents and water that are commercially available are recommended for RP-HPLC. Dissolved gases present a problem in gradient systems where the solubility of the gas in a solvent may be less in a mixture than in a single solvent. Vacuum degassing and agitation by sonication are often used as useful degassing procedures. The solid particles in the solvents are drawn into the HPLC system, they can damage the sealing of pump valves or clog the top of the chromatographic column. Both pre- and post-pump filtration is also recommended.

Chromatographic Column—The selection of a chromatographic column is empirically determined for each protein. Columns with 100 Å or 300 Å pore size and silica support can give optimal separation. For smaller peptides, column packings of octylsilane chemically bonded to totally porous silica articles 3 to 10 µm in diameter (L7) and of octadecylsilane chemically bonded to porous silica or ceramic microparticles 3 to 10 µm in diameter (L1) are more efficient than the butyl silane chemically bonded to totally porous silica particles 5 to 10 µm in diameter (L26).

Solvent—The most commonly used solvent is water with acetonitrile as the organic modifier to which less than 0.1% of trifluoroacetic acid is added. If necessary, add isopropyl alcohol or *n*-propyl alcohol to solubilize the digest components, provided that the addition does not unduly increase the viscosity of the components.

Mobile Phase—Buffered mobile phases containing phosphate are used to provide some flexibility in the selection of pH conditions, since shifts of pH in the 3.0 to 5.0 range enhance the separation of peptides containing acidic residues (e.g., glutamic and aspartic acids). Sodium or potassium phosphates, ammonium acetate, and phosphoric acid, with a pH between 2 and 7 (or higher for polymer-based supports), have also been used with acetonitrile gradients. Acetonitrile-containing trifluoroacetic acid is also used quite often.

Gradient Selection—Gradients can be linear, nonlinear, or include step functions. A shallow gradient is recommended in order to separate complex mixtures. Gradients are optimized to provide clear resolution of one or two peaks that will become "marker" peaks for the test.

Isocratic Selection—Isocratic HPLC systems using a single mobile phase are used on the basis of their convenience of use and improved detector responses. Optimal composition of a mobile phase to obtain clear resolution of each peak is sometimes difficult to establish. Mobile phases for which slight changes in component ratios or in pH significantly affect retention times of peaks in peptide maps should not be used in isocratic HPLC systems.

Other Parameters—Temperature control of the column is usually necessary to achieve good reproducibility. The flow rates for the mobile phases range from 0.1 to 2.0 mL per minute, and the detection of peptides is performed with a UV detector at 200 to 230 nm. Other methods of detection have been used (e.g., postcolumn derivatization), but they are not as robust or as versatile as UV detection.

System Suitability—The section *System Suitability* under *Chromatography* ⟨621⟩ provides an experimental means for measuring the overall performance of the test method. The acceptance criteria for system suitability depend on the identification of critical test parameters that affect data interpretation and acceptance. These critical parameters are also criteria that monitor peptide digestion and peptide analysis. An indicator that the desired digestion endpoint was achieved is the comparison with a reference standard or reference material, which is treated exactly as the article under test. The use of a USP Reference Standard in parallel with the protein under test is critical in the development and establishment of system suitability limits. In addition, a specimen chromatogram should be included with the USP Reference Standard or reference material for comparison purposes. Other indicators may include vi-

sual inspection of protein or peptide solubility, the absence of intact protein, or measurement of responses of a digestion-dependent peptide. The critical system suitability parameters for peptide analysis will depend on the particular mode of peptide separation and detection, and on the data analysis requirements.

When peptide mapping is used as an identification test, the system suitability requirements for the identified peptides cover selectivity and precision. In this case, as well as when identification of variant proteins is done, the identification of the primary structure of the peptide fragments in the peptide map provides both a verification of the known primary structure and the identification of protein variants by comparison with the peptide map of the USP Reference Standard or reference material for the specified protein. The use of a digested USP Reference Standard or reference material for a given protein in the determination of peptide resolution is the method of choice. For an analysis of a variant protein, a characterized mixture of a variant and a reference standard can be used, especially if the variant peptide is located in a less-resolved region of the map. The index of pattern consistency can be simply the number of major peptides detected. Peptide pattern consistency can be best defined by the resolution of peptide peaks. Chromatographic parameters—such as peak-to-peak resolution, maximum peak width, peak tailing factors, and column efficiency—may be used to define peptide resolution. Depending on the protein under test and the method of separation used, single peptide or multiple peptide resolution requirements may be necessary.

The replicate analysis of the digest of the USP Reference Standard or reference material for the protein under test yields measures of precision and quantitative recovery. Recovery of the identified peptides is generally ascertained by the use of internal or external peptide standards. The precision is expressed as the relative standard deviation (RSD). Differences in the recovery and precision of the identified peptides are expected; therefore, the system suitability limits will have to be established for both the recovery and the precision of the identified peptides. These limits are unique for a given protein and will be specified in the individual monograph.

Visual comparison of the relative retention times, the peak responses, the number of peaks, and the overall elution pattern is completed initially. It is then complemented and supported by mathematical analysis of the peak response ratios and by the chromatographic profile of a 1 : 1 (v/v) mixture of sample and USP Reference Standard or reference material digest. If all peaks in the sample digest and in the USP Reference Standard or reference material digest have the same relative retention times and peak response ratios, then the identity of the sample under test is confirmed.

If peaks that initially eluted with significantly different relative retention times are then observed as single peaks in the 1 : 1 mixture, the initial difference would be an indication of system variability. However, if separate peaks are observed in the 1 : 1 mixture, this would be evidence of the nonequivalence of the peptides in each peak. If a peak in the 1 : 1 mixture is significantly broader than the corresponding peak in the sample and USP Reference Standard or reference material digest, it may indicate the presence of different peptides. The use of computer-aided pattern recognition software for the analysis of peptide mapping data has been proposed and applied, but issues related to the validation of the computer software preclude its use in a compendial test in the near future. Other automated approaches have been used that employ mathematical formulas, models, and pattern recognition. Such approaches, for example, the automated identification of compounds by IR spectroscopy and the application of diode-array UV spectral analysis for identification of peptides, have been proposed. These methods have limitations due to inadequate resolutions, co-elution of fragments, or absolute peak response differences between USP Reference Standard or reference material and sample fragments.

The numerical comparison of the retention times and peak areas or peak heights can be done for a selected group of relevant peaks that have been correctly identified in the peptide

maps. Peak areas can be calculated using one peak showing relatively small variation as an internal reference, keeping in mind that peak area integration is sensitive to baseline variation and likely to introduce error in the analysis. Alternatively, the percentage of each peptide peak height relative to the sum of all peak heights can be calculated for the sample under test. The percentage is then compared to that of the corresponding peak of the USP Reference Standard or reference material. The possibility of autohydrolysis of trypsin is monitored by producing a blank peptide map that is the peptide map obtained when a blank solution is treated with trypsin.

The minimum requirement for the qualification of peptide mapping is an approved test procedure that includes system suitability as a test control. In general, for an IND, qualification of peptide mapping for a protein is sufficient. As the regulatory approval process for the protein progresses, additional qualifications of the test can include a partial validation of the analytical procedure to provide assurance that the method will perform as intended in the development of a peptide map for the specified protein.

ANALYSIS AND IDENTIFICATION OF PEPTIDES

This section gives guidance on the use of peptide mapping during development in support of regulatory applications.

The use of a peptide map as a qualitative tool does not require the complete characterization of the individual peptide peaks. However, validation of peptide mapping in support of regulatory applications requires rigorous characterization of each of the individual peaks in the peptide map. Methods to characterize peaks range from *N*-terminal sequencing of each peak followed by amino acid analysis to the use of mass spectroscopy (MS).

For characterization purposes, when *N*-terminal sequencing and amino acids analysis are used, the analytical separation is scaled up. Because scale-up might affect the resolution of peptide peaks, it is necessary, using empirical data, to assure that there is no loss of resolution due to scale-up. Eluates corresponding to specific peptide peaks are collected, vacuum-concentrated, and chromatographed again, if necessary. Amino acid analysis of fragments may be limited by the peptide size. If the *N*-terminus is blocked, it may need to be cleared before sequencing. *C*-terminal sequencing of proteins in combination with carboxypeptidase and MALDITOF-MS can also be used for characterization purposes.

The use of MS for characterization of peptide fragments is by direct infusion of isolated peptides or by the use of on-line LC-MS for structure analysis. In general, it includes electrospray and matrix-assisted laser desorption ionization coupled to time-of-flight analyzer (MALDITOF) as well as fast atom bombardment (FAB). Tandem MS has also been used to sequence a modified protein and to determine the type of amino acid modification that has occurred. The comparison of mass spectra of the digests before and after reduction provides a method to assign the disulfide bonds to the various sulfhydryl-containing peptides.

If regions of the primary structure are not clearly demonstrated by the peptide map, it might be necessary to develop a secondary peptide map. The goal of a validated method of characterization of a protein through peptide mapping is to reconcile and account for at least 95% of the theoretical composition of the protein structure.

The Use of Peptide Mapping for Genetic Stability Evaluation

A validated peptide map can be used to assess the integrity of the predicted primary sequence of a protein product (i.e., its genetic stability). It can also be used to determine lot-to-lot consistency of the biotechnology-derived product process. Furthermore, the performance of the protein expression of the production system is best assessed by peptide mapping of the expressed protein. Peptide maps of protein produced at various times of the protein expression process, including a point well beyond the normal protein expression time, compared with those of a USP Reference Standard or reference material, will evaluate the genetic stability of the expression system as a function of time.

Variant protein sequences can arise from a genetic variation at the DNA level (point mutation) or as an error in the translation process. A validated peptide map is the best approach to the detection of protein variants. However, the limitations of the peptide mapping itself must be taken into consideration. The detection of a structured variant is possible only if the corresponding peptide variant is easily isolated and characterized. To establish genetic stability will require the use of a battery of biochemical methods, provided that the variants have properties different from those of the ''normal'' protein.

Validation

CRITICAL FACTORS

Validation of peptide mapping requires that a protocol be designed, outlining in detail the experiment to be conducted and the criteria for acceptance of the map. Criteria for acceptance of mapping include detection limit, specificity, linearity, range, accuracy, precision, and reagent stability. Reproducibility of the peptide map is a critical element in the utilization of such a map as an identity test and for confirming genetic stability. Those technical aspects of peptide mapping that influence the reproducibility of the map will be discussed.

The setting of limits, with respect to quantification (peak area or height) and identification (retention times) for the selected group of relevant peaks is based on empirical observations. These limits detect significant differences between the sample and USP Reference Standard or reference material within a series of analyses.

Another critical issue is the recovery of peptides and its impact on peak area determination and reproducibility and on the establishment of acceptance criteria. The recovery criteria address all aspects of test methodology, from digestion to chromatographic conditions. Determination of peptide recovery includes quantitative amino acid analysis, spike addition, radiolabeling, and UV summation. An overall recovery of about 80% is considered satisfactory. Recovery of individual peptides is more problematic and is handled on a case-by-case basis. The critical factors considered in the validation of a peptide map are as follows.

Written Test Procedures—These procedures include a detailed description of the analytical method in which reagents, equipment, sample preparation, method of analysis, and analysis of the data are defined.

Validation Protocol—A protocol is prepared that contains a procedure for test validation.

Acceptance Criteria—The criteria can be minimal at the early stages, but need to be better defined as validation studies progress.

Reporting of Results—Results from the validation study are documented with respect to the analytical parameters listed in the validation protocol.

Revalidation of the Test Procedure—If the method used requires alteration that could affect the analytical parameter previously assessed in the validation of the procedure, the test procedure must be revalidated. Significant changes in the processing of the article, in laboratories performing the analysis, in formulation of the bulk or the finished products, and in any other significant parameter will require revalidation of the methods.

REQUIREMENTS

Precision—

Intratest Precision—This is a measure of the reproducibility of peptide mapping. The two critical steps in peptide mapping are fragmentation (i.e., digestion) and separation of peptides. An acceptable precision occurs where the absolute retention times and the relative peak areas are constant from run to run, and the average variation in retention time is small relative to that of a selected internal reference peak. The reproducibility of the map can be enhanced if a temperature-controlled column oven is used, if an extensive equilibration of the system is performed prior to the start of the test, if a blank (control digest mixture without protein) is run first to minimize ''first

run effects," and if a USP Reference Standard or a reference material digest is interspersed periodically with test samples to evaluate chromatographic drift.

The criteria for validation of the fragmentation step are similar to those described below for separation of peptides, but they are met for consecutive tests of a series of separately prepared digests of the protein under test.

The criteria for validation of the separation of peptides step include the following:

1. The average standard deviation of the absolute retention times of all major peaks for a set of consecutive tests of the same digest does not exceed a specified acceptance criterion.

2. The average standard deviation of absolute peak area for all fully resolved major peaks does not exceed a specified percentage.

Intertest Precision—This is a measure of the reproducibility of the peptide mapping when the test is performed on different days, by different analysts, in different laboratories, with reagents or enzymes from different suppliers or different lots from the same supplier, with different instruments, on columns of different makes or columns of the same make from different lots, and on individual columns of the same make from the same lot. Although it would be desirable, from a scientific perspective, to validate all of these variables in terms of their impacts on precision, a practical approach is to validate the test using those variables most likely to be encountered under operational conditions. Additional variables can be included when needed.

The experimental design allows the analyst to make comparisons using peak retention times and areas that are expressed relative to a highly reproducible internal reference peak within the same chromatogram. The relative peak area is expressed as the ratio of the peak area to that of the internal reference peak. The relative retention time can be expressed as the difference between the absolute retention time and that of the reference peak. The use of relative values eliminates the need to make separate corrections for differences due to injector-to-injector volumes, units of measure for peak areas, column dimensions, and instrument dead volumes. The variability in the retention times and peak areas for the *Intertest Precision* experiments is expected to be slightly higher than the variability observed for *Intratest Precision*.

Robustness—Factors such as composition of the *Mobile Phase*, protease quality or chemical reagent purity, column variation and age, and digest stability are likely to affect the overall performance of the test and its reproducibility. Tolerances for each of the key parameters are evaluated and baseline limits established in case the test is used for routine lot release purposes.

Mobile Phase—The composition of the *Mobile Phase* is optimized to obtain the maximum resolution of peptides throughout the elution profile. A balance between optimal resolution and overall reproducibility is desired. A lower pH might improve peak separation but might shorten the life of the column, resulting in lack of reproducibility. Peptide maps at a pH above and below the pH of the procedure are compared to the peptide map obtained at the pH of the procedure and checked for significant differences; they are also reviewed with respect to the acceptance criteria established in the validation protocol.

Protease Quality or Chemical Reagent Purity—A sample of the USP Reference Standard or reference material for the protein under test is prepared and digested with different lots of cleavage agent. The chromatograms for each digest are compared in terms of peak areas, shape, and number. The same procedure can be applied to other critical chemicals or pretreatment procedures used during sample preparation, such as reducing and carboxymethylation reagents.

Column Considerations—Column-to-column variability, even within a single lot, can affect the performance of the column in the development of peptide maps. Column size may also lead to significant differences. A USP Reference Standard or reference material of the protein under test is digested and the digest is chromatographed on different lots of column from

a single manufacturer. The maps are then evaluated in terms of the overall elution profile, retention times, selectivity resolution, and recovery. To evaluate the overall lifetime of the column in terms of robustness, perform a peptide mapping test on different columns and vary significantly the number of injections (e.g., from 10 injections to 250 injections). The resulting maps can then be compared for significant differences in peak broadening, peak area, and overall resolution. As a column ages, an increase in back pressure might be observed that might affect the peptide maps.

A sensible precaution in the use of peptide mapping columns is to select alternative columns in case the original columns become unavailable or are discontinued. Perform a peptide mapping test using equivalent columns from different manufacturers, and examine the maps. Differences in particle shape and size, pore size and volume, carbon load, and endcapping can lead to significant differences in retention times, elution profile selectivity, resolution, and recovery. Slight modifications in the gradient profile may be required to achieve equivalency of mapping when using columns from different manufacturers. [NOTE—The equivalency between instrumentation used for the validation of the test and for routine quality control testing should be considered. It might be preferable to use the same HPLC system for all applications. Otherwise, equivalency of the systems is determined, which may require some changes in the chromatographic test conditions.]

Digest Stability—The length of time a digest can be kept before it is chromatographed, as well as the conditions under which the digest is stored before chromatography, is assessed. Several aliquots from a single digest are stored at different storage conditions and chromatographed. These maps are then evaluated for significant differences.

Reproducibility—Determination of various parameters indicated above is repeated using the same USP Reference Standard or reference material and test sample in at least two different laboratories by two analysts equipped with similar HPLC systems. The generated peptide maps are evaluated for significant differences.■1S (*USP30*)

BRIEFING

⟨1056⟩ Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis—See briefing under *Biotechnology-Derived Articles—Tests* ⟨1047⟩.

(BB PP: I. DeVeau) RTS—43939-5

Add the following:

■⟨1056⟩ BIOTECHNOLOGY-DERIVED ARTICLES—POLYACRYLAMIDE GEL ELECTROPHORESIS

This chapter provides guidance and procedures used for characterization of biotechnology-derived articles by polyacrylamide gel electrophoresis. This chapter is harmonized with the corresponding chapter in *JP* and *EP*. Other characterization tests, also harmonized, are shown in *Biotechnology-Derived Articles—Amino Acid Analysis* ⟨1052⟩, *Biotechnology-Derived Articles—Capillary Electrophoresis* ⟨1053⟩, *Biotechnology-Derived Articles—Isoelectric Focusing* ⟨1054⟩, *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩, and *Biotechnology-Derived Articles—Total Protein Assay* ⟨1057⟩.

INTRODUCTION

Polyacrylamide gel electrophoresis (PAGE) is used for the qualitative characterization of proteins in biological preparations, for control of purity, and for quantitative determinations. This procedure is limited to the analysis of proteins with a weight range of 14,000 to 100,000 Da. It is possible to extend the weight range of an electrophoresis gel by various techniques (e.g., gradient gels or particular buffer systems), but

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such techniques are not discussed in this chapter. Analytical gel electrophoresis is an appropriate method with which to identify and to assess the homogeneity of proteins in drug substances. These methods are routinely used for the estimation of protein subunit molecular weights and for the determination of the subunit compositions of purified proteins.

Ready-to-use gels and reagents are commercially available and can be used instead of those described in this chapter, provided that they give equivalent results and that they meet the validation requirements.

GENERAL PRINCIPLE OF ELECTROPHORESIS

Under the influence of an electrical field, charged particles migrate in the direction of the electrode bearing the opposite polarity. In gel electrophoresis, the movements of the particles are retarded by interactions with the surrounding gel matrix, which acts as a molecular sieve. The opposing interactions of the electrical force and molecular sieving result in differential migration rates according to the sizes, shapes, and charges of particles. Because of their different physicochemical properties, different macromolecules of a mixture migrate at different speeds during electrophoresis and thus are separated into discrete fractions. Electrophoretic separations can be conducted in systems without support phases (e.g., free solution separation in capillary electrophoresis) and in stabilizing media, such as thin-layer plates, films, or gels.

CHARACTERISTICS OF POLYACRYLAMIDE GELS FOR PROTEIN ELECTROPHORESIS

The sieving properties of polyacrylamide gels are established by the three-dimensional network of fibers and pores that is formed as the bifunctional bisacrylamide cross-links adjacent to polyacrylamide chains. Polymerization is catalyzed by a free-radical-generating system composed of ammonium persulfate and *N,N,N′, N′*-tetramethylethylenediamine (TEMED).

As the acrylamide concentration of a gel increases, its effective pore size decreases. The effective pore size of a gel is operationally defined by its sieving properties, that is, by the resistance it imparts to the migration of macromolecules. There are limits to the acrylamide concentrations that can be used. At high acrylamide concentrations, gels break much more easily and are difficult to handle. As the pore size of a gel decreases, the migration rate of a protein through the gel decreases. By adjusting the pore size of a gel, through manipulating the acrylamide concentration, the resolution of the method can be optimized for a given protein product. Thus, a given gel is physically characterized by its respective composition of acrylamide and bisacrylamide.

In addition to the composition of the gel, the state of the protein is an important component of electrophoretic mobility. In the case of proteins, electrophoretic mobility is dependent on the pK value of the charged groups and the size of the molecule. It is influenced by the type, the concentration, and the pH of the buffer; by the temperature and the field strength; and by the nature of the support material.

Denaturation with Sodium Dodecyl Sulfate

Denaturing PAGE using sodium dodecyl sulfate (SDS) is the most common mode of electrophoresis used in assessing the pharmaceutical quality of protein products. Typically, analytical electrophoresis of proteins is carried out under conditions that ensure dissociation of the proteins into their individual polypeptide subunits and that minimize aggregation of these subunits. The strongly anionic detergent SDS is used in combination with heat to dissociate the proteins before they are loaded on the gel. The denatured polypeptides bind SDS, become negatively charged, and exhibit a consistent charge-to-weight ratio regardless of protein type. Because the amount of SDS bound is almost always proportional to the molecular weight of the polypeptide and is typically independent of its

sequence, SDS–polypeptide complexes migrate through polyacrylamide gels in reasonable accordance with the size of the polypeptide.

The electrophoretic mobilities of the resultant detergent–polypeptide complexes all assume the same functional relationship to the molecular weights of the polypeptides. Migration of SDS derivatives is toward the anode in a predictable manner, with low molecular weight complexes migrating faster than larger ones. This means that the molecular weight of a protein can be estimated from its relative mobility in calibrated SDS PAGE and that a single band in such a gel is a criterion of purity.

Modifications to the polypeptide backbone, such as *N*- or *O*-linked glycosylation, however, have a significant impact on the apparent molecular weight of a protein. This is due to the fact that SDS does not bind to a carbohydrate moiety in a manner similar to that of the polypeptide. Thus, a consistent charge-to-weight ratio is not maintained. The apparent molecular weight of proteins having undergone post-translational modifications is not a true reflection of the weight of the polypeptide chain.

Reducing Conditions

Polypeptide subunits and their three-dimensional structure can be maintained in proteins by the presence of disulfide bonds. A goal of SDS PAGE analysis under reducing conditions is to disrupt this structure by reducing disulfide bonds. Complete denaturation and dissociation of proteins by treatment with 2-mercaptoethanol or dithiothreitol (DTT) will result in the unfolding of the polypeptide backbone and subsequent complexation with SDS. Under these conditions, the molecular weight of the polypeptide subunits can be calculated by linear regression in the presence of suitable molecular weight standards.

Nonreducing Conditions

For some analyses, complete dissociation of protein to peptide subunits is not desirable. In the absence of treatment with reducing agents, disulfide covalent bonds remain intact, preserving the oligomeric form of the protein. Oligomeric SDS–protein complexes migrate more slowly than their SDS–polypeptide subunits. In addition, nonreduced proteins may not be completely saturated with SDS and hence may not bind the detergent in a constant weight ratio. This makes molecular weight determinations of these molecules less straightforward than analyses of fully denatured polypeptides, because, for valid comparisons, it is necessary that both standards and unknown proteins be in similar configurations. However, the staining of a single band in such a gel is a criterion of purity.

Characteristics of a Discontinuous Buffer System

The most popular electrophoretic method for the characterization of a complex mixture of proteins involves the use of a discontinuous buffer system consisting of two contiguous, but distinct, gels: a resolving or separating (lower) gel and a stacking (upper) gel. The two gels are cast with different porosities, pHs, and ionic strengths. In addition, different mobile ions are used in the gel and electrode buffers. The buffer discontinuity concentrates large volumes of sample in the stacking gel, resulting in improved resolution. When power is applied, a voltage drop develops across the sample solution that drives the proteins into the stacking gel. Glycinate ions from the electrode buffer follow the proteins into the stacking gel. A moving boundary region is rapidly formed with the highly mobile chloride ions in the front and the relatively slow glycinate ions in the rear. A localized high-voltage gradient forms between the leading and trailing ion fronts, causing the SDS–protein complexes to form into a thin zone (stack) and migrate between the chloride and glycinate phases. Within a broad limit, regardless of the height of the applied sample, all SDS proteins

condense into a very narrow region and enter the resolving gel as a well-defined, thin zone of high protein density. The large-pore stacking gel does not retard the migration of most proteins and serves mainly as an anticonvective medium. At the interface between the stacking and resolving gels, the proteins experience a sharp retardation due to the restrictive pore size of the resolving gel. Once in the resolving gel, proteins continue to be slowed by the sieving of the matrix. The glycinate ions overtake the proteins, which then move in a space of uniform pH formed by tris(hydroxymethyl)aminomethane (Tris) and glycine. Molecular sieving causes the SDS–polypeptide complexes to separate on the basis of their molecular weights.

Preparation of Gels

In a discontinuous buffer SDS–polyacrylamide gel, it is important to pour the resolving gel, let the gel set, and then pour the stacking gel, because the composition of acrylamide–bisacrylamide, buffer, and pH are different.

Gel Stock Solutions—

30% Acrylamide–Bisacrylamide Solution—Prepare a solution containing 290 g of acrylamide and 10 g of methylene bisacrylamide per L of warm water, and filter. [NOTE—Acrylamide and methylene bisacrylamide are slowly converted during storage to acrylic acid and bisacrylic acid, respectively. This deamidation reaction is catalyzed by light and alkali. The pH of the solution must be 7.0 or lower. Store the solution in dark bottles at room temperature. Fresh solutions are prepared every month.]

Ammonium Persulfate Solution—Prepare a small quantity of solution having a concentration of 100 g of ammonium persulfate per L, and store at 4°. [NOTE—Ammonium persulfate provides the free radicals that drive polymerization of acrylamide and bisacrylamide. Ammonium persulfate decomposes slowly; therefore, prepare fresh solutions weekly.]

TEMED—Use an electrophoresis-grade reagent. [NOTE—*TEMED* accelerates the polymerization of acrylamide and bisacrylamide by catalyzing the formation of free radicals from ammonium persulfate. Because *TEMED* works only as a free base, polymerization is inhibited at low pH.]

SDS Solution—Use an electrophoresis-grade reagent. Prepare a solution having a concentration of about 100 g of SDS per L, and store at room temperature.

1.5 M Buffer Solution—Transfer about 90.8 g of Tris to a 500-mL flask, dissolve in 400 mL of water, adjust with hydrochloric acid to a pH of 8.8, dilute with water to volume, and mix.

1 M Buffer Solution—Transfer about 60.6 g of Tris to a 500-mL flask, add 400 mL of water, adjust with hydrochloric acid to a pH of 6.8, dilute with water to volume, and mix.

Plate Preparation—Clean two glass plates (10 cm × 8 cm), the polytef comb, the two spacers, and the silicone rubber tubing (0.6 mm × 35 cm) with mild detergent, rinse thoroughly with water, and blot dry.

Lubricate the spacers and the tubing with nonsilicone grease. Apply the spacers along each of the two short sides of the glass plate 2 mm away from the edges and 2 mm away from the long side corresponding to the bottom of the gel.

Begin to lay the tubing on the glass plate by using one spacer as a guide. Carefully twist the tubing at the bottom of the spacer, and follow the long side of the glass plate. While holding the tubing with one finger along the long side, twist the tubing again, and lay it on the second short side of the glass plate, using the spacer as a guide.

Place the second glass plate in perfect alignment with the first, and hold the gel mold together by hand pressure. Apply two clamps on each of the two short sides of the mold. Carefully apply four clamps on the longer side of the mold, thus forming the bottom of the mold. Verify that the tubing is running along the edge of the glass plates and has not been extruded while placing the clamps. The mold is now ready for the pouring of the gel.

Resolving Gel—In a conical flask, prepare the appropriate volume of solution, containing the desired concentration of acrylamide, as shown in *Table 1*. Mix the components in the order shown. Before adding the *Ammonium Persulfate Solution* and the *TEMED,* pour the solution into a disposable filtration unit equipped with a nitrocellulose filter having a 0.45-µm porosity, and apply vacuum. Allow the solution to degas by swirling the filtration unit, and disconnect the vacuum when no more bubbles are formed in the solution. Add appropriate amounts of *Ammonium Persulfate Solution* and *TEMED,* as shown in *Table 1;* swirl; and pour immediately into the gap between the two glass plates of the mold. Leave sufficient space for the stacking gel (the length of the teeth of the comb plus 1 cm). Using a pipet, carefully overlay the solution with water-saturated isobutyl alcohol. Leave the gel in a vertical position at room temperature for polymerization.

Table 1. Preparation of Resolving Gel

	Component Volume (mL) per Gel Mold Volume Below							
Solution Component	5 mL	l0 mL	15 mL	20 mL	25 mL	30 mL	40 mL	50 mL
6% Acrylamide								
Water	2.6	5.3	7.9	10.6	13.2	15.9	21.2	26.5
30% Acrylamide–Bisacrylamide Solution	1.0	2.0	3.0	4.0	5.0	6.0	8.0	10.0
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.004	0.008	0.012	0.016	0.02	0.024	0.032	0.04
8% Acrylamide								
Water	2.3	4.6	6.9	9.3	11.5	13.9	18.5	23.2
30% Acrylamide–Bisacrylamide Solution	1.3	2.7	4.0	5.3	6.7	8.0	10.7	13.3
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.003	0.006	0.009	0.012	0.015	0.018	0.024	0.03
10% Acrylamide								
Water	1.9	4.0	5.9	7.9	9.9	11.9	15.9	19.8
30% Acrylamide–Bisacrylamide Solution	1.7	3.3	5.0	6.7	8.3	10.0	13.3	16.7
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02

Table 1. Preparation of Resolving Gel *(Continued)*

Solution Component	Component Volume (mL) per Gel Mold Volume Below							
	5 mL	l0 mL	15 mL	20 mL	25 mL	30 mL	40 mL	50 mL
12% Acrylamide								
Water	1.6	3.3	4.9	6.6	8.2	9.9	13.2	16.5
30% Acrylamide–Bisacrylamide Solution	2.0	4.0	6.0	8.0	10.0	12.0	16.0	20.0
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02
14% Acrylamide								
Water	1.4	2.7	3.9	5.3	6.6	8.0	10.6	13.8
30% Acrylamide–Bisacrylamide Solution	2.3	4.6	7.0	9.3	11.6	13.9	18.6	23.2
1.5 M Buffer Solution	1.2	2.5	3.6	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02
15% Acrylamide								
Water	1.1	2.3	3.4	4.6	5.7	6.9	9.2	11.5
30% Acrylamide–Bisacrylamide Solution	2.5	5.0	7.5	10.0	12.5	15.0	20.0	25.0
1.5 M Buffer Solution	1.3	2.5	3.8	5.0	6.3	7.5	10.0	12.5
SDS Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
Ammonium Persulfate Solution	0.05	0.1	0.15	0.2	0.25	0.3	0.4	0.5
TEMED	0.002	0.004	0.006	0.008	0.01	0.012	0.016	0.02

After polymerization is complete (about 30 minutes later), pour off the overlay, and wash the top of the gel several times with water to remove the isobutyl alcohol overlay and any unpolymerized acrylamide. Drain as much fluid as possible from the top of the gel, then remove any remaining water with the edge of a paper towel.

Stacking Gel—In a conical flask, prepare the appropriate volume of solution containing the desired concentration of acrylamide, as shown in *Table 2*. Mix the components in the order shown. Before adding the *Ammonium Persulfate Solution* and the *TEMED*, pour the solution into a disposable filtration unit equipped with a nitrocellulose filter having a 0.45-µm

porosity, and apply vacuum. Allow the solution to degas by swirling the filtration unit, and disconnect the vacuum when no more bubbles are formed in the solution. Add appropriate amounts of *Ammonium Persulfate Solution* and *TEMED* as shown in *Table 2*, swirl, and pour immediately into the gap between the two glass plates of the mold directly onto the surface of the polymerized *Resolving Gel.* Immediately insert a clean polytef comb into the stacking gel solution, being careful to avoid trapping air bubbles. Add more stacking gel solution to fill the spaces of the comb completely. Leave the gel in a vertical position, and allow it to polymerize at room temperature. After polymerization is complete (about 30 minutes later), carefully remove the polytef comb, and proceed as directed below.

Table 2. Preparation of Stacking Gel

	Component Volume (mL) per Gel Mold Volume Below							
Solution Component	1 mL	2 mL	3 mL	4 mL	5 mL	6 mL	8 mL	10 mL
Water	0.68	1.4	2.1	2.7	3.4	4.1	5.5	6.8
30% Acrylamide–Bisacrylamide Solution	0.17	0.33	0.5	0.67	0.83	1.0	1.3	1.7
1.0 M Buffer Solution	0.13	0.25	0.38	0.5	0.63	0.75	1.0	1.25
SDS Solution	0.01	0.02	0.03	0.04	0.05	0.06	0.08	0.1
Ammonium Persulfate Solution	0.01	0.02	0.03	0.04	0.05	0.06	0.08	0.1
TEMED	0.001	0.002	0.003	0.004	0.005	0.006	0.008	0.01

Electrophoretic Separation

Sample Buffer 1—Dissolve 1.89 g of Tris, 5.0 g of SDS, 50 mg of bromophenol blue, and 25.0 mL of glycerol in 100 mL of water. Adjust with hydrochloric acid to a pH of 6.8, and dilute with water to 125 mL. Before use, dilute with an equal volume of water or sample, and mix.

Sample Buffer 2 (for reducing conditions)—Prepare as directed in *Sample Buffer 1* except to add 12.5 mL of 2-mercaptoethanol before adjusting the pH. Alternatively, prepare as directed for *Sample Buffer 1* except to start with about 1.93 g of Tris and add a suitable quantity of DTT to obtain a final 100 µM DTT concentration.

Running Buffer—Dissolve 151.4 g of Tris, 721.0 g of aminoacetic acid, and 50.0 g of SDS in water; dilute with water to 5000 mL; and mix to obtain a stock solution. Immediately before use, dilute this stock solution with water to 10 times its volume, mix, and adjust to a pH between 8.1 and 8.8.

Procedure—Rinse the wells immediately with water or with the *Running Buffer* to remove any unpolymerized acrylamide. (If necessary, straighten the teeth of the *Stacking Gel* with a blunt hypodermic needle attached to a syringe.) Remove the clamps on one short side, carefully pull out the tubing, and replace the clamps. Proceed similarly on the other short side. Remove the tubing from the bottom part of the gel.

Mount the completed gel in the electrophoresis apparatus. Add the electrophoresis buffers to the top and bottom reservoirs. Remove any bubbles that become trapped at the bottom of the gel between the glass plates. [NOTE—Removal is best done with a bent hypodermic needle attached to a syringe. Never prerun the gel before loading the samples, because that will destroy the discontinuity of the buffer systems. Before loading the sample, carefully rinse the slot with *Running Buffer.*]

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Prepare the test and standard solutions in the recommended *Sample Buffer*, and treat as directed in the individual monograph. Apply the appropriate volume of each solution to the *Stacking Gel* wells.

Start the electrophoresis under the conditions recommended by the manufacturer of the equipment. Electrophoresis running time and current or voltage may need to be varied in order to achieve optimum separation. Check that the dye front is moving into the *Resolving Gel.* When the dye has reached the bottom of the gel, stop the electrophoresis. Remove the gel assembly from the apparatus, and separate the glass plates. Remove the spacers, cut off and discard the *Stacking Gel*, and immediately proceed with staining.

Detection of Proteins in Gels

Coomassie staining is the most common protein staining method, with a detection level on the order of 1 to 10 µg of protein per band. Silver staining is the most sensitive method for staining proteins in gels, because a band containing 10 to 100 ng can be detected; but the method is more cumbersome and less rugged. All of the steps in gel staining are performed at room temperature with gentle agitation (e.g., on a rocking platform shaker or equivalent). Gloves must be worn when staining the gels to prevent fingerprint residue staining.

Reagents—

Coomassie Staining Solution—Prepare a solution of Coomassie brilliant blue R-250 having a concentration of 1.25 g per L in a mixture of water, methanol, and glacial acetic acid (5 : 4 : 1). Filter, and store at room temperature.

Destaining Solution—Prepare a mixture of water, methanol, and glacial acetic acid (5 : 4 : 1).

Fixing Solution 1—Prepare a mixture of water, methanol, and trichloroacetic acid (5 : 4 : 1).

Fixing Solution 2—Transfer 250 mL of methanol to a 500-mL volumetric flask, add 0.27 mL of formaldehyde, dilute with water to volume, and mix.

Silver Nitrate Reagent—To a mixture of 40 mL of 1 M sodium hydroxide and 3 mL of ammonium hydroxide, add, dropwise and with stirring, 8 mL of a 200 g per L solution of silver nitrate; dilute with water to 200 mL, and mix.

Developing Solution—Transfer 2.5 mL of a citric acid solution (2 in 100) and 0.27 mL of formaldehyde to a 500.0-mL volumetric flask, dilute with water to volume, and mix.

Stopping Solution—Prepare a 10% (v/v) solution of acetic acid.

Coomassie Staining—Immerse the gel in an excess of *Coomassie Staining Solution,* and incubate for at least 1 hour. Remove the *Coomassie Staining Solution*. Destain the gel with an excess of *Destaining Solution.* Change the *Destaining Solution* several times, until the stained protein bands are clearly distinguishable on a clear background. The more thoroughly the gel is destained, the smaller the amount of protein that can be detected. Destaining can be accelerated by including a few g of anion-exchange resin or a small sponge in the *Destaining Solution.* [NOTE—The acid–alcohol solutions used in this procedure do not completely fix proteins in the gel. This can lead to losses of some low molecular weight proteins during the staining and destaining of thin gels. Permanent fixation is obtainable by incubating the gel in *Fixing Solution 1* for 1 hour before it is immersed in the *Coomassie Staining Solution.*]

Silver Staining—Immerse the gel in an excess of *Fixing Solution 2,* and incubate for 1 hour. Remove *Fixing Solution 2,* add fresh *Fixing Solution 2,* and incubate for at least 1 hour, or overnight if convenient. Discard *Fixing Solution 2,* and wash the gel in an excess of water for 1 hour. Soak the gel for 15 minutes in a 1% solution of glutaraldehyde (v/v). Wash the gel twice, for 15 minutes each time, with an excess of water. Soak the gel in fresh *Silver Nitrate Reagent* for 15 minutes in darkness. Wash the gel three times, for 5 minutes each time, with an excess of water. Immerse the gel for about 1 minute in *Developing Solution* until satisfactory staining has been ob-

tained. Stop the development by incubation in the *Stopping Solution* for 15 minutes, then rinse the gel with water, and proceed with drying as indicated below.

Drying of Gels

For Coomassie staining, after the destaining step, incubate the gel in a glycerol solution (1 in 10) for at least 2 hours. For silver staining, add to the final rinsing step a 5-minute incubation in a glycerol solution (1 in 50).

Immerse two sheets of porous cellophane in water, and incubate for 5 to 10 minutes. Place one of the sheets on a drying frame. Carefully lift the gel, and place it on the cellophane sheet. Remove any trapped air bubbles, and pour a few mL of water around the edges of the gel. Place the second sheet on top, and remove any trapped air bubbles. Complete the assembly of the drying frame. Place in a drying oven, leave at room temperature until dry, or use a commercial gel dryer.

Molecular Weight Determination

Molecular weights of proteins are determined by comparison of their mobilities with those of several marker proteins of known molecular weight. Mixtures of proteins with precisely known molecular weights blended for uniform staining are available for calibrating gels. They are available in various molecular weight ranges. Concentrated stock solutions of proteins of known molecular weight are diluted in a sample buffer and loaded on the same gel as the protein sample to be tested.

Immediately after the gel has been run, the position of the bromophenol blue tracking dye is marked to identify the leading edge of the electrophoretic ion front. This can be done by cutting notches in the edges of the gel or by inserting a needle soaked in India ink into the gel at the dye front. After staining, measure the migration distances of each protein band (markers and unknowns) from the top of the *Resolving Gel*. Divide the migration distance of each protein by the distance traveled by the tracking dye. The normalized migration distances so obtained are called the relative mobilities of the proteins (relative to the dye front) and conventionally denoted as R_F. Construct a (semilogarithmic) plot of the logarithm of the molecular weights (M_R) of the protein standards as functions of the R_F values. [NOTE—The graphs are slightly sigmoid.] From the graph so obtained, estimate the unknown molecular weights by linear regression analysis or interpolation, as long as unknown samples are positioned along the linear part of the graph.

If the proteins of the molecular weight marker are not distributed along 80% of the length of the gel and over the required separation range (i.e., the range covering the product and its dimer or the products and its related impurities), and the separation obtained for the relevant protein bands does not show a linear relationship between the logarithm of the molecular weight and the R_F, the test is not valid.

Quantification of Impurities

Where the impurity limit is specified in the individual monograph, a reference solution corresponding to that level of impurity is prepared by diluting the test solution. For example, where the limit is 5.0%, a reference solution is a 1 in 20 dilution of the test solution. No impurity—any band other than the main band—in the electrophoretogram obtained from the test solution is more intense than the main band obtained with the reference solution.

Under validated conditions and when using the Coomassie staining procedure, impurities may be quantified by normalization to the main band, using an integrating densitometer. In this case, the responses must be validated for linearity.■1S (*USP30*)

In-Process Revision

BRIEFING

⟨1057⟩ Biotechnology-Derived Articles—Total Protein Assay—See briefing under *Biotechnology-Derived Articles—Amino Acid Analysis* ⟨1047⟩.

(BB PP: I. DeVeau) RTS—43939-6

Add the following:

■⟨1057⟩ BIOTECHNOLOGY-DERIVED ARTICLES—TOTAL PROTEIN ASSAY

This chapter provides guidance and procedures used for characterization of biotechnology-derived articles. This chapter is harmonized with the corresponding chapter in *JP* and *EP*. Other characterization tests, also harmonized, are provided in *Biotechnology-Derived Articles—Amino Acid Analysis* ⟨1052⟩, *Biotechnology-Derived Articles—Capillary Electrophoresis* ⟨1053⟩, *Biotechnology-Derived Articles—Isoelectric Focusing* ⟨1054⟩, *Biotechnology-Derived Articles—Peptide Mapping* ⟨1055⟩, and *Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis* ⟨1056⟩.

INTRODUCTION

The following procedures are provided as illustrations of the determination of total protein content in pharmacopeial preparations. Other techniques, such as HPLC, are also acceptable if total protein recovery is demonstrated. Many of the total protein assay methods described below can be performed successfully using kits from commercial sources. [NOTE—Where water is required, use distilled water.]

Method 1

Protein in solution absorbs UV light at a wavelength of 280 nm due to the presence of aromatic amino acids, mainly tyrosine and tryptophan. This property is the basis of *Method 1*. Protein determination at 280 nm is mainly a function of the tyrosine and tryptophan content of the protein. If the buffer used to dissolve the protein has a high absorbance relative to that of water, there is an interfering substance in the buffer. This interference can be compensated for when the spectrophotometer is adjusted to zero buffer absorbance. The results may be compromised if the interference results in a large absorbance that challenges the limit of sensitivity of the spectrophotometer. Furthermore, at low concentrations protein can be absorbed onto the cuvette, thereby reducing the content in solution. This can be prevented by preparing samples at higher concentrations or by using a nonionic detergent in the preparation. [NOTE—Keep the *Test Solution*, the *Standard Solution,* and the buffer at the same temperature during testing.]

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration of 0.2 to 2 mg per mL.

Standard Solution—Unless otherwise specified in the individual monograph, prepare a solution of USP Reference Standard or reference material for the protein under test in the same buffer and at the same concentration as the *Test Solution.*

Procedure—Concomitantly determine the absorbances of the *Standard Solution* and the *Test Solution* in quartz cells at a wavelength of 280 nm with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the buffer as the blank. To obtain accurate results, the response should be linear in the range of protein concentrations to be assayed.

Light-Scattering—The accuracy of the UV spectroscopic determination of protein can be decreased by the scattering of light by the test specimen. If the proteins in solution exist as particles comparable in size to the wavelength of the measuring light (250 to 300 nm), scattering of the light beam results in an apparent increase in absorbance of the test specimen. To calculate the absorbance at 280 nm due to light-scattering, determine the absorbances of the *Test Solution* at wavelengths of 320, 325, 330, 335, 340, 345, and 350 nm. Using the linear regression method, plot the log of the observed absorbance versus the log of the wavelength, and deter-

mine the standard curve best fitting the plotted points. From the graph so obtained, extrapolate the absorbance value due to light-scattering at 280 nm. Subtract the absorbance due to light-scattering from the total absorbance at 280 nm to obtain the absorbance value of the protein in solution. Filtration with a filter having a 0.2-µm porosity or clarification by centrifugation may be performed to reduce the effect of light-scattering, especially if the solution is noticeably turbid.

Calculations—Calculate the concentration, C_U, of protein in the test specimen by the formula:

$$C_S(A_U / A_S)$$

in which C_S is the concentration of the *Standard Solution;* and A_U and A_S are the corrected absorbances of the *Test Solution* and the *Standard Solution,* respectively (see *Spectrophotometry and Light-Scattering* ⟨851⟩).

Method 2

This method, commonly referred to as the Lowry assay, is based on the reduction by protein of the phosphomolybdic–tungstic mixed acid chromogen in the Folin-Ciocalteu's phenol reagent, resulting in an absorbance maximum at 750 nm. The Folin-Ciocalteu's phenol reagent reacts primarily with tyrosine residues in the protein, which can lead to variation in the response of the assay to different proteins. Because the method is sensitive to interfering substances, a procedure for precipitation of the protein from the test specimen may be used. Where separation of interfering substances from the protein in the test specimen is necessary, proceed as directed below for *Interfering Substances* prior to preparation of the *Test Solution.* The effect of interfering substances can be minimized by dilution, provided the concentration of the protein under test remains sufficient for accurate measurement.

Standard Solutions—Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution.* Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 5 and 100 µg of protein per mL, the concentrations being evenly spaced.

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions*. An appropriate buffer will produce a pH in the range of 10.0 to 10.5.

Blank—Use the buffer used for the *Test Solution* and the *Standard Solutions.*

Reagents and **Solutions—**

Copper Sulfate Reagent—Dissolve 100 mg of cupric sulfate and 200 mg of sodium tartrate in water, dilute with water to 50 mL, and mix. Dissolve 10 g of sodium carbonate in water to a final volume of 50 mL, and mix. Slowly pour the sodium carbonate solution into the copper sulfate solution with mixing. Prepare this solution fresh daily.

SDS Solution—Dissolve 5 g of sodium dodecyl sulfate in water, and dilute with water to 100 mL.

Sodium Hydroxide Solution—Dissolve 3.2 g of sodium hydroxide in water, dilute with water to 100 mL, and mix.

Alkaline Copper Reagent—Prepare a mixture of *Copper Sulfate Reagent, SDS Solution,* and *Sodium Hydroxide Solution* (1 : 2 : 1). This reagent may be stored at room temperature for up to 2 weeks.

Diluted Folin-Ciocalteu's Phenol Reagent—Mix 10 mL of Folin-Ciocalteu's phenol TS with 50 mL of water. Store in an amber bottle, at room temperature.

Procedure—To 1 mL of each *Standard Solution,* the *Test Solution,* and the *Blank,* add 1 mL of *Alkaline Copper Reagent,* and mix. Allow to stand at room temperature for 10 minutes. Add 0.5 mL of the *Diluted Folin-Ciocalteu's Phenol Reagent* to each solution, mix each tube immediately, and allow to stand at room temperature for 30 minutes. Determine the absorbances of the solutions from the *Standard Solutions* and the *Test Solution* at the wavelength of maximum absor-

bance at 750 nm with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the solution from the *Blank* to set the instrument to zero.

Calculations—[NOTE—The relationship of absorbance to protein concentration is nonlinear; however, if the standard curve concentration range is sufficiently small, it will approach linearity.] Using the linear regression method, plot the absorbances of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From the standard curve so obtained and the absorbance of the *Test Solution,* determine the concentration of protein in the *Test Solution.*

INTERFERING SUBSTANCES

In the following procedure, deoxycholate–trichloroacetic acid is added to a test specimen to remove interfering substances by precipitation of proteins before testing. This technique also can be used to concentrate proteins from a dilute solution.

Sodium Deoxycholate Reagent—Prepare a solution of sodium deoxycholate in water having a concentration of 150 mg in 100 mL.

Trichloroacetic Acid Reagent—Prepare a solution of trichloroacetic acid in water having a concentration of 72 g in 100 mL.

Procedure—Add 0.1 mL of *Sodium Deoxycholate Reagent* to 1 mL of a solution of the protein under test. Mix on a vortex mixer, and allow to stand at room temperature for 10 minutes. Add 0.1 mL of *Trichloroacetic Acid Reagent*, and mix on a vortex mixer. Centrifuge at 3000 × *g* for 30 minutes, decant the liquid, and remove any residual liquid with a pipet. Redissolve the protein pellet in 1 mL of *Alkaline Copper Reagent.* Proceed as directed for the *Test Solution*.

NOTE—Color development reaches a maximum in 20 to 30 minutes during incubation at room temperature, after which there is a gradual loss of color. Most interfering substances cause a lower color yield; however, some detergents cause a slight increase in color. A high salt concentration may cause a precipitate to form. Because different protein species may give different color response intensities, the standard protein and test protein should be the same.

Method 3

This method, commonly referred to as the Bradford assay, is based on the absorption shift from 470 nm to 595 nm observed when the brilliant blue G dye binds to protein. The brilliant blue G dye binds most readily to arginyl and lysyl residues in the protein, which can lead to variation in the response of the assay to different proteins.

Standard Solutions—Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution.* Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 100 µg and 1 mg of protein per mL, the concentrations being evenly spaced.

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions*.

Blank—Use the buffer used to prepare the *Test Solution* and the *Standard Solutions*.

Coomassie Reagent—Dissolve 100 mg of brilliant blue G* in 50 mL of alcohol. [NOTE—Not all dyes have the same brilliant blue G content, and different products may give different results.] Add 100 mL of phosphoric acid, dilute with water to 1 L, and mix. Pass the solution through filter paper (Whatman No. 1 or equivalent), and store the filtered reagent in an amber bottle at room temperature. [NOTE—Slow precipitation of the dye will occur during storage of the reagent. Filter the reagent before use.]

* Dye purity is important in the reagent preparation. It is intended to propose a reagent footnote to indicate that Serva Blue G (Crescent Chemical Company, Hauppauge, NY) is an acceptable grade.

Procedure—Add 5 mL of the *Coomassie Reagent* to 100 µL of each *Standard Solution,* the *Test Solution*, and the *Blank,* and mix by inversion. Avoid foaming, which will lead to poor reproducibility. Determine the absorbances of the solutions from the *Standard Solutions* and the *Test Solution* at 595 nm with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the *Blank* to set the instrument to zero. [NOTE—Do not use quartz (silica) spectrophotometer cells: the dye binds to this material. Because different protein species may give different color response intensities, the standard protein and test protein should be the same.]

There are relatively few interfering substances, but detergents and ampholytes in the test specimen should be avoided. Highly alkaline specimens may interfere with the acidic reagent.

Calculations—[NOTE—The relationship of absorbance to protein concentration is nonlinear; however, if the standard curve concentration range is sufficiently small, it will approach linearity.] Using the linear regression method, plot the absorbances of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From the standard curve so obtained and the absorbance of the *Test Solution,* determine the concentration of protein in the *Test Solution.*

Method 4

This method, commonly referred to as the bicinchoninic acid or BCA assay, is based on reduction of the cupric (Cu^{2+}) ion to cuprous (Cu^{1+}) ion by protein. The bicinchoninic acid reagent is used to detect the cuprous ion. The method has few interfering substances. When interfering substances are present, their effect may be minimized by dilution, provided that the concentration of the protein under test remains sufficient for accurate measurement.

Standard Solutions—Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution.* Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 10 and 1200 µg of protein per mL, the concentrations being evenly spaced.

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions*.

Blank—Use the buffer used to prepare the *Test Solution* and the *Standard Solutions*.

Reagents—

BCA Reagent—Dissolve about 10 g of bicinchoninic acid, 20 g of sodium carbonate monohydrate, 1.6 g of sodium tartrate, 4 g of sodium hydroxide, and 9.5 g of sodium bicarbonate in water. Adjust, if necessary, with sodium hydroxide or sodium bicarbonate to a pH of 11.25. Dilute with water to 1 L, and mix.

Copper Sulfate Reagent—Dissolve about 2 g of cupric sulfate in water to a final volume of 50 mL.

Copper–BCA Reagent—Mix 1 mL of *Copper Sulfate Reagent* and 50 mL of *BCA Reagent.*

Procedure—Mix 0.1 mL of each *Standard Solution,* the *Test Solution,* and the *Blank* with 2 mL of the *Copper–BCA Reagent.* Incubate the solutions at 37° for 30 minutes, note the time, and allow to come to room temperature. Within 60 minutes following the incubation time, determine the absorbances of the solutions from the *Standard Solutions* and the *Test Solution* in quartz cells at 562 nm with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the *Blank* to set the instrument to zero. The color intensity continues to increase gradually after the solutions are cooled to room temperature. If substances that will cause interference in the test are present, proceed as directed for *Interfering Substances* under *Method 2*. Because different protein species may give different color response intensities, the standard protein and test protein should be the same.

In-Process Revision

Calculations—[NOTE—The relationship of absorbance to protein concentration is nonlinear; however, if the standard curve concentration range is sufficiently small, it will approach linearity.] Using the linear regression method, plot the absorbances of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From the standard curve so obtained and the absorbance of the *Test Solution,* determine the concentration of protein in the *Test Solution*.

Method 5

This method, commonly referred to as the Biuret assay, is based on the interaction of cupric (Cu^{2+}) ion with protein in an alkaline solution and the resultant development of absorbance at 545 nm.

Standard Solutions—Unless otherwise specified in the individual monograph, prepare a solution of Albumin Human for which the protein content has been previously determined by nitrogen analysis (using the nitrogen-to-protein conversion factor of 6.25) or of the USP Reference Standard or reference material for the protein under test in sodium chloride solution (9 in 1000). Dilute portions of this solution with sodium chloride solution (9 in 1000) to obtain not fewer than three *Standard Solutions* having concentrations between 0.5 and 10 mg per mL, the concentrations being evenly spaced. [NOTE—Low responses may be observed if the sample under test has a significantly different level of proline than that of Albumin Human. A different standard protein may be employed in such cases.]

Test Solution—Prepare a solution of the test protein in sodium chloride solution (9 in 1000) having a concentration within the range of the concentrations of the *Standard Solutions.*

Blank—Use sodium chloride solution (9 in 1000).

Biuret Reagent—Dissolve about 3.46 g of cupric sulfate in 10 mL of hot water, and allow to cool (*Solution 1*). Dissolve about 34.6 g of sodium citrate dihydrate and 20.0 g of sodium carbonate in 80 mL of hot water, and allow to cool (*Solution 2*). Mix *Solution 1* and *Solution 2,* and dilute with water to 200 mL. This *Biuret Reagent* is stable at room temperature for 6 months. Do not use the reagent if it develops turbidity or contains any precipitate.

Procedure—To one volume of a solution of the *Test Solution* add an equal volume of sodium hydroxide solution (6 in 100), and mix. Immediately add a volume of *Biuret Reagent* equivalent to 0.4 volume of the *Test Solution,* and mix. Allow to stand at a temperature between 15° and 25° for not less than 15 minutes. Within 90 minutes after the addition of the *Biuret Reagent*, determine the absorbances of the *Standard Solutions* and the solution from the *Test Solution* at the wavelength of maximum absorbance at 545 nm with a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the *Blank* to set the instrument to zero. [NOTE—Any solution that develops turbidity or a precipitate is not acceptable for calculation of protein concentration.]

Calculations—Using the least-squares linear regression method, plot the absorbances of the *Standard Solutions* versus the protein concentrations, determine the standard curve best fitting the plotted points, and calculate the correlation coefficient for the line. [NOTE—Within the given range of the standards, the relationship of absorbance to protein concentration is approximately linear.] A suitable system is one that yields a line having a correlation coefficient of not less than 0.99. From the standard curve and the absorbance of the *Test Solution,* determine the concentration of protein in the test specimen, making any necessary correction.

Interfering Substances—To minimize the effect of interfering substances, the protein can be precipitated from the initial test specimen as follows. Add 0.1 volume of 50% trichloroacetic acid to 1 volume of a solution of the test specimen, withdraw the supernatant layer, and dissolve the precipitate in a small volume of 0.5 N sodium hydroxide. Use the solution so obtained to prepare the *Test Solution.*

Comments—This test shows minimal difference between equivalent IgG and albumin samples. Addition of the sodium hydroxide and the *Biuret Reagent* as a combined reagent, insufficient mixing after the addition of the sodium hydroxide, or an extended time between the addition of the sodium hydroxide solution and the addition of the *Biuret Reagent* will give IgG samples a higher response than albumin samples. The trichloroacetic acid method used to minimize the effects of interfering substances can also be used to determine the protein content in test specimens at concentrations below 500 µg per mL.

Method 6

This fluorometric method is based on the derivatization of the protein with *o*-phthalaldehyde (OPA), which reacts with the primary amines of the protein (i.e., NH_2-terminal amino acid and the ϵ-amino group of the lysine residues). The sensitivity of the test can be increased by hydrolyzing the protein before testing. Hydrolysis makes the α-amino group of the constituent amino acids of the protein available for reaction with the *o*-phthalaldehyde reagent. The method requires very small quantities of the protein.

Primary amines, such as tris(hydroxymethyl)aminomethane and amino acid buffers, react with *o*-phthalaldehyde and must be avoided or removed. Ammonia at high concentrations will react with *o*-phthalaldehyde as well. The fluorescence obtained when amine reacts with *o*-phthalaldehyde can be unstable. The use of automated procedures to standardize this procedure may improve the accuracy and precision of the test.

Standard Solutions—Unless otherwise specified in the individual monograph, dissolve the USP Reference Standard or reference material for the protein under test in the buffer used to prepare the *Test Solution.* Dilute portions of this solution with the same buffer to obtain not fewer than five *Standard Solutions* having concentrations between 10 and 200 µg of protein per mL, the concentrations being evenly spaced.

Test Solution—Dissolve a suitable quantity of the protein under test in the appropriate buffer to obtain a solution having a concentration within the range of the concentrations of the *Standard Solutions.*

Blank—Use the buffer used to prepare the *Test Solution* and the *Standard Solutions.*

Reagents—

Borate Buffer—Dissolve about 61.83 g of boric acid in water, and adjust with potassium hydroxide to a pH of 10.4. Dilute with water to 1 L, and mix.

Stock OPA Reagent—Dissolve about 120 mg of *o*-phthalaldehyde in 1.5 mL of methanol, add 100 mL of *Borate Buffer,* and mix. Add 0.6 mL of polyoxyethylene (23) lauryl ether, and mix. This solution is stable at room temperature for at least 3 weeks.

OPA Reagent—To 5 mL of *Stock OPA Reagent* add 15 µL of 2-mercaptoethanol. Prepare at least 30 minutes prior to use. This reagent is stable for one day.

Procedure—Adjust each of the *Standard Solutions* and the *Test Solution* to a pH between 8 and 10.5. Mix 10 µL of the *Test Solution* and each of the *Standard Solutions* with 100 µL of *OPA Reagent*, and allow to stand at room temperature for 15 minutes. Add 3 mL of 0.5 N sodium hydroxide, and mix. Using a suitable fluorometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), determine the fluorescent intensities of solutions from the *Standard Solutions* and the *Test Solution* at an excitation wavelength of 340 nm and an emission wavelength between 440 and 455 nm. [NOTE—The fluorescence of an individual specimen is read only once because irradiation decreases the fluorescent intensity.]

Calculations—The relationship of fluorescence to protein concentration is linear. Using the linear regression method, plot the fluorescent intensities of the solutions from the *Standard Solutions* versus the protein concentrations, and determine the standard curve best fitting the plotted points. From

the standard curve so obtained and the fluorescent intensity of the *Test Solution,* determine the concentration of protein in the test specimen.

Method 7

This method is based on nitrogen analysis as a means of protein determination. Interference caused by the presence of other nitrogen-containing substances in the test specimen can affect the determination of protein by this method. Nitrogen analysis techniques destroy the protein under test but are not limited to protein presentation in an aqueous environment.

Procedure 1—Determine the nitrogen content of the protein under test as directed under *Nitrogen Determination* ⟨461⟩. Commercial instrumentation is available for the Kjeldahl nitrogen assay.

Procedure 2—Commercial instrumentation is available for nitrogen analysis. Most nitrogen analysis instruments use pyrolysis (i.e., combustion of the sample in oxygen at temperatures approaching 1000°), which produces nitric oxide (NO) and similar oxides of nitrogen (NO_x) from the nitrogen present in the test protein. Some instruments convert the nitric oxides to nitrogen gas, which is quantified with a thermal conductivity detector. Other instruments mix nitric oxide (NO) with ozone (O_3) to produce excited nitrogen dioxide (NO_2), which emits light when it decays and can be quantified with a chemiluminescence detector. A protein reference material or reference standard that is relatively pure and is similar in composition to the test proteins is used to optimize the injection and pyrolysis parameters and to evaluate consistency in the analysis.

Calculations—The protein concentration is calculated by dividing the nitrogen content of the sample by the known nitrogen content of the protein. The known nitrogen content of the protein can be determined from the chemical composition of the protein or by comparison with the nitrogen content of the USP Reference Standard or reference material. ■1S (*USP30*)

BRIEFING

⟨**1058**⟩ **Analytical Instrument Qualification,** page 1453 of *PF* 31(5) [Sept–Oct. 2005]. On the basis of comments received, it is proposed to revise this text in order to reflect current practices. Among these changes, the *Performance Qualification* section has been modified in order to accept the system suitability test as proof of suitable performance. In addition, minor editorial changes have been made.

(GC: H. Pappa) RTS—43205-1; 43206-1; 43207-1; 43830-1; 43965-1; 43968-1; 44086-1; 44087-1; 44089-1; 44090-1; 44113-1; 44113-2

Add the following:

■⟨1058⟩ ANALYTICAL INSTRUMENT QUALIFICATION

INTRODUCTION

A large variety of laboratory instruments and tools, ranging from simple nitrogen evaporators to complex multiple-function technologies (see *Instrument Categories*), are used in the pharmaceutical industry to acquire data to help ensure that products are suitable for their intended use. ~~and that they do not pose high safety risks. The~~ An analyst's objective is to consistently obtain reliable and valid data suitable for the intended purpose. Depending on the applications, users validate their procedures and perform system suitability tests and in-process quality control ~~checks~~ check samples to help ensure that the acquired data are reliable. ~~These activities help enhance the quality of data, and there are specific guidances and procedures for performing these activities.~~ With the increasing sophistication and automation of analytical instruments, an increasing demand has been placed on users to qualify their instruments.

In-Process Revision

Unlike method validation and system suitability activities, analytical instrument qualification (AIQ) currently has no specific guidance or procedures. Competing opinions ~~abound~~ exist regarding instrument qualification and validation procedures and the roles and responsibilities of those who perform them. Consequently, various approaches have been used for instrument qualification, approaches that require varying amounts of resources and generate widely differing amounts of documentation. This chapter provides a scientific approach to AIQ and considers AIQ as one of the major components required for generating reliable and consistent data. Note that a risk-based approach may be used to provide flexibility in the qualification process, depending on the complexity and intended use of the instrumentation. This chapter provides an efficient science- and risk-based process for AIQ. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments. The approach provided in this chapter focuses on scientific value rather than on producing documents.

Validation versus Qualification

Because there is ambiguity in the use of the terms ''validation'' and ''qualification'', in this chapter the term ''validation'' ~~will be~~ is used for processes, ~~and software,~~ including analytical procedures and software procedures, and the term ''qualification'' ~~will be~~ is used for instruments. Thus, the phrase ''analytical instrument qualification'' (AIQ) is used for the process of ensuring that an instrument is suitable for its intended application. ~~The term ''validation'' is reserved for processes including analytical procedures and software procedures.~~

COMPONENTS OF DATA QUALITY

There are four critical components involved in the generation of reliable and consistent data (quality data). *Figure 1* shows these components as layered activities within a quality triangle. Each layer adds to the overall quality. Analytical instrument qualification forms the ~~base~~ basis for generating quality data. The other components essential for generating quality data are analytical method validation, system suitability tests, and quality control ~~checks~~ check samples. These quality components are described below.

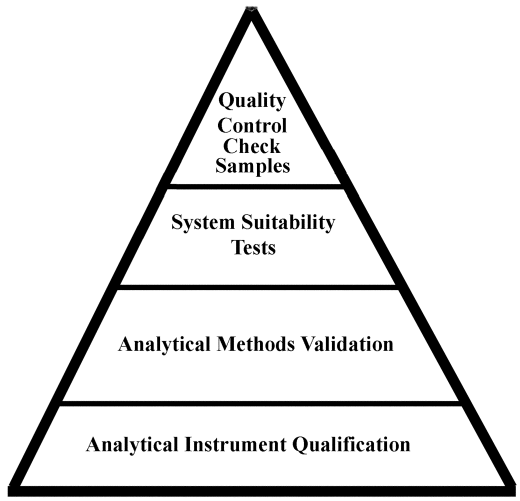

Figure 1. Components of data quality.

Analytical Instrument Qualification

AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose. ~~and that it is properly maintained and calibrated.~~ Use of a qualified instrument in analyses contributes to confidence in the ~~veracity~~ validity of generated data.

Analytical Method Validation

Analytical method validation is the collection of documented evidence that an analytical procedure does what it purports to do and addresses the required attributes of the procedure. Use of a validated procedure with qualified analytical instruments provides confidence that the procedure will generate test data of acceptable quality. ~~Users of compendial procedures perform validation using the criteria provided in general information chapter *Validation of Compendial Methods*~~

In-Process Revision

⟨~~1225~~⟩. Additional guidance on validation of compendial procedures may be found in the general information chapter *Validation of Compendial Procedures* ⟨1225⟩.

System Suitability Tests

System suitability tests verify that the system will perform ~~according to~~ in accordance with ~~the analyst's expectations and according to~~ the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test. USP general chapter *Chromatography* ⟨621⟩ presents a more detailed discussion of system suitability tests as related to chromatographic systems.

Quality Control ~~Checks~~ Check Samples

Most analyses are performed on instruments ~~calibrated or~~ standardized using reference materials or calibration standards. ~~The calibration or standardization process uses a single- or multiple-point calibration, depending on the instrument and the intended application. The calibration or standardization of an instrument during analysis ensures that the instrument response correlates with the known quantity or quality of the calibration standard or reference material. In addition to calibration or standardization, some~~ Some analyses also require the inclusion of quality control check samples to provide an in-process or ongoing assurance of the test's suitable performance.

The extent of system suitability tests or quality control ~~checks~~ check samples varies for different analyses, depending on their intended use. ~~Chemical analyses, which are largely subject to Good Manufacturing Practices (GMP) regulations and require tighter precision and accuracy, may require more system suitability tests than bioanalytical work, which is largely subject to Good Laboratory Practice (GLP) regulations. Bioanalytical work requires sensitive, specific, broad-range analysis and therefore is generally performed with more quality control checks during sample analysis.~~ Generally, chemical analyses exhibit tighter precision and accuracy than bioanalytical work, and for these analyses system suitability tests are often more appropriate. Due to the inherent variability, bioanalytical analyses are generally performed with more quality control checks during sample analysis. Control check samples are also appropriate when high-variability tests or instruments ~~(i.e., those with a relative standard deviation [RSD] higher than 5%)~~ are considered. Other use-specific considerations may also determine the extent of system suitability tests or quality-control-check sample analysis. Whatever the case, the sum total of such controls provides an important step in delivering quality data for the intended purpose.

In summary, analytical instrument qualification and analytical method validation ensure the quality of analysis *before* conducting the tests. System suitability tests and quality control checks ensure the quality of analytical results *immediately before* or *during* sample analysis.

ANALYTICAL INSTRUMENT QUALIFICATION PROCESS

The following sections address in detail the AIQ process. The other three components of building quality into analytical data—analytical method validation, system suitability tests, and quality control ~~checks~~ check samples—are not within the scope of this chapter.

Qualification Phases

Instrument qualification is not a single continuous process, but instead results from several discrete activities. For convenience, these activities can be grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

Some of these qualification terms have their roots in manufacturing-process validation. Note, however, that adoption of process validation terms does not imply that all process validation activities are necessary for AIQ. Also, some AIQ activities cover more than one qualification phase and could arguably be performed within any of the phases. It is important that the required AIQ activities be performed; however, within which qualification phase an activity is performed or reported is not as important. *Table 1* accommodates these overlapping activities by letting users perform them under one or another phase as necessary. The user should describe where the activity is performed and reported.

Table 1. Timing, Applicability, and Activities for Each Phase of Analytical Instrument Qualification*

DQ	IQ		OQ		PQ
		Timing and applicability			
Prior to purchase of a new ~~type~~ model of instrument	At installation of each instrument (new, old, or existing unqualified)		After installation or major repair of each instrument		Periodically at specified intervals for each instrument
		Activities			
Assurance of vendor's DQ	System description	⇆	Fixed parameters		Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument delivery				~~SOPs for~~ Establish practices to address operation, calibration, maintenance, and change control
Instrument's fitness for use in laboratory	Utilities/facility/environment				
	Network and data storage	⇆	Secure data storage, backup, and archive		
	Assembly and installation				
	Installation verification	⇆	Instrument function tests	⇆	Performance checks

* Activities under each phase are usually performed as given in the table. However, in some cases, it may be more appropriate to perform or combine a given activity with another phase. Such activities spanning more than one qualification phase are shown as connected by double arrows. If an activity listed under a given phase is performed under another phase, it is not necessary to repeat the activity under the phase where the activity is listed. Performing the activity is far more important than the phase under which the activity is performed.

DESIGN QUALIFICATION

Design qualification (DQ) is the documented collection of activities that define the functional and operational specifications of the instrument, based on the intended purpose. Design qualification (DQ) is most suitably performed by the instrument developer or manufacturer. Because the instrument design is already in place for commercial off-the-shelf (COTS) systems, users do not need to repeat ~~all aspects of~~ DQ. However, users should ensure that COTS instruments are suitable for their intended applications and that the manufacturer has adopted a quality system for developing, manufacturing, and testing. Users should also establish that manufacturers and vendors adequately support installation, service, and training. Methods for ascertaining the manufacturer's design qualification and an instrument's suitability for its intended use depend on the nature of the instrument, the complexity of the proposed application, and the extent of the user's previous interaction with the manufacturer. Vendor audits or required vendor-supplied documentation satisfy part of the DQ requirements. The required scope and comprehensiveness of the audits and documentation ~~vary with users' familiarity with the instrument and their previous interactions with the vendor~~ should be based on the risk the instrument will impose on operations.

~~Informal processes also form an important part of DQ. Informal personal communications and networking with peers at technical or user group meetings significantly inform users about the suitability of instrument design for various applications and the quality of vendor support services. Informal site visits to other users' and vendors' facilities to obtain data on representative samples that used the specified instrument are another good source of information about suitability for intended use. In many instances an assessment of the quality of vendor support, gleaned from informal discussions with peer users, significantly influences instrument selection.~~

INSTALLATION QUALIFICATION

~~Installation qualification (IQ) is the documented collection of activities necessary for installing an instrument in the user's environment.~~ Installation qualification (IQ) is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, and is properly installed in the selected environment, and that this environment is suitable for the intended purpose. IQ applies to an instrument that is new or was pre-owned, or to any instrument that exists on site but has not been previously qualified. Relevant parts of IQ would also apply to a qualified instrument that has been ~~packed and~~ transported to another location or is being reinstalled for other reasons, such as prolonged storage. The activities and documentation typically associated with IQ are as follows.

System Description—Provide a description of the instrument or the collection of instrument components, including its manufacturer, model, serial number, software version, location, etc. Use drawings and flow charts where appropriate.

Instrument Delivery—Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Utilities/Facility/Environment—Verify that the installation site satisfactorily meets vendor-specified environmental requirements. ~~A commonsense judgment for the environment suffices: one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.~~

Network and Data Storage—Some analytical systems require users to provide network connections and data storage capabilities at the installation site. When required, connect the instrument to the network, and check its functionality.

Assembly and Installation—Assemble and install the instrument, and perform any preliminary diagnostics and testing. Assembly and installation of complex instruments are best done by the vendor, specialized engineers, or qualified in-house personnel, whereas users can assemble and install simple ones. For complex instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance. Any abnormal event observed during assembly and installation merits documenting. ~~If the pre-owned, unqualified existing instrument or transported instrument requires assembly and installation, perform the tasks as specified above, then perform the installation verification procedure, described below.~~ Installation packages purchased from the vendor may, however, need to be supplemented with user-specific criteria.

Installation Verification—Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and, when present, the installing engineer should confirm that the installation was successful before proceeding with the next qualification phase.

OPERATIONAL QUALIFICATION

After a successful IQ, the instrument is ready for OQ testing. Operational qualification (OQ) is the documented collection of activities necessary to demonstrate that an instrument will function according to its operational specification in the selected environment. The OQ phase may consist of these test parameters.

Fixed Parameters—These tests measure the instrument's nonchanging parameters such as length, height, weight, voltage inputs, acceptable pressures, and loads. If the vendor-supplied specifications for these parameters satisfy the user, the test requirements may be waived. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument, and therefore never need redetermination. [NOTE—These tests could also be performed during the IQ phase (see *Table 1*); if so, fixed parameters need not be redetermined as part of OQ testing.]

Secure Data Storage, Backup, and Archiving—When ~~required~~ applicable, test secure data handling such as storage, backup, and archiving at the user's site according to written procedures.

Instrument Function Tests—~~Important instrument~~ Instrument functions should be tested to verify that the instrument operates as intended by the manufacturer. ~~and required by the user.~~ The user should select ~~important~~ instrument parameters for testing according to the instrument's intended use. Vendor-supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor ~~and user specifications~~ specifications in the user's environment.

The extent of OQ testing that an instrument undergoes depends on its intended applications. Therefore, no specific OQ tests for any instrument or application are offered in this chapter. ~~Nevertheless, as a guide to the types of tests possible during OQ, consider the following, which apply to an HPLC unit:~~

- ~~pump flow rate~~
- ~~gradient linearity~~
- ~~detector wavelength accuracy~~
- ~~detector linearity~~
- ~~column oven temperature~~
- ~~injector precision and accuracy~~
- ~~peak retention time precision~~

Routine analytical tests do not constitute OQ testing. OQ tests are specifically designed to verify the instrument's operation according to specifications in the user's environment, and repeating the testing at regular intervals may not be required. However, when the instrument undergoes major repairs or modifications, relevant OQ tests should be repeated to verify whether the instrument continues to operate satisfac-

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torily. Relevant OQ tests should also be repeated for an instrument that has been transported to another location, although a move within the laboratory, or from one room to another, that does not disturb instrument operation may not require requalification.

OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate interchanging of such components without requalification. ~~and should be performed whenever possible.~~ Holistic tests, which involve the entire system, are also acceptable. ~~in lieu of modular testing. Having successfully completed OQ testing, the instrument is qualified for use in regulated samples analysis.~~

PERFORMANCE QUALIFICATION

Performance qualification (PQ) is the documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use. After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through performance qualification. The PQ phase may include the following parameters.

Performance Checks—Set up a test or series of tests to verify the acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications ~~Some~~ and may consist of analyzing known components or standards. The tests should be based on good science and reflect the general intended use of the instrument. ~~These~~ Some system suitability tests or quality control checks that are performed concurrently with the test samples can be used to demostrate that the instrument is performing suitably. PQ tests may resemble those performed during OQ, but the specifications for their results can be set differently if required. ~~PQ tests should be performed routinely on a working instrument, not only on a new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications.~~ Nevertheless, user specifications for PQ tests should ~~evince~~ demonstrate trouble-free instrument operation for the intended applications. ~~PQ tests should be performed independently of the routine analytical testing performed on the instrument.~~ As is the case with OQ testing, PQ tests can be modular or holistic. However, because many modules within a system interact, holistic tests generally prove to be more effective because they evaluate the entire system, not simply the system's individual modules.

Testing frequency depends on the ruggedness of the instrument and the criticality of the tests performed. Testing may be unscheduled—for example, each time the instrument is used. It may also be scheduled for regular intervals, such as weekly or monthly. Experience with the instrument can influence this decision. ~~Generally, the same PQ tests are repeated~~ It may be useful to repeat the same PQ tests each time so that a history of the instrument's performance can be compiled. Alternatively, the instrument may be incorporated into an integrated support system to assure that it remains continually qualified. Some system suitability tests or quality control checks that are performed concurrently with the test samples also imply that the instrument is performing suitably. ~~However, although system suitability tests can supplement periodic PQ tests, they cannot replace them.~~

Preventive Maintenance and Repairs—When an instrument fails to meet PQ test specifications, it requires maintenance or repair. A periodic preventive maintenance may also be recommended for many instruments. The relevant PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

~~**Standard Operating Procedure[s]**~~ **Practices for Operation, Calibration, ~~and~~ Maintenance, and Change Control**—Establish ~~standard operating procedures~~ practices to maintain and calibrate the instrument. ~~Use a logbook, binder, or electronic record to document each~~ Each maintenance and calibration activity should be documented.

ROLES AND RESPONSIBILITIES

Users

Users are ultimately responsible for instrument operations and data quality. The user's group encompasses analysts, their supervisors, and organization management. Users should be adequately trained in the instrument's use, and their training records should be maintained as required by the regulations.

Users should also be responsible for qualifying their instruments, because their training and expertise in the use of instruments make them the best-qualified group to design the instrument test(s) and specification(s) necessary for successful AIQ. Consultants, equipment vendors, validation specialists, and quality assurance (QA) personnel can advise and assist as needed, but the final responsibility for qualifying instruments lies with the users. The users must also maintain the instrument in a qualified state by routinely performing PQ.

Quality ~~Assurance~~ Unit

The ~~QA role~~ role of the Quality Unit in AIQ remains the same as for any other regulated ~~study~~ activity. ~~QA~~ Quality personnel should understand the instrument qualification process, and they should learn about the instrument's application by working with the users. Finally, they should review the AIQ process to determine whether it meets regulatory requirements, and ~~they should make certain that the users attest to the scientific validity of the process~~ the intended use of the equipment supported by scientifically valid and documented data.

Manufacturers

Manufacturers and developers are responsible for DQ when designing the instrument. They are also responsible for validation of relevant processes used in manufacturing and assembly of the hardware and for software associated with the instrument. Manufacturers and developers are also responsible for writing stand-alone software for analytical work in a documented quality manner and for the validation of this software. Manufacturers should test the assembled instruments before shipping them to users.

Manufacturers and vendors should make available to users a summary of their validation efforts and the results of final instrument and software tests, and they should provide the critical functional test scripts that can be used to qualify the instrument and software at the user site. For instance, manufacturers and vendors can provide a large database and scripts for functional testing of the network's bandwidth for laboratory information management system (LIMS) software.

Finally, it is desirable that manufacturers and vendors should notify all known users about hardware or software defects discovered after a product's release; offer user training, service, repair, and installation support; and invite user audits as necessary.

SOFTWARE VALIDATION

Software used for analytical work can be classified into three categories: firmware; instrument control, data acquisition, and processing software; and stand-alone software.

Firmware

Computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and users generally cannot alter firmware design or function. Firmware is therefore considered a component of the instrument itself. Indeed, the qualification of hardware is not possible without operating it via its firmware. Thus, when the hardware (that is, the analytical instrument) is qualified at the user's site, the integrated firmware is also essentially qualified. No separate on-site qualification of the firmware is needed. Any changes made to firmware versions should be tracked through change control of the instrument (see *Change Control,* below).

Instrument Control, Data Acquisition, and Processing Software

Software for instrument control, data acquisition, and processing for many of today's computerized instruments is loaded on a computer connected to the instrument. Operation of the instrument is then controlled via the software, leaving fewer operating controls on the instrument. Also, the software is needed for data acquisition and postacquisition calculations. Thus, both hardware and software, their functions inextricably intertwined, are critical to providing analytical results.

The manufacturer should perform DQ, validate this software, and provide users with a summary of validation. At the user site, holistic qualification, which involves the entire instrument and software system, is more efficient than modular validation of the software alone. Thus, the user qualifies the instrument control, data acquisition, and processing software by qualifying the instrument according to the AIQ process.

Stand-Alone Software

An authoritative guide for validating stand-alone software, such as LIMS, is available.[1] The validation process is administered by the software developer, who also specifies the development model appropriate for the software. Validation takes place in a series of activities planned and executed through various stages of the development cycle.

The software validation guide cited in the previous paragraphs indicates that user-site testing is an essential part of the software development cycle. Note, however, that user-site testing, though essential, is only part of the validation process for stand-alone software and does not constitute complete validation. Refer to the software validation guide for activities that must be performed at the user site for testing stand-alone software used in analytical work.

CHANGE CONTROL

Changes to the instrument and software become inevitable as manufacturers add new features and correct known defects. However, implementing all such changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary and should also assess the effects of changes to determine what, if any, requalification is required. The change control process enables them to do this.

Change control follows the DQ/IQ/OQ/PQ classification process. For DQ, evaluate the changed parameters, and determine whether need for the change warrants implementing it. If implementation of the change is needed, install the changes to the system during IQ. Evaluate which of the existing OQ and PQ tests need revision, deletion, or addition as a result of the installed change. Where the change calls for additions, deletions, or revisions to the OQ or PQ tests, follow the procedure outlined below.

Operational Qualification—Revise OQ tests as necessitated by the change. Perform the revised OQ testing. If the OQ did not need revision, repeat only the relevant tests affected by the change. This ensures the instrument's effective operation after the change is installed.

Performance Qualification—Revise PQ tests as necessitated by the change. Perform the PQ testing after installation of the change if similar testing is not already performed during OQ. In the future, perform the revised PQ testing.

For changes to firmware and to software for instrument control, data acquisition, and processing, change control is performed through DQ/IQ/OQ/PQ of the affected instrument. Change control for stand-alone software requires user-site testing of changed functionality.

[1] *General Principles of Software Validation: Final Guidance for Industry and FDA Staff,* U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD, January 11, 2002. http://www.fda.gov/cdrh/comp/guidance/938.html (accessed September 2004).

AIQ DOCUMENTATION

Two types of documents result from AIQ: static and dynamic.

Static Documents

Static documents are obtained during the DQ, IQ, and OQ phases and should be ~~kept in a "Qualification" binder~~ retained in an accessible manner. Where multiple instruments of one kind exist, documents common to all instruments ~~should go into one binder or section,~~ and documents specific to an instrument ~~should go into that instrument's binder or section~~ may be retained separately. During change control, additional documents ~~can be placed with~~ may supplement the static ones, but previous documents should ~~not be removed~~ be retained. When necessary, such documents may be archived.

Dynamic Documents

Dynamic documents are generated during the OQ and PQ phases when the instrument is maintained or tested for performance. ~~Arranged in a binder or logbook, they provide a running record for the instruments and should be kept with them. These documents may should also be archived as necessary.~~ These documents provide a running record for the instruments and should be retained in a suitable manner which allows for appropriate protection and access.

INSTRUMENT CATEGORIES

Modern laboratories typically include a suite of tools varying from simple nitrogen evaporators to complex automated instruments. Therefore, applying a single set of principles to qualifying such dissimilar instruments would be scientifically inappropriate. Users are most capable of establishing the level of qualification needed for an instrument. On the basis of the level needed, it is convenient to categorize instruments into three groups: A, B, and C, as defined below. Examples of instruments in each group are provided. Note that the list of instruments provided here is for illustration only and is not meant to be exhaustive. It does not provide the exact category for an instrument at a user site. That category should be determined by users for their specific instruments or applications.

The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.

Group A

Conformance of Group A instruments to user requirements is determined by visual observation. Since requirements are often straightforward, documentation of requirements may not be required. No independent qualification process is required. Examples of instruments in this group are nitrogen evaporators, magnetic stirrers, vortex mixers, mortar and pestle sets, ~~water baths,~~ and glass pipets.

Group B

Conformance of Group B instruments to user requirements is determined according to an instrument's standard operating procedures. Conformity assessments are generally unambiguous. Installation of Group B instruments is relatively simple, and causes of their failure are readily discernible by simple observation. Examples of instruments in this group are balances, incubators, ~~IR spectrometers,~~ melting point apparatus, muffle furnaces, light microscopes, pH meters, variable pipets, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, ovens, water baths, and viscosimeters.

Group C

Conformance of Group C instruments to user requirements is complex and highly method-specific; conformity bounds are determined by the application. Installing these instruments can be a complicated undertaking and may require the assistance

of specialists. A full qualification process, as outlined in this document, should apply to these instruments. Examples of instruments in this group include the following:

- atomic absorption spectrometers
- differential scanning calorimeters
- dissolution apparatus
- electron microscopes
- flame absorption spectrometers
- high-pressure liquid chromatographs
- mass spectrometers
- microplate readers
- thermal gravimetric analyzers
- X-ray fluorescence spectrometers
- X-ray powder diffractometers
- densitometers
- diode-array detectors
- elemental analyzers
- gas chromatographs
- IR spectrometers
- near IR spectrometers
- Raman spectrometers
- UV/Vis spectrometers
- inductively coupled argon–plasma emission spectrometers

~~Again, it must be emphasized that the placement of these instruments in the given three groups is for illustrative purposes only. The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.~~

~~CONCLUSION~~

~~The purpose of the use of analytical instruments is to generate reliable data. Analytical instrument qualification helps fulfill this purpose. No authoritative guide existed that considered the risk of instrument nonperformance and combined that risk with users' scientific knowledge and ability to use the instrument to deliver reliable and consistent data. In the absence of such a guide, the qualification of analytical instruments became a subjective and often fruitless document-generating exercise.~~

~~This chapter is based on the outcome of a user workshop conference on the subject and provides an efficient science- and risk-based process for AIQ. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments. The process provided in this chapter focuses on scientific value rather than on producing documents. Implementing such a process should increase efficiency and remove ambiguous or varying interpretations by different groups.~~ ■1S (*USP30*)

BRIEFING

⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations, page 1706 of *PF* 30(5) [Sept.–Oct. 2004]. On the basis of comments received, it is proposed to revise this proposed new general information chapter to delete the *Composite Inventory of Typical Ambulance Service Medications*. This list of the most commonly used medications carried in EMS vehicles is being omitted because of the ever changing nature of the list and to ensure that exclusivity is not assumed. Other changes are editorial in nature.

(P&S: D. Hunt) RTS—42495-1

Add the following:

■⟨1070⟩ EMERGENCY MEDICAL SERVICES VEHICLES AND AMBULANCES—STORAGE OF PREPARATIONS

The storage and handling of pharmaceuticals in emergency vehicles and ambulances should be done so that the attributes of the official articles are preserved. ~~For examples, see the list below for typical articles.~~ There are a number of practices that

need consideration when an effective plan is formulated, evaluated, put in place, and periodically re-evaluated. Those practices are listed here.

Monitoring devices should be in place to record weekly temperatures, and allow the calculation of mean kinetic temperature for conformance to controlled room temperature storage for those vehicles utilized continuously. Measurement should also be made during a typical challenging 24-hour period, and the derived temperature should be used for the calculation of MKT and storage temperature of the sample.

PHARMACEUTICAL STORAGE CABINET MONITORING; LOCATION OF PARKED VEHICLES

Ambulances and other emergency medical response vehicles that routinely carry Pharmacopeial articles should be monitored to verify that temperature profiles and on-board pharmaceutical storage cabinets or cold chests are within established limits. Suitable monitoring devices are to be placed in the pharmaceutical cabinet of each vehicle that records highest and lowest temperatures, at the least, of each hot summer and cold winter day. To avoid temperature extremes, ambulance personnel should consider parking in the shade or in air-conditioned garages in the summer or in heated garages in the winter.

STOCK ROTATION

A program of regular stock rotation should be in place for articles with low rates of turnover. Rotation is understood as transfer of the articles with suitable marking of stock items to an appropriate climate controlled facility or storage cabinet such as in an ambulance bay. Off-vehicle storage of each article is subject to the storage requirement in the approved labeling or the pertinent USP monograph.

PORTABLE CARRYING CASE STORAGE AND MONITORING

The portable bag or carrying case in which drugs are kept is to be insulated, and when not in use, should be kept in a pharmaceutical storage cabinet or at controlled room temperature within facilities. Storage in portable bags or cases only, rather than in on-board cabinets, should be considered to facilitate stock rotation where indicated. The use of time–temperature indicators is recommended to monitor cumulative insult to the contents of all compartments.

ADDITIONAL REQUIREMENTS FOR SOME ARTICLES

All articles are to be protected from excessive heat (40°). If the article requires storage in a cold or dry place or at controlled room temperature, then suitable measures are to be taken to maintain it within the defined limits, see *General Notices—Preservation, Packaging, Storage, and Labeling*. Articles that have the most stringent storage requirements determine the storage of mixed loads.

STORAGE AND HANDLING OF SENSITIVE PREPARATIONS

~~*Environmentally Sensitive Preparations* (see ⟨386⟩)~~ Environmentally sensitive preparations are not to be stored in emergency response vehicles unless the on-board cabinet in which the medications is stored is climate controlled or a time–temperature indicator is attached to each package. If environmentally sensitive preparations must be kept in the EMS vehicle, then the supply of medications should be rotated with reserve stock on a schedule based on local climate, but not longer than every 3 days.

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USE OF TIME–TEMPERATURE INDICATORS

Attach time–temperature indicators to individual *thermally sensitive preparations* where time outside of the on-board cabinet can exceed 4 days total. On-board cabinets must be insulated and while medications are inside, active heating and cooling devices should be used in accord with the local climate and as specified for the preparations.

~~**COMPOSITE INVENTORY OF TYPICAL AMBULANCE SERVICE MEDICATIONS**~~

~~NOTE—Each vehicle may carry only a portion of the articles herein, or others.~~

~~Adenosine Injection~~

~~Afrin~~

~~Albuterol Sulfate Injection~~

~~Amiodarone~~

~~Amyl Nitrite Inhalant~~

~~Aspirin Tablets~~

~~Atropine Sulfate Injection~~

~~Atropine and 2-PAM Antidote [Mark 1 Kits]~~

~~Atrovent~~

~~Bretylium Tosylate Injection~~

~~Calcium Chloride Injection~~

~~Calcium Gluconate Injection~~

~~Activated Charcoal~~

~~Dextrose 50%, Dextrose 25% Injection~~

~~Diazepam Gel~~

~~Diazepam Injection~~

~~Diltiazem~~

~~Diphenhydramine Injection~~

~~Dopamine Injection~~

~~Epinephrine 1 : 10000, Epinephrine 1 : 1000 Injection~~

~~Furosemide Injection~~

~~Glucagon for Injection~~

~~Lidocaine Hydrochloride Injection, Lidocaine 1% Gel~~

~~Magnesium Sulfate~~

~~Methylprednisone~~

~~Metoprolol~~

~~Midazolam~~

~~Morphine Sulfate Injection~~

~~Nalbuphine~~

~~Naloxone Hydrochloride Injection~~

~~Nitroglycerin Spray, Nitroglycerin Tablets, Nitroglycerin Ointment~~

~~Oxytocin Injection~~

~~Promethazine~~

~~Sodium Bicarbonate Injection~~

~~Sodium Nitrite Injection~~

~~Sodium Thiosulfate Injection~~

~~Terbutaline Injection~~

~~Tetracaine Ophthalmic Solution, Ointment~~

~~Thiamine Hydrochloride Injection~~

~~Toradol Injection~~ ■1S (*USP30*)

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Acetaldehyde, *USP 29* page 3106. To facilitate the procurement of this reagent and other reagents appearing in this issue of *PF* (see related cross-references), it is proposed to include CAS numbers and relevant synonyms, as necessary.

(HDQ: M. Marques) RTS—43350-1

Change to read:

Acetaldehyde

■*(Ethanal; acetic aldehyde),* ■1S (*USP30*)
CH_3CHO—**44.05**

■[*75-07-0*]■1S (*USP30*)
—Colorless liquid. Miscible with water and with alcohol. Use ACS reagent grade.

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BRIEFING

Acetanilide, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-3

Change to read:

Acetanilide

■*(Phenylacetamide; Antifebrin),*■1S (*USP30*)
C_8H_9NO—**135.16**

■[*103-84-4*]■1S (*USP30*)
—White, shiny crystals, usually in scales, or a white, crystalline powder. ▲*USP29* Is stable in air. Freely soluble in alcohol and in chloroform; soluble in boiling water, in ether, and in glycerin; slightly soluble in water.

Melting range ⟨741⟩: between 114° and 116°.

Reaction—Its saturated solution is neutral to litmus.

Loss on drying ⟨731⟩—Dry it over sulfuric acid for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition (Reagent test): not more than 0.05%.

BRIEFING

Acetic Acid, Glacial, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-5

Change to read:

Acetic Acid, Glacial, CH_3COOH—**60.05**

■[*64-19-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Acetic Anhydride, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-6

Change to read:

Acetic Anhydride

■*(Acetic Oxide; Acetyl Oxide),*■1S (*USP30*)
$(CH_3CO)_2O$—**102.09**

■[*108-24-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Acetone, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-8

Change to read:

Acetone

■*(Propanone; Dimethylformaldehyde),*■1S (*USP30*)
CH_3COCH_3—**58.08**

■[*67-64-1*]■1S (*USP30*)
—Use ACS reagent grade.
[NOTE—For UV spectrophotometric determinations, use ACS reagent grade Acetone Suitable for Use in UV Spectrophotometry.]

BRIEFING

Acetonitrile, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-10

Change to read:

Acetonitrile *(Methyl Cyanide;*

■*Cyanomethane),*■1S (*USP30*)
CH_3CN—**41.05**

■[*75-05-8*]■1S (*USP30*)
—Use ACS reagent grade.

In-Process Revision

BRIEFING

Acetophenone, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-12

Change to read:

Acetophenone

■*(Phenylethanone; Phenyl Methyl Ketone),*■1S (*USP30*)
$CH_3COC_6H_5$—**120.15**

■[*98-86-2*]■1S (*USP30*)
—Liquid. Slightly soluble in water, freely soluble in alcohol and in ether.

Melting range ⟨741⟩: between 19° and 20°.
Refractive index ⟨831⟩: about 1.534 at 20°.
Specific gravity ⟨841⟩: about 1.03.

BRIEFING

***p*-Acetotoluidide,** *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-14

Change to read:

***p*-Acetotoluidide,** $C_9H_{11}NO$—**149.19**

■[*103-89-9*]■1S (*USP30*)
—White to off-white powder.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-μm layer of phase G2; the injection port temperature is maintained at 230°; the detector temperature is maintained at 300°; and the column temperature is maintained at 130° and programmed to rise 10° per minute to 280°. The area of the $C_9H_{11}NO$ peak is not less than 98.5% of the total peak area.

Melting range ⟨741⟩: between 145° and 151°.

BRIEFING

Acetylacetone, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-15

Change to read:

Acetylacetone *(2,4-Pentanedione;*

■*Diacetylmethane),*■1S (*USP30*)
$C_5H_8O_2$—**100.12**

■[*123-54-6*]■1S (*USP30*)
—Clear, colorless to slightly yellow, flammable liquid. Soluble in water; miscible with alcohol, with chloroform, with acetone, with ether, and with glacial acetic acid.

Assay—Not less than 98% of $C_5H_8O_2$, a suitable gas chromatograph equipped with a flame-ionization detector being used and helium being used as the carrier gas. The following conditions have been found suitable: a 3-mm × 1.83-m stainless steel column containing 10% phase G on support S1A; the injection port and detector temperatures are maintained at 250° and 310°, respectively; the column temperature is programmed to rise 8° per minute, from 50° to 220°.

Refractive index ⟨831⟩: between 1.4505 and 1.4525, at 20°.

BRIEFING

Acetyl Chloride, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-17

Change to read:

Acetyl Chloride, CH_3COCl—**78.50**

■[*75-36-5*]■1S (*USP30*)
—Clear, colorless liquid. ▲▲*USP29* Is decomposed by water and by alcohol. Miscible with benzene and with chloroform. Use ACS reagent grade.

Specific gravity ⟨841⟩: about 1.1.

In-Process Revision

BRIEFING

Acetylcholine Chloride, *USP 29* page 3106—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-18

Change to read:

Acetylcholine Chloride

■*(Trimethylethanaminium Chloride; Acecoline),*■1S (*USP30*)
$[CH_3COOCH_2CH_2N(CH_3)_3]Cl$—**181.66**

■[*60-31-1*]■1S (*USP30*)
—White, crystalline ▲*USP29* powder. Very deliquescent; very soluble in water; freely soluble in alcohol.

Melting range ⟨741⟩—When previously dried at 110° in a capillary tube for 1 hour, it melts between 149° and 152°.

Reaction—A solution (1 in 10) is neutral to litmus.

Residue on ignition (Reagent test): negligible, from 200 mg.

Solubility in alcohol—A solution of 500 mg in 5 mL of alcohol is complete and colorless.

Percent of acetyl (CH_3CO)—Weigh accurately about 400 mg, previously dried at 105° for 3 hours, and dissolve in 15 mL of water in a glass-stoppered conical flask. Add 40.0 mL of 0.1 N sodium hydroxide VS, and heat on a steam bath for 30 minutes. Insert the stopper, allow to cool, add phenolphthalein TS, and titrate the excess alkali with 0.1 N sulfuric acid VS. Determine the exact normality of the 0.1 N sodium hydroxide by titrating 40.0 mL after it has been treated in the same manner as in the test. Each mL of 0.1 N sodium hydroxide is equivalent to 4.305 mg of CH_3CO. Between 23.2% and 24.2% is found.

Percent of chlorine (Cl)—Weigh accurately about 400 mg, previously dried at 105° for 3 hours, and dissolve in 50 mL of water in a glass-stoppered, 125-mL flask. Add with agitation 30.0 mL of 0.1 N silver nitrate VS, then add 5 mL of nitric acid and 5 mL of nitrobenzene, shake, add 2 mL of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS: each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of Cl. Between 19.3% and 19.8% of Cl is found.

BRIEFING

Acrylic Acid, *USP 29* page 3107—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43350-20

Change to read:

Acrylic Acid

■*(2-Propenoic Acid; Vinylformic Acid),*■1S (*USP30*)
$C_3H_4O_2$—**72.06**

■[*79-10-7*]■1S (*USP30*)
—Colorless liquid. Miscible with water, with alcohol, and with ether.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩), equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 150°; the detector temperature is maintained at 300°; and the column temperature is maintained at 50° and programmed to rise 10° per minute to 200°. The area of the $C_3H_4O_2$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.419° and 1.423° at 20°.

BRIEFING

Adipic Acid, *USP 29* page 3107—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-1

Change to read:

Adipic Acid

■*(Hexanedioic Acid; 1,4-Butanedicarboxylic Acid),*■1S (*USP30*)
$C_6H_{10}O_4$—**146.14**

■[*124-04-9*]■1S (*USP30*)
—Colorless to white, crystalline powder. Slightly soluble in water and in cyclohexane; soluble in alcohol, in methanol, and in acetone; practically insoluble in benzene and in petroleum benzin.

Assay—Weigh accurately about 0.3 g, and dissolve in 50 mL of alcohol. Add 25 mL of water, mix, and titrate with 0.5 N sodium hydroxide VS to a pH of 9.5. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 36.54 mg of $C_6H_{10}O_4$. Not less than 98% is found.

Melting range ⟨741⟩: between 151° and 155°, but the range between beginning and end of melting does not exceed 2°.

BRIEFING

Alprenolol Hydrochloride, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-2

Change to read:

Alprenolol Hydrochloride, $C_{15}H_{23}NO_2 \cdot HCl$—**285.8**

■[*13707-88-5*]■1S (*USP30*)
—Use a suitable grade.

In-Process Revision

BRIEFING

Alum, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-3

Change to read:

Alum *(Ammonium Alum, Aluminum Ammonium Sulfate),* $AlNH_4(SO_4)_2 \cdot 12H_2O$—**453.33**

■[*7784-26-1*]■1S (*USP30*)
—Large, colorless crystals or crystalline fragments or a white powder. Soluble in 7 parts of water and in about 0.5 part of boiling water; insoluble in alcohol. Use ACS reagent grade.

BRIEFING

Alumina, Activated, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-4

Change to read:

Alumina, Activated

■*(Aluminum Oxide),*■1S (*USP30*)

■[*1344-28-1*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Alumina, Anhydrous, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-5

Change to read:

Alumina, Anhydrous (*Aluminum Oxide; Alumina specially prepared for use in chromatographic analysis*)

■[*1344-28-1*]■1S (*USP30*)
—A white or practically white powder, 80- to 200-mesh. It does not soften, swell, or decompose in water. It is not acid-washed. Store it in well-closed containers.

BRIEFING

Aluminon, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-6

Change to read:

Aluminon *(Aurin Tricarboxylic Acid, [tri]Ammonium Salt),* $C_{22}H_{23}N_3O_9$—**473.43**

■[*569-58-4*]■1S (*USP30*)
—Yellowish-brown, glassy powder. Freely soluble in water. Use ACS reagent grade.

BRIEFING

Aluminum, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-7

Change to read:

Aluminum, Al—**At. Wt. 26.98154**

■[*7429-90-5*]■1S (*USP30*)
—Use ACS reagent grade, which also meets the requirements of the following test.

Arsenic—Place 750 mg in a generator bottle (see *Arsenic in Reagents* under *General Tests for Reagents*), omitting the pledget of cotton. Add 10 mL of water and 10 mL of sodium hydroxide solution (3 in 10), and allow the reaction to proceed for 30 minutes: not more than a barely perceptible stain is produced on the mercuric bromide test paper.

BRIEFING

Aluminum Oxide, Acid-Washed, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-8

Change to read:

Aluminum Oxide, Acid-Washed (*Alumina specially prepared for use in chromatographic analysis*)—

■[*1344-28-1*]■1S (*USP30*)
—White or practically white powder or fine granules. Very hygroscopic. Store in tight containers.

pH of Slurry—The pH of a well-mixed slurry of 5 g in 150 mL of ammonia-free and carbon dioxide-free water, after 10 minutes' standing, is between 3.5 and 4.5.

Loss on ignition—Weigh accurately about 1 g, and ignite, preferably in a muffle furnace at 800° to 825°, to constant weight: it loses not more than 5.0% of its weight.

Silica—Fuse 500 mg with 10 g of potassium bisulfate for 1 hour in a platinum crucible, cool, and dissolve in hot water: not more than a small amount of insoluble matter remains.

Suitability for chromatographic adsorption—Dissolve 50 mg of *o*-nitroaniline in benzene to make 50.0 mL. Dilute 10 mL of the resulting solution with benzene to 100.0 mL, and mix (*Solution A*).

Weigh quickly about 2 (±0.005) g of specimen in a glass-stoppered weighing bottle, and rapidly transfer it to a dry, glass-stoppered test tube. Add 20.0 mL of *Solution A*, insert the stopper, shake vigorously for 3 minutes, and allow to settle.

Pipet 10 mL of the clear supernatant into a 100-mL volumetric flask, dilute with benzene to volume, and mix (*Solution B*).

Determine the absorbances of *Solutions A* and *B* at 395 nm, with a suitable spectrophotometer, using benzene as the blank. Calculate the quantity, in mg, adsorbed per g of test specimen by the formula:

$$[2(1 - A_B / A_A)] / W$$

in which A_A and A_B are the absorbances of *Solutions A* and *B,* respectively; and W is the weight, in g, of the aluminum oxide. Not less than 0.3 mg of *o*-nitroaniline is adsorbed for each g of the aluminum oxide.

BRIEFING

Aluminum Potassium Sulfate, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-9

Change to read:

Aluminum Potassium Sulfate, $AlK(SO_4)_2 \cdot 12H_2O$—**474.39**

■[*10042-67-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Amaranth, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-10

Change to read:

Amaranth, $C_{20}H_{11}N_2Na_3O_{10}S_3$—**604.48**

■[*915-67-3*]■1S (*USP30*)
—A deep brown or dark reddish-brown fine powder. Use a suitable grade.

BRIEFING

Aminoacetic Acid, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-11

Change to read:

Aminoacetic Acid *(Glycine),* NH_2CH_2COOH—**75.07**

■[*56-40-6*]■1S (*USP30*)
—White, crystalline powder. Very soluble in water; slightly soluble in alcohol.

Nitrogen content (Reagent test)—Determine by the Kjeldahl method, using a test specimen previously dried at 105° for 2 hours: between 18.4% and 18.8% of N is found, corresponding to not less than 98.5% of $C_2H_5NO_2$.

Insoluble matter (Reagent test): not more than 1 mg, from 10 g (0.01%).

Residue on ignition (Reagent test): not more than 0.05%.

Chloride (Reagent test)—One g shows not more than 0.1 mg of Cl (0.01%).

Sulfate (Reagent test, *Method I*)—Two g shows not more than 0.1 mg of SO_4 (0.005%).

Heavy metals (Reagent test): 0.001%, 5 mL of 1 N hydrochloric acid being used to acidify the solution of the test specimen.

Iron ⟨241⟩—One g, dissolved in 47 mL of water containing 3 mL of hydrochloric acid, shows not more than 0.01 mg of Fe (0.001%).

BRIEFING

4-Aminoantipyrine, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-12

Change to read:

4-Aminoantipyrine, $C_{11}H_{13}N_3O$—**203.24**

■[*83-07-8*]■1S (*USP30*)
—Light yellow, crystalline powder. A 500-mg portion dissolves completely in 30 mL of water and yields a clear solution.

Melting range ⟨741⟩: between 108° and 110°.

In-Process Revision

BRIEFING

4-Amino-6-chloro-1,3-benzenedisulfonamide, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-13

Change to read:

4-Amino-6-chloro-1,3-benzenedisulfonamide, $C_6H_8ClN_3O_4S_2$—**285.73**

■[*121-30-2*]■1S (*USP30*)
—White ▲▲*USP29* powder. Insoluble in water and in chloroform; soluble in ammonia TS.

Residue on ignition (Reagent test): not more than 2 mg from 2 g (0.1%).

Absorbance—A 1 in 200,000 solution in methanol exhibits absorbance maxima at about 223 nm, 265 nm, and 312 nm. Its absorptivity (see *Spectrophotometry and Light-Scattering* ⟨851⟩) at 265 nm is about 64.0.

BRIEFING

4-Amino-2-chlorobenzoic Acid, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-14

Change to read:

4-Amino-2-chlorobenzoic Acid, $C_6H_3Cl(NH_2)(COOH)$—**171.58**

■[*2457-76-3*]■1S (*USP30*)
—White crystals or white, crystalline powder.

Melting range ⟨741⟩: between 208° and 212°.

BRIEFING

2-Amino-5-chlorobenzophenone, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-15

Change to read:

2-Amino-5-chlorobenzophenone, $C_{13}H_{10}ClNO$—**231.68**

■[*719-59-5*]■1S (*USP30*)
—Use USP 2-Amino-5-chlorobenzophenone RS.

BRIEFING

1-(2-Aminoethyl)piperazine, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-16

Change to read:

1-(2-Aminoethyl)piperazine, $C_6H_{15}N_3$—**129.20**

■[*140-31-8*]■1S (*USP30*)
—Viscous, colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G2. The injection port temperature is maintained at 280°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280° and held there for 10 minutes. The detector temperature is maintained at 300°. The area of the main peak is not less than 97% of the total peak area.

Refractive index ⟨831⟩: between 1.4978 and 1.5010 at 20°.

BRIEFING

Aminoguanidine Bicarbonate, *USP 29* page 3108—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-17

Change to read:

Aminoguanidine Bicarbonate

■*(Aminoguanidine Hydrogen Carbonate),*■1S (*USP30*)
$CH_6N_4 \cdot H_2CO_3$—**136.11.**

■[*2582-30-1*]■1S (*USP30*)
—White powder.

Assay—Dissolve about 34 mg, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 N perchloric acid is equivalent to 13.61 mg of $CH_6N_4 \cdot H_2CO_3$. Not less than 98.5% is found.

Melting point ⟨741⟩: about 170°, with decomposition.

BRIEFING

***N*-Aminohexamethyleneimine,** *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-18

Change to read:

***N*-Aminohexamethyleneimine** *(N-Aminohomopiperidine, 1-Aminohomopiperidine),* $C_6H_{14}N_2$—**114.19**

■[*5906-35-4*]■1S *(USP30)*
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G2. The injection port temperature is maintained at 180°; the column temperature is maintained at 80° and programmed to rise 10° per minute to 230° and then maintained at 230° for 5 minutes. The detector temperature is maintained at 300°. The area of the main peak is not less than 95% of the total peak area.

Refractive index ⟨831⟩: between 1.4840 and 1.4860 at 20°.

BRIEFING

4-Amino-3-hydroxy-1-naphthalenesulfonic Acid, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-19

Change to read:

4-Amino-3-hydroxy-1-naphthalenesulfonic Acid, $C_{10}H_9NO_4S$—**239.25**

■[*116-63-2*]■1S *(USP30)*
—Light purple powder. Use ACS reagent grade.

BRIEFING

***m*-Aminophenol,** *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43352-20

Change to read:

***m*-Aminophenol**

■*(3-Amino-1-Hydroxybenzene),*■1S *(USP30)*
C_6H_7NO—**109.13**

■[*591-27-5*]■1S *(USP30)*
—Cream-colored to pale yellow flakes. Sparingly soluble in cold water; freely soluble in hot water, in alcohol, and in ether.

Assay—Dissolve about 1.5 g, accurately weighed, in about 400 mL of water in a 500-mL volumetric flask, dilute with water to volume, and mix. Transfer 25.0 mL of this solution to an iodine flask, add 50.0 mL of 0.1 N bromine VS, dilute with 50 mL of water, add 5 mL of hydrochloric acid, and immediately insert the stopper in the flask. Shake for 1 minute, allow to stand for 2 minutes, and add 5 mL of potassium iodide TS through the slightly loosened stopper. Shake thoroughly, allow to stand for 5 minutes, remove the stopper, and rinse it and the neck of the flask with 20 mL of water, adding the rinsing to the flask. Titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. From the volume of 0.1 N sodium thiosulfate used, calculate the volume, in mL, of 0.1 N bromine consumed by the test specimen. Each mL of 0.1 N bromine is equivalent to 1.819 mg of C_6H_7NO: not less than 99.5% is found.

Melting range ⟨741⟩: between 121° and 123°.

Loss on drying ⟨731⟩—Dry it over calcium chloride for 4 hours: the loss in weight is negligible.

Residue on ignition (Reagent test): negligible, from 2 g.

BRIEFING

***p*-Aminophenol,** *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-1

Change to read:

***p*-Aminophenol**

■*(p-Hydroxyaniline),*■1S *(USP30)*
C_6H_7NO—**109.13**

■[*123-30-8*]■1S *(USP30)*
—Fine, yellowish, crystalline powder. Slightly soluble in water and in alcohol.

Melting range ⟨741⟩: between 187° and 189°.

BRIEFING

3-Amino-1-propanol, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-3

In-Process Revision

Change to read:

3-Amino-1-propanol, $H_2N(CH_2)_3OH$—**75.11**

■[*156-87-6*]■1S (*USP30*)
—Liquid.
Boiling range (Reagent test): between 184° and 188°.
Refractive index ⟨831⟩: between 1.461 and 1.463 at 20°.

BRIEFING

Ammonia Water, Stronger, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43998-1

Change to read:

Ammonia Water, Stronger *(Ammonium Hydroxide)*—

■[*1336-21-6*]■1S (*USP30*)
—Use ACS reagent grade Ammonium Hydroxide.

BRIEFING

Ammonia Water, 25 Percent, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-6

Change to read:

Ammonia Water, 25 Percent—

■[*1336-21-6*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Ammonium Acetate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-7

Change to read:

Ammonium Acetate, $NH_4C_2H_3O_2$—**77.08**

■[*631-61-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Bisulfate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-8

Change to read:

Ammonium Bisulfate

■*(Ammonium Hydrogen Sulfate),*■1S (*USP30*)
NH_4HSO_4—**115.11**

■[*7803-63-6*]■1S (*USP30*)
—White crystals. Freely soluble in water; practically insoluble in alcohol, in acetone, and in pyridine.

Assay—Dissolve about 300 mg, accurately weighed, in 50 mL of a mixture of water and alcohol (25 : 25). Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 11.51 mg of NH_4HSO_4. Not less than 98% is found.

BRIEFING

Ammonium Bromide, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-9

Change to read:

Ammonium Bromide, NH_4Br—**97.94**

■[*12124-97-9*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Carbonate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-10

Change to read:

Ammonium Carbonate

■*(Hartshorn Salt)*—■1S (*USP30*)

■[*506-87-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Chloride, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-11

Change to read:

Ammonium Chloride

■*(Salmiac),*■1S (*USP30*)
NH_4Cl—**53.49**

■[*12125-02-9*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Citrate, Dibasic, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-12

Change to read:

Ammonium Citrate, Dibasic

■*(Citric Acid Diammonium Salt),*■1S (*USP30*)
$(NH_4)_2HC_6H_5O_7$—**226.18**

■[*3012-65-5*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Fluoride, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-13

Change to read:

Ammonium Fluoride, NH_4F—**37.04**

■[*12125-01-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Hydroxide, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-14

Change to read:

Ammonium Hydroxide

■*(Ammonium aqueous)*—[*1336-21-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Molybdate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-15

Change to read:

Ammonium Molybdate, $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$—**1235.86**

■[*13106-76-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Nitrate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-16

Change to read:

Ammonium Nitrate, NH_4NO_3—**80.04**

■[*6484-52-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Oxalate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-17

Change to read:

Ammonium Oxalate, $(NH_4)_2C_2O_4 \cdot H_2O$—**142.11**

■[*6009-70-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Persulfate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-18

Change to read:

Ammonium Persulfate

■*(Ammonium Peroxydisulfate),*■1S (*USP30*)
$(NH_4)_2S_2O_8$—**228.20**

■[*7727-54-0*]■1S (*USP30*)
—Use ACS reagent grade Ammonium Peroxydisulfate.

BRIEFING

Ammonium Phosphate, Dibasic, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-19

Change to read:

Ammonium Phosphate, Dibasic *(Diammonium Hydrogen Phosphate),* $(NH_4)_2HPO_4$—**132.06**

■[*7783-28-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Phosphate, Monobasic, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43353-20

Change to read:

Ammonium Phosphate, Monobasic *(Ammonium Dihydrogen Phosphate),* $NH_4H_2PO_4$—**115.03**

■[*7722-76-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Reineckate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-1

Change to read:

Ammonium Reineckate *(Reinecke Salt),* $NH_4[Cr(NH_3)_2(SCN)_4] \cdot H_2O$—**354.44**

■[*13573-16-5*]■1S (*USP30*)
—Dark red crystals or red, crystalline powder. Moderately soluble in cold water; more soluble in hot water. Gradually decomposes in solution.

Sensitiveness—Dissolve 50 mg in 10 mL of water. Add 0.2 mL of the solution to 1 mL of a solution of 10 mg of choline chloride in 20 mL of water, and shake gently: a distinct precipitate forms within 5 to 10 seconds.

BRIEFING

Ammonium Sulfamate, *USP 29* page 3109—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-2

Change to read:

Ammonium Sulfamate, $NH_4OSO_2NH_2$—**114.13**

■[*7773-06-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Sulfate, *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-3

Change to read:

Ammonium Sulfate, $(NH_4)_2SO_4$—**132.14**

■[*7783-20-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Thiocyanate, *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-4

Change to read:

Ammonium Thiocyanate

■*(Ammonium Rhodanide),*■1S (*USP30*)
NH_4SCN—**76.12**

■[*1762-95-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ammonium Vanadate, *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-5

Change to read:

Ammonium Vanadate *(Ammonium Metavanadate),* NH_4VO_3—**116.98**

■[*7803-55-6*]■1S (*USP30*)
—White, crystalline powder. Slightly soluble in cold water; soluble in hot water and in dilute ammonia TS.

Assay—Weigh accurately about 500 mg, transfer to a suitable container, add 30 mL of water and 2 mL of dilute sulfuric acid (1 in 4), swirl to dissolve, and pass sulfur dioxide gas through the solution until reduction is complete and the solution is bright blue in color. Boil gently while passing a stream of carbon dioxide through the solution to remove any excess sulfur dioxide, then cool, and titrate with 0.1 N potassium permanganate VS. Each mL of 0.1 N potassium permanganate consumed is equivalent to 11.7 mg of NH_4VO_3. Not less than 98.0% is found.

Solubility in ammonium hydroxide—Dissolve 1 g in a mixture of 3 mL of ammonium hydroxide and 50 mL of warm water: the solution is clear and colorless.

Carbonate—To 500 mg add 1 mL of water and 2 mL of diluted hydrochloric acid: no effervescence is produced.

Chloride—Dissolve 250 mg in 40 mL of hot water, add 2 mL of nitric acid, and allow to stand for 1 hour. Filter, and to the filtrate add 0.5 mL of silver nitrate TS: any turbidity produced does not exceed that of a blank containing 0.5 mg of added Cl (0.2%).

Sulfate—Dissolve 500 mg in 50 mL of hot water, and add 2 mL of diluted hydrochloric acid and 1.5 g of hydroxylamine hydrochloride. Heat at 60° for 3 minutes, filter, cool, and add to the filtrate 2 mL of barium chloride TS: no turbidity or precipitate is produced within 30 minutes.

BRIEFING

Amyl Acetate, *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-6

Change to read:

Amyl Acetate *(Isoamyl Acetate),* $CH_3CO_2C_5H_{11}$—**130.18**

■[*2308-18-1*]■1S (*USP30*)
—Clear, colorless liquid. ▲▲*USP29* Slightly soluble in water. Miscible with alcohol, with amyl alcohol, with benzene, and with ether.

Specific gravity ⟨841⟩: about 0.87.

Boiling range (Reagent test, *Method I*): not less than 90%, between 137° and 142°.

Solubility in diluted alcohol—A 1.0-mL portion dissolves in 20 mL of diluted alcohol to form a clear solution.

Acidity—Add 5.0 mL to 40 mL of neutralized alcohol, and, if the pink color is discharged, titrate with 0.10 N sodium hydroxide: not more than 0.20 mL is required to restore the pink color (about 0.02% as CH_3COOH).

Water—A 5-mL portion gives a clear solution with 5 mL of carbon disulfide.

BRIEFING

Amyl Alcohol, *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-7

Change to read:

Amyl Alcohol *(Isoamyl Alcohol),* $C_5H_{11}OH$—**88.15**

■[*598-75-4*]■1S (*USP30*)
—Use ACS reagent grade Isopentyl Alcohol.

In-Process Revision

BRIEFING

***tert*-Amyl Alcohol,** *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-8

Change to read:

***tert*-Amyl Alcohol,** $C_5H_{12}O$—**88.15**

■[*75-85-4*]■1S (*USP30*)
—Clear, colorless, flammable, volatile liquid. ▲▲*USP29*

Specific gravity ⟨841⟩: about 0.81.

Boiling range (Reagent test): not less than 95%, between 100° and 103°.

Residue on evaporation—Evaporate 50 mL (40 g) on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 1.6 mg (0.004%).

Acids and *esters*—Dilute 20 mL with 20 mL of alcohol, add 5.0 mL of 0.1 N sodium hydroxide VS, and reflux gently for 10 minutes. Cool, add 2 drops of phenolphthalein TS, and titrate the excess sodium hydroxide with 0.1 N hydrochloric acid VS: not more than 0.75 mL of the 0.10 N sodium hydroxide is consumed, correction being made for the amount consumed in a blank (0.06% as amyl acetate).

Aldehydes—Shake 5 mL with 5 mL of potassium hydroxide solution (30 in 100) in a glass-stoppered cylinder for 5 minutes, and allow to separate: no color develops in either layer.

BRIEFING

Aniline, *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-9

Change to read:

Aniline, $C_6H_5NH_2$—**93.13**

■[*62-53-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Aniline Blue, *USP 29* page 3110—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-10

Change to read:

Aniline Blue (*Certified Biological Aniline Blue*)

■[*8004-91-9*]■1S (*USP30*)
—A water-soluble dye consisting of a mixture of the tri-sulfonates of triphenylpararosaniline and of diphenylrosaniline.

BRIEFING

Anisole, *USP 29* page 3111—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-11

Change to read:

Anisole, $CH_3OC_6H_5$—**108.14**

■[*100-66-3*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen (about 0.5 µL) into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, nitrogen being used as the carrier gas. The following conditions have been found suitable: a 30-m capillary column is coated with phase G3; the injection port and detector are maintained at 140° and 300°, respectively; the column temperature is maintained at 70° and programmed to rise 10° per minute to 170°. The area of the anisole peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: 1.5160 at 20°.

BRIEFING

Anthracene, *USP 29* page 3111—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-12

Change to read:

Anthracene, $C_{14}H_{10}$—**178.23**

■[*120-12-7*]■1S (*USP30*)
—White to off-white crystals or platelets. Darkens in sunlight. Insoluble in water; sparingly soluble in alcohol, in benzene, and in chloroform.

Melting range ⟨741⟩: between 215° and 218°.

BRIEFING

Anthrone, *USP 29* page 3111—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-13

Change to read:

Anthrone, $C_{14}H_{10}O$—**194.23**

■[*90-44-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Antimony Pentachloride, *USP 29* page 3111—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-14

Change to read:

Antimony Pentachloride, $SbCl_5$—**299.02**

■[*7647-18-9*]■1S (*USP30*)
—Clear, reddish-yellow, oily, hygroscopic, caustic liquid. Fumes in moist air and solidifies by absorption of one molecule of water. Is decomposed by water, soluble in dilute hydrochloric acid and in chloroform. Boils at about 92° at a pressure of 30 mm of mercury and has a specific gravity of about 2.34 at 25°.

Caution—Antimony pentachloride causes severe burns, and the vapor is hazardous.

Assay (*$SbCl_5$*)—Accurately weigh a glass-stoppered, 125-mL flask, quickly introduce about 0.3 mL of the test specimen, and reweigh. Dissolve with 20 mL of diluted hydrochloric acid (1 in 5), and add 10 mL of potassium iodide solution (1 in 10) and 1 mL of carbon disulfide. Titrate the liberated iodine with 0.1 N sodium thiosulfate VS. The brown color will gradually disappear from the solution, and the last traces of free iodine will be collected in the carbon disulfide, giving a pink color. When this pink color disappears the endpoint has been reached. Each mL of 0.1 N sodium thiosulfate is equivalent to 14.95 mg of $SbCl_5$: not less than 99.0% of $SbCl_5$ is found.

Sulfate (Reagent test, *Method II*)—Dissolve 4.3 mL (10 g) in the minimum volume of hydrochloric acid, dilute with water to 150 mL, neutralize with ammonium hydroxide, and filter. To the filtrate add 2 mL of hydrochloric acid: the solution, 10 mL of barium chloride TS being used, yields not more than 1.3 mg of residue, correction being made for a complete blank test (0.005%).

Arsenic—Add 10 mL of a recently prepared solution of 20 g of stannous chloride in 30 mL of hydrochloric acid to 100 mg of specimen dissolved in 5 mL of hydrochloric acid. Mix, transfer to a color-comparison tube, and allow to stand for 30 minutes. Any color in the solution of the specimen should not be darker than that in a control containing 0.02 mg of arsenic (As), which has been treated in the same manner as the test specimen, when viewed downward over a white surface (0.02% of As).

Iron ⟨241⟩—To the residue from the test for *Substances not precipitated by hydrogen sulfide* add 2 mL of hydrochloric acid and 5 drops of nitric acid, and evaporate on a steam bath to dryness. Take up the residue in 2 mL of hydrochloric acid, and dilute with water to 47 mL: the solution shows not more than 0.01 mg of Fe (0.001%).

Other heavy metals (as Pb)—Dissolve the precipitate on the filter paper from the test for *Substances not precipitated by hydrogen sulfide* with 75 mL of a solution containing 6 g of sodium sulfide and 4 g of sodium hydroxide dissolved in water and diluted with water to 100 mL. Collect the filtrate in the original flask containing the remainder of the sulfide precipitate. Warm the solution to dissolve the soluble sulfides, and allow the insoluble sulfides to settle. Filter, wash thoroughly with hydrogen sulfide TS, and dissolve any precipitate remaining on the filter paper with 10 mL of hot diluted hydrochloric acid. Dilute the filtrate with water to 50 mL. Neutralize a 25-mL portion of this solution with 1 N sodium hydroxide, and add 1 mL of 1 N acetic acid and 10 mL of hydrogen sulfide TS. Any brown color should not exceed that produced by 0.05 mg of lead ion in an equal volume of solution containing 1 mL of 1 N acetic acid and 10 mL of hydrogen sulfide TS (0.005%).

Substances not precipitated by hydrogen sulfide (*as SO_4*)—Dissolve 0.90 mL (2 g) in 5 mL of hydrochloric acid, and dilute with 95 mL of water. Precipitate the antimony completely with hydrogen sulfide, allow the precipitate to settle, and filter, being careful not to transfer much of the precipitate to the filter paper. (Retain the precipitate.) To 50 mL of the filtrate, add 0.5 mL of sulfuric acid, evaporate in a tared porcelain crucible to dryness, and ignite at 800 ± 25° for 15 minutes. (Retain the residue.) The weight of the ignited residue should not be more than 0.0010 g greater than the weight obtained in a complete blank test (0.10%).

BRIEFING

Antimony Trichloride, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-15

Change to read:

Antimony Trichloride (*Antimonous Chloride*), $SbCl_3$—**228.12**

■[*10025-91-9*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Aprobarbital, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-16

Change to read:

Aprobarbital, $C_{10}H_{14}N_2O_3$—**210.23**

■[*77-02-1*]■1S (*USP30*)
—Fine, white crystalline powder. Slightly soluble in cold water; soluble in alcohol, in chloroform, and in ether.

In-Process Revision

Assay—Dissolve about 200 mg, previously dried at 105° for 2 hours and accurately weighed, in 20 mL of dimethylformamide in a 100-mL conical flask. Add 4 drops of thymol blue solution (1 in 200 in methanol), and titrate with 0.1 N lithium methoxide using a 10-mL buret, a magnetic stirrer, and a cover for the flask to protect against atmospheric carbon dioxide. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N lithium methoxide is equivalent to 21.02 mg of $C_{10}H_{14}N_2O_3$. Between 98.5% and 101.0% of $C_{10}H_{14}N_2O_3$ is found.

Melting range ⟨741⟩: between 140° and 143°.

BRIEFING

Arsenazo III Acid, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-18

Change to read:

Arsenazo III Acid, $C_{22}H_{18}As_2N_4O_{14}S_2$—**776.38**

■[*1668-00-4*]■1S (*USP30*)
—Brown powder. Stable in air. Store at room temperature in a dry area.

Melting temperature ⟨741⟩: greater than 320°.

BRIEFING

Arsenic Trioxide, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-19

Change to read:

Arsenic Trioxide, As_2O_3—**197.84**

■[*1327-53-3*]■1S (*USP30*)
—Use ACS reagent grade.

[NOTE—Arsenic Trioxide of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Office of Standard Reference Materials, www.nist.gov, as standard sample No. 83.]

BRIEFING

L-Asparagine, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43354-20

Change to read:

L-Asparagine (*L-2-Aminosuccinamic Acid*), $COOHCH(NH_2)CH_2CONH_2 \cdot H_2O$—**150.13**

■[*70-47-3*]■1S (*USP30*)
—Colorless ▲*USP29* crystals. One g dissolves in 50 mL of water; soluble in acids and in alkalies; insoluble in alcohol and in ether. Its neutral or alkaline solutions are levorotatory; its acid solutions are dextrorotatory.

Specific rotation ⟨781⟩: between +31° and +33°, determined in a solution in diluted hydrochloric acid containing the equivalent of 5 g (on the anhydrous basis, as determined by drying at 105° for 5 hours) in each 100 mL.

Residue on ignition (Reagent test): not more than 0.1%.

Chloride (Reagent test)—One g shows not more than 0.03 mg of Cl (0.003%).

Sulfate (Reagent test, *Method I*)—One g shows not more than 0.05 mg of SO_4 (0.005%).

Heavy metals (Reagent test): 0.002%.

Nitrogen content, *Method II* ⟨461⟩: between 18.4% and 18.8% of N is found.

BRIEFING

Barium Chloride, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43747-1

Change to read:

Barium Chloride, $BaCl_2 \cdot 2H_2O$—**244.26**

■[*10361-37-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Barium Chloride, Anhydrous, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-1

Change to read:

Barium Chloride, Anhydrous, $BaCl_2$—**208.23**

■[*10361-37-2*]■1S (*USP30*)
—This may be made by drying barium chloride in thin layers at 125° until the loss in weight between two successive, 3-hour drying periods does not exceed 1%.

BRIEFING

Barium Hydroxide, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-2

Change to read:

Barium Hydroxide, $Ba(OH)_2 \cdot 8H_2O$—**315.46**

■[*12230-71-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Barium Nitrate, *USP 29* page 3112—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-3

Change to read:

Barium Nitrate, $Ba(NO_3)_2$—**261.34**

■[*10022-31-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Benzaldehyde, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-4

Change to read:

Benzaldehyde, C_7H_6O—**106.12**

■[*100-52-7*]■1S (*USP30*)
—Colorless, strongly refractive liquid. ▲▲*USP29* Soluble in water; miscible with alcohol, with ether, and with fixed and volatile oils.

Assay—Pipet about 1 mL into a tared, glass-stoppered weighing bottle, and weigh accurately. Loosen the stopper, and transfer both the weighing bottle and its contents to a 250-mL conical flask containing 25 mL of a hydro-alcoholic solution of hydroxylamine hydrochloride (prepared by dissolving 34.7 g of hydroxylamine hydrochloride in 160 mL of water, then adding alcohol to make 1000 mL, and neutralizing to bromophenol blue by the addition of sodium hydroxide TS). Using a graduated cylinder to measure the volume, rinse the sides of the flask with an additional 50 mL of this reagent solution. Allow the solution to stand for 10 minutes, add 1 mL of bromophenol blue TS, and titrate the liberated hydrochloric acid with 1 N sodium hydroxide VS. Perform a blank determination with the same quantities of the same reagents, and make any necessary correction. Each mL of 1 N sodium hydroxide consumed is equivalent to 106.1 mg of C_7H_6O. Not less than 98% is found.

Specific gravity ⟨841⟩: between 1.041 and 1.046.

Refractive index ⟨831⟩: between 1.5440 and 1.5465 at 20°.

Hydrocyanic acid—Shake 0.5 mL with 5 mL of water, add 0.5 mL of sodium hydroxide TS and 0.1 mL of ferrous sulfate TS, and warm the mixture gently. Add a slight excess of hydrochloric acid: no greenish-blue color or blue precipitate is observed within 15 minutes.

BRIEFING

Benzamidine Hydrochloride Hydrate, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-5

Change to read:

Benzamidine Hydrochloride Hydrate

■*(Benzenecarboximidamide Monohydrochloride, Hydrate),*■1S (*USP30*)
~~$C_xH_yN_z \cdot HCl$~~

■$C_7H_8N_2 \cdot HCl \cdot xH_2O$■1S (*USP30*)
—**156.6** [~~*1670-14-0*~~]

■[*206752-36-5*]■1S (*USP30*)
—White to off-white powder. Use a suitable grade.
[NOTE—A suitable grade is available from Sigma-Aldrich, www.sigma-aldrich.com.]

In-Process Revision

BRIEFING

Benzanilide, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-6

Change to read:

Benzanilide, $C_{13}H_{11}NO$—**197.23**

■[*93-98-1*]■1S (*USP30*)
—Off-white, light gray to grayish-green powder. Insoluble in water; sparingly soluble in alcohol; slightly soluble in ether.

Melting range ⟨741⟩: between 162° and 165°.

Solubility in acetone—A 1.0-g portion dissolves completely in 50 mL of acetone to yield a clear solution.

BRIEFING

Benzene, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-7

Change to read:

Benzene, C_6H_6—**78.11**

■[*71-43-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Benzenesulfonamide, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-8

Change to read:

Benzenesulfonamide, $C_6H_5SO_2NH_2$—**157.19**

■[*98-10-2*]■1S (*USP30*)
—White to pale beige crystals.

Melting range ⟨741⟩: between 150° and 153°.

BRIEFING

Benzenesulfonyl Chloride, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-9

Change to read:

Benzenesulfonyl Chloride, $C_6H_5SO_2Cl$—**176.62**

■[*98-09-9*]■1S (*USP30*)
—Colorless, oily liquid. Insoluble in cold water; soluble in alcohol and in ether. Solidifies at 0°.

Melting range ⟨741⟩: between 14° and 17°.

Boiling range (Reagent test): between 251° and 252°.

BRIEFING

Benzhydrol, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-10

Change to read:

Benzhydrol (α-*Phenylbenzenemethanol*), $C_{13}H_{12}O$—**184.23**

■[*91-01-0*]■1S (*USP30*)
—White to pale yellow crystals. Very slightly soluble in water; soluble in alcohol, in ether, and in chloroform.

Melting range ⟨741⟩: between 65° and 67°, but the range between beginning and end of melting does not exceed 2°.

BRIEFING

Benzoic Acid, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-11

Change to read:

Benzoic Acid, C_6H_5COOH—**122.12**

■[*65-85-0*]■1S (*USP30*)
—Use ACS reagent grade.

[NOTE—Benzoic Acid of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Office of Standard Reference Materials, www.nist.gov, as standard sample No. 350.]

BRIEFING

Benzophenone, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-12

Change to read:

Benzophenone, $(C_6H_5)_2CO$—**182.22**

■[*119-61-9*]■1S (*USP30*)
—White, crystalline powder.
Melting range ⟨741⟩: between 47° and 49°.

BRIEFING

***p*-Benzoquinone,** *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-13

Change to read:

***p*-Benzoquinone**

■*(Quinone),*■1S (*USP30*)
$C_6H_4O_2$—**108.09**

■[*106-51-4*]■1S (*USP30*)
—Dark yellow powder having a green cast. Slightly soluble in water; soluble in alcohol, in ether, and in fixed alkali solutions. May darken on standing. Darkened material may be purified by sublimation in vacuum.
Melting range ⟨741⟩: between 113° and 115°.

BRIEFING

3-Benzoylbenzoic Acid, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-14

Change to read:

3-Benzoylbenzoic Acid, $C_{14}H_{10}O_3$—**226.23**

■[*579-18-0*]■1S (*USP30*)
—White to off-white powder.
Assay—Prepare a mixture of 1% trifluoroacetic acid in water and 1% trifluoroacetic acid in acetonitrile (55 : 45) for the mobile phase. Inject about 20 µL into a suitable liquid chromatograph (see *Chromatography* ⟨621⟩) equipped with a 230-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The area of the $C_{14}H_{10}O_3$ peak is not less than 98.5% of the total peak area.

BRIEFING

Benzoyl Chloride, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-15

Change to read:

Benzoyl Chloride, C_6H_5COCl—**140.57**

■[*98-88-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Benzoylformic Acid, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-16

Change to read:

Benzoylformic Acid *(Phenylglyoxylic Acid),* $C_6H_5COCO_2H$—**150.14**

■[*611-73-4*]■1S (*USP30*)
—Powder. Soluble in methanol.
Melting range ⟨741⟩: between 62° and 67°.

BRIEFING

Benzphetamine Hydrochloride, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-17

Change to read:

Benzphetamine Hydrochloride, $C_{17}H_{21}N \cdot HCl$—**275.82**

■[*5411-22-3*]■1S (*USP30*)
—White to off-white, ▲*USP29* crystalline powder. Freely soluble in water, in alcohol, and in chloroform; slightly soluble in ether.
Assay—Dissolve about 500 mg, accurately weighed, in a mixture of 50 mL of glacial acetic acid and 10 mL of mercuric acetate TS, add 1 drop of crystal violet TS, and titrate with 0.1 N perchloric acid VS to

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a blue-green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 27.58 mg of $C_{17}H_{21}N \cdot HCl$. Between 98.0% and 101.0%, calculated on the dried basis, is found.

Melting range ⟨741⟩: between 152° and 158°.

Specific rotation ⟨781⟩: between +22° and +26°, determined in a solution containing 200 mg in 10 mL, the specimen having been previously dried in vacuum at 60° for 3 hours.

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 3 hours: it loses not more than 1% of its weight.

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

BRIEFING

2-Benzylaminopyridine, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-18

Change to read:

2-Benzylaminopyridine, $C_{12}H_{12}N_2$—**184.24**

■[*6935-27-9*]■1S *(USP30)*
—Use a suitable grade.

BRIEFING

1-Benzylimidazole, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-19

Change to read:

1-Benzylimidazole, $C_{10}H_{10}N_2$—**158.20**

■[*4238-71-5*]■1S *(USP30)*
—White crystals.

Assay—Transfer about 40 mg, accurately weighed, to a 100-mL beaker. Dissolve in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically using a combination calomel-platinum electrode. Perform a blank determination and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 15.82 mg of $C_{10}H_{10}N_2$. Not less than 99% is found.

BRIEFING

Benzyltrimethylammonium Chloride, *USP 29* page 3113—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43362-20

Change to read:

Benzyltrimethylammonium Chloride, $C_6H_5CH_2N(CH_3)_3Cl$—**185.69**

■[*56-93-9*]■1S *(USP30)*
—Available as a 60% aqueous solution. Is clear and is colorless or not more than slightly yellow. ▲▲*USP29*

Assay—Pipet 2 mL into a 50-mL volumetric flask, and add water to volume. Pipet 20 mL of the solution into a 125-mL conical flask, add about 30 mL of water, then add 0.25 mL of dichlorofluorescein TS, and titrate with 0.1 N silver nitrate VS. Each mL of 0.1 N silver nitrate is equivalent to 18.57 mg of $C_6H_5CH_2N(CH_3)_3Cl$. Between 59.5% and 60.5% is found.

BRIEFING

Bibenzyl, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-1

Change to read:

Bibenzyl *(Dibenzyl),* $C_{14}H_{14}$—**182.26**

■[*103-29-7*]■1S *(USP30)*
—Colorless crystals. Freely soluble in chloroform and in ether; sparingly soluble in alcohol; practically insoluble in water.

Melting range ⟨741⟩: between 53° and 55°.

BRIEFING

Biphenyl, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-2

Change to read:

Biphenyl, $C_{12}H_{10}$—**154.21**

■[*92-52-4*]■1S *(USP30)*
—Colorless to white crystals or crystalline powder. ▲▲*USP29* Insoluble in water; soluble in alcohol and in ether. Boils at about 254°.

Melting range ⟨741⟩ : between 68° and 72°.

BRIEFING

2,2′-Bipyridine, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-3

Change to read:

2,2′-Bipyridine (α,α′-*Dipyridyl*), $C_{10}H_8N_2$—**156.18**

■[*366-18-7*]■1S (*USP30*)
—White or pink, crystalline powder. Soluble in water and in alcohol. Melts at about 69°, and boils at about 272°.

Sensitiveness—Prepare the following solutions: (*A*)—Dissolve 350 mg of ferrous ammonium sulfate in 50 mL of water containing 1 mL of sulfuric acid, and add 500 mg of hydrazine sulfate, then add water to make 500 mL. For use, dilute this solution with water in the ratio of 1 in 100 mL. (*B*)—Dissolve 8.3 g of sodium acetate and 12 mL of glacial acetic acid in water to make 100 mL. Add 1 mL of a solution of the specimen (1 in 1000) to a mixture of 10 mL of water and 1 mL of each of solutions *A* and *B:* a pink color results immediately.

Solubility—A 100-mg portion dissolves completely in 10 mL of water.

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

BRIEFING

4,4′-Bis(4-amino-1-naphthylazo)-2,2′-stilbenedisulfonic Acid, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-4

Change to read:

4,4′-Bis(4-amino-1-naphthylazo)-2,2′-stilbenedisulfonic Acid, $C_{34}H_{26}N_6O_6S_2$—**678.74**

■[*5463-64-9*]■1S (*USP30*)
—Use a suitable grade.

[NOTE—A suitable grade is available from TCI America, www.tciamerica.com.]

BRIEFING

Bis(2-ethylhexyl) Maleate, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-5

Change to read:

Bis(2-ethylhexyl) Maleate, $C_{20}H_{36}O_4$—**340.50**

■[*142-16-5*]■1S (*USP30*)
—Colorless to pale yellow, clear liquid. Miscible with acetone and with alcohol. Specific gravity about 0.945.

Assay—Place about 2.5 g, accurately weighed, in a 250-mL flask, add 50.0 mL of 0.5 N alcoholic potassium hydroxide VS, and reflux for 45 minutes. Cool, add 0.5 mL of phenolphthalein TS, and titrate the excess alkali with 0.5 N hydrochloric acid VS. Perform a blank determination at the same time, using the same amount of 0.5 N alcoholic potassium hydroxide (see *Residual Titrations* under *Titrimetry* ⟨541⟩). The difference, in mL, between the volumes of 0.5 N hydrochloric acid consumed in the test titration and blank titration, multiplied by 85.1, represents the quantity, in mg, of bis(2-ethylhexyl) maleate in the portion taken. Not less than 97% is found.

BRIEFING

Bis(2-ethylhexyl) Phthalate, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-6

Change to read:

Bis(2-ethylhexyl) Phthalate, C_6H_4-1,2-[$COOCH_2(C_2H_5)CH(CH_2)_3CH_3]_2$—**390.56**

■[*117-81-7*]■1S (*USP30*)
—Colorless to light yellow liquid.

Refractive index ⟨831⟩: between 1.4855 and 1.4875, at 20°.

BRIEFING

Bis(2-ethylhexyl) Sebacate, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-7

Change to read:

Bis(2-ethylhexyl) Sebacate *(Dioctyl Sebacate),* $C_8H_{17}OOC(CH_2)_8COOC_8H_{17}$—**426.67**

■[*122-62-3*]■1S (*USP30*)
—Pale straw-colored liquid. Insoluble in water. Refractive index about 1.448. Suitable for use in gas chromatography.

Specific gravity, 20°/20° ⟨841⟩: between 0.913 and 0.917.

Boiling range: between 243° and 248° at 5 mm of mercury.

[NOTE—A suitable grade is "Dioctyl Sebacate," available from Sigma-Aldrich, www.sigma-aldrich.com.]

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BRIEFING

Bis(2-ethylhexyl)phosphoric Acid, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-8

Change to read:

Bis(2-ethylhexyl)phosphoric Acid [*Bis*(*2-ethylhexyl*) *Phosphate*], $[CH_3(CH_2)_3CH(C_2H_5)CH_2]_2HPO_4$—**322.42**

■[*298-07-7*]■1S (*USP30*)
—Light yellow, viscous liquid. Insoluble in water; freely soluble in chloroform and in ethyl acetate. Refractive index: about 1.443. Specific gravity: about 0.997.

Assay—Dissolve about 250 mg, accurately weighed, in 50 mL of dimethylformamide, add 3 drops of a 1 in 100 solution of thymol blue in dimethylformamide, and titrate with 0.1 N sodium methoxide VS to a blue endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium methoxide is equivalent to 32.24 mg of $(C_8H_{17})_2HPO_4$. Between 95% and 105% is found.

Solubility—One volume dissolves in 9 volumes of chloroform to yield a clear solution, and 1 volume dissolves in 9 volumes of ethyl acetate to yield a clear solution.

Color—A 1 in 100 solution in chloroform exhibits an absorptivity of not more than 0.03 at 420 nm.

BRIEFING

Bis(trimethylsilyl)acetamide, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-9

Change to read:

Bis(trimethylsilyl)acetamide *(N,O-Bis*(*trimethylsilyl*)*acetamide; BSA),* $CH_3CON[Si(CH_3)_3]_2$—**203.43**

■[*10416-59-8*]■1S (*USP30*)
—Clear, colorless liquid. Readily hydrolyzes when exposed to moist air. Handle under nitrogen, and store in a cool place.

Assay—Not less than 90% of $CH_3CON[Si(CH_3)_3]_2$, a suitable gas chromatograph equipped with a thermal conductivity detector being used. The following conditions are suitable and provide a retention time of approximately 15 minutes.

COLUMN: 3-mm × 1.83-m stainless steel containing 5% phase G1 on support S1A.

INJECTION TEMPERATURE: 160°.

COLUMN TEMPERATURE: 90°, programmed to rise 4° per minute to 160°.

CARRIER GAS: Helium.

Refractive index ⟨831⟩: between 1.4150 and 1.4170 at 20°.

BRIEFING

Bis(trimethylsilyl)trifluoroacetamide, *USP 29* page 3114—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-10

Change to read:

Bis(trimethylsilyl)trifluoroacetamide (*N,O-Bis(trimethylsilyl)trifluoroacetamide; BSTFA*), $CF_3CON[Si(CH_3)_3]_2$—**257.40**

■[*25561-30-2*]■1S (*USP30*)
—Clear, colorless liquid. Readily hydrolyzes when exposed to moist air. Store in a cool place.

Assay—Not less than 98% of $CF_3CON[Si(CH_3)_3]_2$, a suitable gas chromatograph equipped with a thermal conductivity detector being used. The following conditions are suitable and provide a retention time of approximately 15 minutes.

COLUMN: 3-mm × 1.83-m stainless steel containing 5% phase G1 on support S1A.

INJECTION TEMPERATURE: 170°.

COLUMN TEMPERATURE: 70°, programmed to rise 4° per minute to 140°.

CARRIER GAS: Helium.

Refractive index ⟨831⟩: between 1.3820 and 1.3860 at 20°.

BRIEFING

Bis(trimethylsilyl)trifluoroacetamide with Trimethylchlorosilane, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-11

Change to read:

Bis(trimethylsilyl)trifluoroacetamide with Trimethylchlorosilane

■[*25561-30-2*]■1S (*USP30*)
—Use a suitable grade.

[NOTE—A suitable grade is available from Sigma-Aldrich, www.sigma-aldrich.com.]

BRIEFING

Blue Tetrazolium, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-12

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Change to read:

Blue Tetrazolium (*3,3′-(3,3′-Dimethoxy[1,1′-biphenyl]-4,4′-diyl)-bis[2,5-diphenyl-2H-tetrazolium]dichloride*), $C_{40}H_{32}Cl_2N_8O_2$—**727.64**

■[*1871-22-3*]■1S (*USP30*)
—Lemon-yellow crystals. Slightly soluble in water; freely soluble in chloroform and in methanol; insoluble in acetone and in ether.

Solubility in methanol—Dissolve 1 g in 100 mL of methanol: complete solution results, and the solution is clear.

Color—Transfer a portion of the methanol solution obtained in the preceding test to a 1-cm cell, and determine its absorbance at 525 nm, against water as the blank: the absorbance does not exceed 0.20.

Molar absorptivity ⟨851⟩—Its molar absorptivity in methanol, at 252 nm, is not less than 50,000.

Suitability test—

STANDARD PREPARATION—Dissolve in alcohol a suitable quantity of USP Hydrocortisone RS, previously dried at 105° for 3 hours and accurately weighed, and prepare by stepwise dilution a solution containing about 10 µg per mL.

PROCEDURE—Pipet 10-, 15-, and 20-mL portions of *Standard preparation* into separate, glass-stoppered, 50-mL conical flasks. Add 10 mL and 5 mL, respectively, of alcohol to the flasks containing the 10- and 15-mL portions of *Standard preparation,* and swirl to mix. To each of the flasks, and to a fourth flask containing 20 mL of alcohol, add 2.0 mL of a solution prepared by dissolving 50 mg of blue tetrazolium in 10 mL of alcohol, mix, and then add 2.0 mL of a solution prepared by diluting 1 mL of tetramethylammonium hydroxide TS with alcohol to 10 mL. Mix, allow the flasks to stand in the dark for 90 minutes, and determine the absorbances of the three solutions of the steroid standard at 525 nm, with a suitable spectrophotometer, using the solution in the fourth flask as the blank. Plot the absorbances on the abscissa and the amount of hydrocortisone on the ordinate scale of arithmetic coordinate paper, and draw the curve of best fit: the absorbance of each solution is proportional to the concentration, and the absorbance of the solution containing 200 µg of hydrocortisone is not less than 0.50.

BRIEFING

Boric Acid, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-13

Change to read:

Boric Acid, H_3BO_3—**61.83**

■[*10043-35-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Boron Trifluoride, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-14

Change to read:

Boron Trifluoride, BF_3—**67.81**

■[*7637-07-2*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

14% Boron Trifluoride–Methanol, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-15

Change to read:

14% Boron Trifluoride–Methanol

■[*373-57-9*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Brilliant Green, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-16

Change to read:

Brilliant Green *(Malachite Green G),* $C_{27}H_{34}N_2O_4S$—**482.64**

■[*3051-11-4*]■1S (*USP30*)
—Glistening, golden-yellow crystals. Soluble in water and in alcohol. Absorption maximum: 623 nm.

In-Process Revision

BRIEFING

Bromine, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-17

Change to read:

Bromine, Br—**At. Wt. 79.904**

■[*7726-95-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

***p*-Bromoaniline,** *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-18

Change to read:

***p*-Bromoaniline,** C_6H_6BrN—**172.02**

■[*106-40-1*]■1S (*USP30*)
—White to off-white crystals. Insoluble in water; soluble in alcohol and in ether.

Assay—Transfer about 650 mg, accurately weighed, to a suitable container, and dissolve in 50 mL of glacial acetic acid TS. Add crystal violet TS, and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 17.20 mg of C_6H_6BrN. Not less than 98% is found.

Melting range ⟨741⟩: between 60° and 65°, within a 2° range.

BRIEFING

***N*-Bromosuccinimide,** *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-19

Change to read:

***N*-Bromosuccinimide,** $C_4H_4BrNO_2$—**177.98**

■[*128-08-5*]■1S (*USP30*)
—White to off-white crystals or powder. ▲▲*USP29* Freely soluble in water, in acetone, and in glacial acetic acid. *[Caution—Highly irritating to eyes, skin, and mucous membranes.]*

Assay—Transfer 200 mg, accurately weighed, to a conical flask, add 25 mL of 0.5 N alcoholic potassium hydroxide, cover with a watch glass, heat to boiling, and boil for 5 minutes. Cool, transfer the solution to a beaker, rinsing the flask with water until the total volume of solution plus rinsings is about 100 mL, and add 10 mL of glacial acetic acid. Insert suitable electrodes, and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Each mL of 0.1 N silver nitrate is equivalent to 17.80 mg of $C_4H_4BrNO_2$. Not less than 98% is found.

BRIEFING

Brucine Sulfate, *USP 29* page 3115—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43363-20

Change to read:

Brucine Sulfate, $(C_{23}H_{26}N_2O_4)_2 \cdot H_2SO_4 \cdot 7H_2O$—**1013.11**

■[*5787-00-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

1,3-Butanediol, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-2

Change to read:

1,3-Butanediol *(1,3-Butylene Glycol),* $C_4H_{10}O_2$—**90.12**

■[*107-88-0*]■1S (*USP30*)
—Viscous, colorless liquid. Very hygroscopic. Soluble in water, in alcohol, in acetone, and in methyl ethyl ketone; practically insoluble in aliphatic hydrocarbons, in benzene, and in toluene.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 3-mm × 1.8-m stainless steel column containing 20% phase G16 on support S1A; the injection port temperature is maintained at 265°; the column temperature is maintained at 150° and programmed to rise 8° per minute to 210°. The area of the butanediol peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: between 1.4390 and 1.4410 at 20°.

BRIEFING

2,3-Butanedione, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-3

Change to read:

2,3-Butanedione *(Diacetyl),* $CH_3COCOCH_3$—**86.09**

■[*431-03-8*]■1S (*USP30*)
—Bright yellow to yellowish-green liquid. ▲▲*USP29* Soluble in water. Miscible with alcohol and with ether. Boils at about 88°.

Assay—

HYDROXYLAMINE HYDROCHLORIDE SOLUTION—Dissolve 20 g of hydroxylamine hydrochloride in 40 mL of water, and dilute with alcohol to 400 mL. Add, with stirring, 300 mL of 0.5 N alcoholic potassium hydroxide, and filter. Discard after 2 days.

PROCEDURE—Transfer about 1 g, accurately weighed, to a glass-stoppered, 250-mL flask, add 75.0 mL of *Hydroxylamine hydrochloride solution,* and insert the stopper in the flask. Reflux the mixture for 1 hour, then cool to room temperature. Add bromophenol blue TS, and titrate with 0.5 N hydrochloric acid VS to a greenish-yellow endpoint. [NOTE—Alternatively, the solution may be titrated potentiometrically to a pH of 3.4.] Perform a blank test with the same quantities of reagent used for the test specimen, and make any necessary correction. Each mL of 0.5 N hydrochloric acid is equivalent to 43.05 mg of $CH_3COCOCH_3$. Not less than 97% of $CH_3COCOCH_3$ is found.

Congealing temperature ⟨651⟩: between –2.0° and –5.5°.

Refractive index ⟨831⟩: between 1.3935 and 1.3965, at 20°.

Specific gravity ⟨841⟩: about 0.98.

BRIEFING

Butyl Acetate, Normal, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-4

Change to read:

Butyl Acetate, Normal, $CH_3COO(CH_2)_3CH_3$—**116.16**

■[*123-86-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Butyl Alcohol, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-5

Change to read:

Butyl Alcohol *(1-Butanol; Normal Butyl Alcohol),* $CH_3(CH_2)_2CH_2OH$—**74.12**

■[*71-36-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Butyl Alcohol, Secondary, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-6

Change to read:

Butyl Alcohol, Secondary (*2-Butanol*), $CH_3CH_2CH(OH)CH_3$—**74.12**

■[*78-92-2*]■1S (*USP30*)
—Use ACS reagent grade Isobutyl Alcohol.

BRIEFING

Butyl Alcohol, Tertiary, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-7

Change to read:

Butyl Alcohol, Tertiary, $(CH_3)_3COH$—**74.12—**

■[*75-65-0*]■1S (*USP30*)
Use ACS reagent grade *tert*-Butyl Alcohol.

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BRIEFING

Butyl Benzoate, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-8

Change to read:

Butyl Benzoate, $C_{11}H_{14}O_2$—**178.23**

■[*136-60-7*]■1S (*USP30*)
—Thick, oily, colorless to pale yellow liquid. Practically insoluble in water; soluble in alcohol and in ether.

Assay—When examined by gas-liquid chromatography, it shows a purity of not less than 98%. The following conditions have been found suitable for assaying it: use a 3-mm × 1.8-m stainless steel column packed with liquid phase G4 on support S1A. Helium is the carrier gas, the injection port temperature is maintained at 180°, the column temperature is maintained at 190°, and the flame-ionization detector is maintained at 280°. The retention time is about 15 minutes.

Refractive index ⟨831⟩: between 1.4980 and 1.5000, at 20°.

BRIEFING

Butyl Ether, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-9

Change to read:

Butyl Ether *(n-Dibutyl Ether),* $C_8H_{18}O$—**130.23**

■[*142-96-1*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

***n*-Butyl Chloride,** *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-10

Change to read:

***n*-Butyl Chloride** *(1-Chlorobutane),* C_4H_9Cl—**92.57**

■[*109-69-3*]■1S (*USP30*)
—Clear, colorless, volatile liquid. ▲▲*USP29 [Caution—Highly flammable.]* Practically insoluble in water. Miscible with alcohol and with ether.

Assay—When examined by gas–liquid chromatography, it shows a purity of not less than 98%. The following conditions have been found suitable for assaying the article: a 3-mm × 1.8-m stainless steel column packed with phase G16 on support S1. Helium, flowing at a rate of about 40 mL per minute, is the carrier gas, the detector temperature is about 310°, the injection port temperature is about 230°, and the column temperature is programmed to rise at 10° per minute from 35° to 150°. A flame-ionization detector is employed.

Boiling range ⟨721⟩: between 76° and 80°, within a 2° range.

Refractive index ⟨831⟩: between 1.4015 and 1.4035 at 20°.

Acidity—Add phenolphthalein TS to 75 mL, and titrate with 0.1 N potassium hydroxide in methanol to a faint pink color that persists, with shaking, for 1.5 seconds: not more than 0.91 mL is required (about 0.005% as HCl).

Water ⟨921⟩: not more than 0.02%, determined by the *Titrimetric Method*.

Residue after evaporation—Evaporate about 60 mL (50 g), accurately weighed, in a tared platinum dish on a steam bath, and dry at 105° for 1 hour: not more than 0.005% is found.

BRIEFING

***tert*-Butyl Methyl Ether,** *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-11

Change to read:

***tert*-Butyl Methyl Ether,** $C_5H_{12}O$—**88.15**

■[*1634-04-4*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 100°; the detector temperature is maintained at 300°; and the column temperature is maintained at ambient temperature and programmed to rise 10° per minute to 150°. The area of the $C_5H_{12}O$ peak is not less than 99.8% of the total peak area.

Refractive index ⟨831⟩: between 1.367 and 1.371 at 20°.

BRIEFING

***n*-Butylamine,** *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-12

Change to read:

***n*-Butylamine,** $CH_3CH_2CH_2CH_2NH_2$—**73.14**

■[*109-73-9*]■1S (*USP30*)
—Colorless to pale yellow, flammable liquid. Miscible with water, with alcohol, and with ether. Store it in tight containers. Specific gravity: about 0.740.

Distilling range, Method I ⟨721⟩—Not less than 95% distils between 76° and 78°.

Water, Method I ⟨921⟩: not more than 1.0%, determined by the *Titrimetric Method*.

Chloride (Reagent test)—One g (1.5 mL) shows not more than 0.01 mg of Cl (0.001%).

Acidic impurities—To 50 mL add 5 drops of a saturated solution of azo violet in benzene, and titrate quickly with 0.1 N sodium methoxide VS to a deep blue endpoint, observing precautions to prevent absorption of atmospheric carbon dioxide as by use of an atmosphere of nitrogen: not more than 1.0 mL of 0.1 N sodium methoxide is required for neutralization.

BRIEFING

***tert*-Butylamine,** *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-13

Change to read:

***tert*-Butylamine,** $C_3H_9CNH_2$—**73.14**

■[*75-64-9*]■1S (*USP30*)
—Liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 230°; the detector temperature is maintained at 300°; the column temperature is maintained at 130° and programmed to rise 10° per minute to 280°. The area of the $C_3H_9CNH_2$ peak is not less than 99.5% of the total peak area.

Refractive index ⟨831⟩: between 1.3770 and 1.3790 at 20°.

BRIEFING

4-*tert*-Butylphenol, *USP 29* page 3116—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-15

Change to read:

4-*tert*-Butylphenol, $C_{10}H_{14}O$—**150.22**

■[*98-54-4*]■1S (*USP30*)
—White, crystalline flakes or needles. Practically insoluble in water; soluble in alcohol and in ether.

Melting range ⟨741⟩: between 98° and 101°.

BRIEFING

Butyraldehyde. It is proposed to add this new reagent used in the test for *Free vinyl acetate* under *Polyvinyl Acetate,* a new monograph also being proposed in this issue of *PF*.

(HDQ: M. Marques) RTS—44074-1

Add the following:

■**Butyraldehyde** *(Butanal),* C_4H_8O—**72.11** [*123-72-8*]—Use a suitable grade, purified by redistillation, with a content of not less than 99.5%.■1S (*USP30*)

BRIEFING

Butyric Acid, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-16

Change to read:

Butyric Acid, $C_4H_8O_2$—**88.11**

■[*107-92-6*]■1S (*USP30*)
—Clear, colorless to faint yellow liquid. Miscible with water and with methanol.

Assay—Weigh accurately about 500 mg, transfer to a suitable container, add 30 mL of water, and mix. Add 40 mL of water, and mix. Add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Each mL of 0.1 N sodium hydroxide is equivalent to 8.81 mg of $C_4H_8O_2$: not less than 99.0% of $C_4H_8O_2$ is found.

Refractive index ⟨831⟩: about 1.398 at 20°.

In-Process Revision

BRIEFING

Butyrolactone, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-17

Change to read:

Butyrolactone *(Dihydro-2-(3H)-furanone, γ-butyrolactone)*—**86.1**

■[*96-48-0*]■1S *(USP30)*
—Clear, colorless to practically colorless, oily liquid. Miscible with water. Soluble in methanol and in ether.

Boiling range ⟨721⟩: between 193° and 208°.

Refractive index ⟨831⟩: about 1.435, at 20°.

Specific gravity ⟨841⟩: between 1.128 and 1.135.

BRIEFING

Cadmium Acetate, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-18

Change to read:

Cadmium Acetate, $C_4H_6CdO_4 \cdot 2H_2O$—**266.53**

■[*543-90-8*]■1S *(USP30)*
—Colorless, transparent to translucent crystals. ▲▲*USP29* Freely soluble in water; soluble in alcohol.

Insoluble matter (Reagent test): not more than 1 mg, from 20 g (0.005%).

Chloride (Reagent test)—One g shows not more than 0.01 mg of Cl (0.001%).

Sulfate (Reagent test, *Method II*)—Dissolve 10 g in 100 mL of water, add 1 mL of hydrochloric acid, and filter: the residue weighs not more than 1.2 mg more than the residue obtained in a complete blank test (0.005%).

Substances not precipitated by hydrogen sulfide—Dissolve 2 g in a mixture of 135 mL of water and 15 mL of 1 N sulfuric acid, heat to boiling, and pass a rapid stream of hydrogen sulfide through the solution as it cools. Filter, and to 75 mL of the clear filtrate add 0.25 mL of sulfuric acid, then evaporate to dryness, and ignite gently: the residue weighs not more than 1 mg (0.1%).

BRIEFING

Cadmium Nitrate, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-19

Change to read:

Cadmium Nitrate, $Cd(NO_3)_2 \cdot 4H_2O$—**308.48**

■[*10325-94-7*]■1S *(USP30)*
—Colorless, hygroscopic crystals. Very soluble in water; soluble in alcohol.

Insoluble matter (Reagent test): not more than 1 mg, from 20 g (0.005%).

Chloride (*Cl*) (Reagent test)—One g shows not more than 0.01 mg of Cl (0.001%).

Sulfate (Reagent test, *Method II*)—Evaporate a mixture of 12 g of specimen and 25 mL of hydrochloric acid on a steam bath to dryness. Add another 15 mL of hydrochloric acid, and again evaporate to dryness. Dissolve the residue in 100 mL of water, filter, and add 1 mL of hydrochloric acid: the residue weighs not more than 1.0 mg more than the residue obtained in a blank test (0.003%).

Copper (*Cu*)—Dissolve 0.5 g in 10 mL of water, add 10 mL of *Ammonium Citrate Solution* (see *Lead* ⟨251⟩), and adjust the reaction to a pH of about 9 by the addition of 1 N ammonium hydroxide (about 30 mL). Add 1 mL of sodium diethyldithiocarbamate solution (1 in 1000), and mix. Add 5 mL of amyl alcohol, shake for about 1 minute, and allow the layers to separate: any yellow color in the amyl alcohol layer is not darker than that of a blank to which 0.01 mg of Cu has been added (0.002%).

Iron (*Fe*)—Dissolve 1 g in 15 mL of water, add 2 mL of hydrochloric acid, and boil for 2 minutes. Cool, and add about 30 mg of ammonium persulfate and 15 mL of a solution of potassium thiocyanate in normal butyl alcohol (made by dissolving 10 g of potassium thiocyanate in 10 mL of water, warming the solution to about 30°, diluting with normal butyl alcohol to 100 mL, and shaking until clear). Shake vigorously for 30 seconds, and allow the layers to separate: any red color in the clear alcoholic layer is not darker than that of a blank to which 0.01 mg of Fe has been added (0.001%).

Lead (*Pb*)—Dissolve 1.0 g in 10 mL of water, add 0.2 mL of glacial acetic acid, and filter if necessary. To a 7-mL portion of water add 0.2 mL of glacial acetic acid and 3 mL of *Standard Lead Solution* (see *Lead* ⟨251⟩), and mix, to provide a blank. Then add to each solution 1.0 mL of potassium chromate solution (1 in 10), and mix: after 5 minutes, the test solution is not more turbid than the blank (0.003%).

Substances not precipitated by hydrogen sulfide—Dissolve 2 g in 145 mL of water, add 5 mL of sulfuric acid (1 in 10), heat to boiling, and pass a rapid stream of hydrogen sulfide through the solution as it cools. Filter, and to 75 mL of the clear filtrate add 0.25 mL of sulfuric acid, then evaporate to dryness, and ignite gently: the residue weighs not more than 1 mg (0.1%).

BRIEFING

Calcium Acetate, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43364-20

Change to read:

Calcium Acetate, $Ca(C_2H_3O_2)_2 \cdot H_2O$—**176.18**

■[*62-54-4*]■1S (*USP30*)
—White, crystalline granules or powder. Soluble in about 3 parts of water; slightly soluble in alcohol. Use ACS reagent grade.

BRIEFING

Calcium Carbonate, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-1

Change to read:

Calcium Carbonate, $CaCO_3$—**100.09**

■[*471-34-1*]■1S (*USP30*)
—Use ACS reagent grade.
[NOTE—Calcium Carbonate of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Office of Standard Reference Materials, www.nist.gov, as standard sample No. 915.]

BRIEFING

Calcium Carbonate, Chelometric Standard, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-2

Change to read:

Calcium Carbonate, Chelometric Standard, $CaCO_3$—**100.09**

■[*471-34-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Calcium Chloride, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-3

Change to read:

Calcium Chloride, $CaCl_2 \cdot 2H_2O$—**147.01**

■[*10043-52-4*]■1S (*USP30*)
—Use ACS reagent grade Calcium Chloride Dihydrate.

BRIEFING

Calcium Chloride, Anhydrous, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-4

Change to read:

Calcium Chloride, Anhydrous *(for drying),* $CaCl_2$—**110.98**

■[*10043-52-4*]■1S (*USP30*)
—Use ACS reagent grade Calcium Chloride Desiccant.

BRIEFING

Calcium Citrate, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-5

Change to read:

Calcium Citrate, $Ca_3(C_6H_5O_7)_2 \cdot 4H_2O$—**570.49**

■[*813-94-5*]■1S (*USP30*)
—A white, ▲▲*USP29* crystalline powder. Slightly soluble in water; freely soluble in 3 N hydrochloric acid and in 2 N nitric acid; insoluble in alcohol. To 15 mL of hot 2 N sulfuric acid add in small portions and with stirring about 500 mg of calcium citrate. Boil the mixture for 5 minutes, and filter while hot: the cooled filtrate responds to the identification test for *Citrate* ⟨191⟩.

Assay—Accurately weigh about 400 mg of the salt, previously dried at 150° to constant weight, and transfer to a 250-mL beaker. Dissolve the test specimen in 150 mL of water containing 2 mL of 3 N hydrochloric acid, add 15 mL of 1 N sodium hydroxide and 250 mg of hydroxy naphthol blue, and titrate with 0.05 M edetate disodium VS until the solution turns deep blue. Each mL of 0.05 M edetate disodium is equivalent to 8.307 mg of $Ca_3(C_6H_5O_7)_2$: between 97.5% and 101% is found.

In-Process Revision

Calcium oxide and carbonate—Triturate 1 g of calcium citrate with 5 mL of water for 1 minute: the mixture does not turn red litmus blue. Then add 5 mL of warm 3 N hydrochloric acid: only a few isolated bubbles escape.

Hydrochloric acid-insoluble matter—Dissolve 5 g by heating with a mixture of 10 mL of hydrochloric acid and 50 mL of water for 30 minutes: not more than 2.5 mg of insoluble residue remains (0.05%).

Loss on drying ⟨731⟩—Dry it at 150° to constant weight: it loses between 12.2% and 13.3% of its weight.

Arsenic ⟨211⟩—Proceed with 0.50 g as directed for organic compounds (6 ppm of As).

Heavy metals, Method I ⟨231⟩: 0.002%.

BRIEFING

Calcium Hydroxide, *USP 29* page 3117—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-6

Change to read:

Calcium Hydroxide—

■[*1305-62-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Calcium Lactate, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-7

Change to read:

Calcium Lactate, $(CH_3CHOHCOO)_2Ca \cdot 5H_2O$—**308.29**

■[*814-80-2*]■1S (*USP30*)
—White ▲*USP29* granules or powder. Is somewhat efflorescent and at 120° becomes anhydrous. One g dissolves in 20 mL of water; practically insoluble in alcohol. Store it in tight containers.

Assay—Accurately weigh about 500 mg, previously dried at 120° for 4 hours, transfer to a suitable container, and dissolve in 150 mL of water containing 2 mL of diluted hydrochloric acid. Add 15 mL of sodium hydroxide TS and 300 mg of hydroxy naphthol blue indicator, and titrate with 0.05 M edetate disodium VS until the solution is deep blue. Each mL of 0.05 M edetate disodium is equivalent to 10.91 mg of $C_6H_{10}CaO_6$. Not less than 98% is found.

Loss on drying ⟨731⟩—Dry it at 120° for 4 hours: it loses between 25.0% and 30.0% of its weight.

Acidity—Add phenolphthalein TS to 20 mL of a 1 in 20 solution, and titrate with 0.10 N sodium hydroxide: not more than 0.50 mL is required to produce a pink color.

Heavy metals (Reagent test)—Dissolve 1 g in 2.5 mL of diluted hydrochloric acid, dilute with water to 40 mL, and add 10 mL of hydrogen sulfide TS: any brown color produced is not darker than that of a control containing 0.02 mg of added Pb (0.002%).

Magnesium and alkali salts—Mix 1 g with 40 mL of water, carefully add 5 mL of hydrochloric acid, heat the solution, boil for 1 minute, and add rapidly 40 mL of oxalic acid TS. Add immediately to the warm mixture 2 drops of methyl red TS, then add ammonia TS dropwise, from a buret, until the mixture is just alkaline. Cool to room temperature, transfer to a 100-mL graduated cylinder, dilute with water to 100 mL, mix, and allow to stand for 4 hours or overnight. Filter, and transfer to a platinum dish 50 mL of the clear filtrate, to which has been added 0.5 mL of sulfuric acid. Evaporate the mixture on a steam bath to a small bulk. Carefully heat over a free flame to dryness, and continue heating to complete decomposition and volatilization of ammonium salts. Finally ignite the residue at 800 ± 25° for 15 minutes: the residue weighs not more than 5 mg (1%).

Volatile fatty acid—Stir about 500 mg with 1 mL of sulfuric acid, and warm: the mixture does not emit an odor of volatile fatty acid.

BRIEFING

Calcium Nitrate, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-8

Change to read:

Calcium Nitrate, $Ca(NO_3)_2 \cdot 4H_2O$—**236.15**

■[*13780-06-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Calcium Sulfate, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-9

Change to read:

Calcium Sulfate, $CaSO_4 \cdot 2H_2O$—**172.17**

■[*7778-18-9*]■1S (*USP30*)
—Use ACS reagent grade.

In-Process Revision

BRIEFING

***dl*-10-Camphorsulfonic Acid,** *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-10

Change to read:

***dl*-10-Camphorsulfonic Acid,** $C_{10}H_{16}O_4S$—**232.30**

■[*35963-20-3*]■1S (*USP30*)
—White to off-white, crystals or powder. Is optically inactive.
Melting range ⟨741⟩: decomposes at about 199°.

BRIEFING

Capric Acid, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-11

Change to read:

Capric Acid *(Decanoic Acid),* $C_{10}H_{20}O_2$—**172.26**

■[*334-48-5*]■1S (*USP30*)
—White, solidified melt or fragments. Soluble in alcohol, in chloroform, and in ether; practically insoluble in water.

Assay—Inject an appropriate sample dissolved in acetone into a gas chromatograph (see *Chromatography* ⟨621⟩) that is equipped with a flame-ionization detector and contains a 0.53-mm × 30-m capillary column coated with a layer of phase G25. The carrier gas is helium, flowing at a rate of 9 mL per minute. The chromatograph is programmed as follows. Initially the column temperature is equilibrated at 150°, then the temperature is increased at a rate of 10° per minute to 250°. The injection port temperature is maintained at 240°, and the detector temperature at 265°. The area of the capric acid peak is not less than 98.5% of the toal peak area.

Melting range ⟨741⟩: between 30° and 33°.

BRIEFING

Carbazole, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-12

Change to read:

Carbazole, $C_{12}H_9N$—**167.21**

■[*86-74-8*]■1S (*USP30*)
—Off-white to tan powder.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; and the column temperature is maintained at 280°. The area of the $C_{12}H_9N$ peak is not less than 95.5% of the total peak area.

BRIEFING

Carbon Disulfide, CS, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-13

Change to read:

Carbon Disulfide, CS

■[*75-15-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Carbon Tetrachloride, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-14

Change to read:

Carbon Tetrachloride, CCl_4—**153.82**

■[*56-23-5*]■1S (*USP30*)
—Use a grade meeting the specifications of ACS *Reagent Chemicals,* 8th Edition.

In-Process Revision

BRIEFING

Carboxymethoxylamine Hemihydrochloride, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-15

Change to read:

Carboxymethoxylamine Hemihydrochloride, $2(C_2H_5NO_3) \cdot HCl$—**218.59**

■[*2921-14-4*]■1S (*USP30*)
—White, crystalline powder. Use a suitable grade.

BRIEFING

Casein, *USP 29* page 3118—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-16

Change to read:

Casein—

■[*9000-71-9*]■1S (*USP30*)
—White or slightly yellow, ▲▲*USP29* granular powder. Insoluble in water and in other neutral solvents; readily dissolved by ammonia TS and by solutions of alkali hydroxides, usually forming a cloudy solution.

Residue on ignition (Reagent test)—Ignite 2 g: the residue weighs not more than 20 mg (1.0%).

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 10.0% of its weight.

Alkalinity—Shake 1 g with 20 mL of water for 10 minutes, and filter: the filtrate is not alkaline to red litmus paper.

Soluble substances—When the filtrate from the *Alkalinity* test is evaporated and dried at 105°, the residue weighs not more than 1 mg (0.1%).

Fats—Dissolve 1 g in a mixture of 10 mL of water and 5 mL of alcoholic ammonia TS, and shake out with two 20-mL portions of solvent hexane. Evaporate the hexane at a low temperature, and dry at 80°: the weight of the residue does not exceed 5 mg (0.5%).

Nitrogen content, Method I ⟨461⟩: between 15.2% and 16.0% of N is found, on the anhydrous basis.

Where vitamin-free casein is required, use casein that has been rendered free from the fat-soluble vitamins by continuous extraction with hot alcohol for 48 hours followed by air-drying to remove the solvent.

BRIEFING

Catechol, *USP 29* page 3118. It is proposed to include a synonym and CAS number and to specify that a suitable grade be used for this reagent.

(HDQ: M. Marques) RTS—43373-17; 43995-1

Change to read:

Catechol *(o-Dihydroxybenzene;*

■*Pyrocathecol),*■1S (*USP30*)
$C_6H_4(OH)_2$—**110.11**

■[*120-80-9*]■1S (*USP30*)
—White crystals, which become discolored on exposure to air and light. Readily soluble in water, in alcohol, in benzene, in ether, in chloroform, and in pyridine, forming clear solutions.

~~*Melting range* ⟨741⟩: between 104° and 105°.~~

~~*Residue on ignition* (Reagent test)—Ignite 500 mg with 5 drops of sulfuric acid: the residue weighs not more than 1 mg (0.2%).~~

■Use a suitable grade with a content of not less than 99%.■1S (*USP30*)

BRIEFING

Cedar Oil, *USP 29* page 3119—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-18

Change to read:

Cedar Oil (for clearing microscopic sections)—

■[*8000-27-9*]■1S (*USP30*)
—A selected, distilled oil from the wood of the red cedar, *Juniperus virginiana* Linné (Fam. Pinaceae), should be used for this purpose. Refractive index: about 1.504 at 20°. For use with homogeneous immersion lenses, a specially prepared oil having a refractive index of 1.5150 ± 0.0002 at 20° is required.

BRIEFING

Ceric Sulfate, *USP 29* page 3119—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-19

Change to read:

Ceric Sulfate, $Ce(SO_4)_2$ with a variable amount of water—(anhydrous)—**332.24**

■[*13590-82-4*]■1S (*USP30*)
—It may also contain sulfates of other associated rare earth elements. Yellow to orange-yellow crystals or crystalline powder. Practically insoluble in cold water; slowly soluble in cold dilute mineral acids, but more readily soluble when heated with these solvents.

Assay—Weigh accurately about 800 mg, transfer to a flask, add 25 mL of water and 3 mL of sulfuric acid, and warm until dissolved. Cool, and add 60 mL of a mixture of 1 volume of phosphoric acid and 20 volumes of water. Add 25 mL of potassium iodide solution (1 in 10), insert the stopper in the flask, and allow to stand for 15 minutes. Replace the air over the solution with carbon dioxide, and while continuing the flow of carbon dioxide into the flask, titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Each mL of 0.1 N sodium thiosulfate is equivalent to 33.22 mg of $Ce(SO_4)_2$. Not less than 80.0% is found.

Chloride (Reagent test)—Dissolve 1 g in a mixture of 5 mL of nitric acid and 4 mL of water. Filter, if necessary, and dilute with water to 20 mL. To 10 mL of the dilution add 1 mL of silver nitrate TS, allow to stand for 10 minutes, and filter until clear. To the remaining 10 mL of test solution add 1 mL of silver nitrate TS: any turbidity produced does not exceed that in a control prepared by adding 0.05 mg of Cl to the filtrate obtained from the first 10 mL of test solution (0.01%).

Heavy metals—Heat 500 mg with a mixture of 10 mL of water and 0.5 mL of sulfuric acid until solution is complete. Cool, dilute with water to 50 mL, and bubble hydrogen sulfide gas through the solution until it is saturated: the precipitate that is formed is white or not darker than pale yellow.

Iron—Dissolve 100 mg in a mixture of 5 mL of water and 2 mL of hydrochloric acid, warming if necessary, and cool. Transfer to a glass-stoppered cylinder, dilute with water to 25 mL, and add 5 mL of ammonium thiocyanate TS and 25 mL of ether. Shake gently, but well, and allow the layers to separate: any pink color in the ether layer is not darker than that of a control, similarly prepared, containing 0.02 mg of added Fe (0.02%).

BRIEFING

Chenodeoxycholic Acid, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43373-20

Change to read:

Chenodeoxycholic Acid, $C_{24}H_{40}O_4$—**392.57**

■[*474-25-9*]■1S (*USP30*)
—White to off-white powder.

Assay—When tested by thin-layer chromatography, with the use of plates coated with chromatographic reversed-phase C18 mixture, a developing system consisting of 1 N acetic acid in methanol and 1 N acetic acid (19 : 1), and sprayed with a mixture of sulfuric acid and methanol (1 : 1), heated at 110° for 20 minutes, and examined visually and under long-wavelength UV light, a single spot is exhibited.

Melting range ⟨741⟩: between 165° and 168°.

BRIEFING

Chloramine T, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43374-1

Change to read:

Chloramine T *(Sodium p-Toluenesulfonchloramide),* $C_7H_7ClNNaO_2S \cdot 3H_2O$—**281.69—**

■[*127-65-1*]■1S (*USP30*)
Use ACS reagent grade.

BRIEFING

Chlorine, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43374-2

Change to read:

Chlorine, Cl_2—**70.9**

■[*7782-50-5*]■1S (*USP30*)
—Greenish-yellow gas. High-purity grade available from most suppliers of specialty gases.

In-Process Revision

BRIEFING

1-Chloroadamantane, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43374-3

Change to read:

1-Chloroadamantane, $C_{10}H_{15}Cl$—**170.68**

■[*935-56-8*]■1S (*USP30*)
—White crystalline solid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the $C_{10}H_{15}Cl$ peak is not less than 97.5% of the total peak area.

BRIEFING

3-Chloroaniline, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43374-4

Change to read:

3-Chloroaniline, C_6H_6ClN—**127.57**

■[*108-42-9*]■1S (*USP30*)
—Colorless to light brown liquid. Soluble in acid and in most organic solvents; practically insoluble in water.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the C_6H_6ClN peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩*:* between 1.592 and 1.596 at 20°.

BRIEFING

Chlorobenzene, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43374-5

Change to read:

Chlorobenzene, C_6H_5Cl—**112.56**

■[*108-90-7*]■1S (*USP30*)
—Clear, colorless liquid. ▲*USP29* Insoluble in water; soluble in alcohol, in benzene, in chloroform, and in ether. Use ACS reagent grade.

BRIEFING

***m*-Chlorobenzoic Acid,** *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43374-6

Change to read:

***m*-Chlorobenzoic Acid** *(3-Chlorobenzoic Acid),* $C_7H_5ClO_2$—**156.57**

■[*535-80-8*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

4-Chlorobenzoic Acid, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43374-7

Change to read:

4-Chlorobenzoic Acid, ClC_6H_4COOH—**156.57**

■[*74-11-3*]■1S (*USP30*)
—White, crystalline solid.

Assay—Dissolve about 700 mg, accurately weighed, in a mixture of 100 mL of hot alcohol and 50 mL of water. Titrate with 0.5 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 78.28 mg of ClC_6H_4COOH. Not less than 98% is found.

Solubility—One g dissolved in 25 mL of 0.5 N sodium hydroxide yields a clear and complete solution.

BRIEFING

4-Chlorobenzophenone, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-1

Change to read:

4-Chlorobenzophenone, $C_{13}H_9ClO$—**216.66**

■[*134-85-0*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Chloroform, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-2

Change to read:

Chloroform, $CHCl_3$—**119.38**

■[*67-66-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Chlorogenic Acid, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-3

Change to read:

Chlorogenic Acid, $C_{16}H_{18}O_9$—**354.31**

■[*327-97-9*]■1S (*USP30*)
—White to off-white powder. Use a suitable grade.

Assay—When tested by thin-layer chromatography (see *Chromatography* ⟨621⟩) with the use of plates coated with chromatographic silica gel mixture and a developing system consisting of a mixture of butyl alcohol, water, and acetic acid (60 : 25 : 15), and examined under short-wavelength UV light, a single spot is exhibited, with trace impurities.

BRIEFING

1-Chloronaphthalene, *USP 29* page 3120—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-4

Change to read:

1-Chloronaphthalene *(α-Chloronaphthalene),* $C_{10}H_7Cl$—**162.62**

■[*90-13-1*]■1S (*USP30*)
—Colorless to light yellow liquid.

Assay—Use a gas chromatograph equipped with a flame-ionization detector. The following conditions have been found suitable: a 3.2-mm × 1.83-m stainless steel column is packed with 7% phase G2 on support S1A; the injection port temperature is maintained at 250° and the detector temperature at 310°; and the column temperature is programmed to increase at a rate of 10° per minute from 50° to 250°. Not less than 90% of $C_{10}H_7Cl$ is found, of which not more than 10% is 2-chloronaphthalene.

Refractive index ⟨831⟩: between 1.6320 and 1.6340, at 20°.

BRIEFING

2-Chloronicotinic Acid, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-5

Change to read:

2-Chloronicotinic Acid, $C_6H_4ClNO_2$—**157.55**

■[*2942-59-8*]■1S (*USP30*)
—Off-white powder.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; and the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_6H_4ClNO_2$ peak is not less than 98% of the total peak area.

In-Process Revision

BRIEFING

2-Chloro-4-nitroaniline, 99%, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-6

Change to read:

2-Chloro-4-nitroaniline, 99%, $C_6H_5ClN_2O_2$—**172.57**

■[*121-87-9*]■1S (*USP30*)
—White to off-white powder.
Melting range ⟨741⟩: between 107° and 109°.

BRIEFING

Chloroplatinic Acid, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-8

Change to read:

Chloroplatinic Acid, $H_2PtCl_6 \cdot 6H_2O$—**517.90**

■[*18497-13-7*]■1S (*USP30*)
—Use ACS reagent grade Chloroplatinic Acid Hexahydrate.

BRIEFING

5-Chlorosalicylic Acid, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-9

Change to read:

5-Chlorosalicylic Acid, $C_7H_5ClO_3$—**172.57**

■[*321-14-2*]■1S (*USP30*)
—White to off-white powder.
Assay—When tested by thin-layer chromatography (see *Chromatography* ⟨621⟩) with the use of plates coated with chromatographic silica gel mixture and a developing system consisting of a mixture of cyclohexane, chloroform, and acetic acid (14 : 4 : 2), and examined visually and under long-wavelength UV light or iodine spray, a single spot is exhibited.
Melting range ⟨741⟩: between 172° and 178°.

BRIEFING

Chlorotrimethylsilane, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-10

Change to read:

Chlorotrimethylsilane

■*(Trimethylsylyl Chloride),*■1S (*USP30*)
C_3H_9ClSi—**108.64**

■[*75-77-4*]■1S (*USP30*)
—Clear, colorless to light yellow liquid. Fumes when exposed to moist air.
Caution—It reacts vigorously with water, alcohols, and other hydrogen donors. Store in tight glass containers.
Refractive index ⟨831⟩: between 1.3850 and 1.3890 at 20°.

BRIEFING

Cholestane, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-11

Change to read:

Cholestane, $C_{27}H_{48}$—**372.67**

■[*481-21-0*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Cholesteryl Benzoate, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-12

Change to read:

Cholesteryl Benzoate, $C_{34}H_{50}O_2$—**490.76**

■[*604-32-0*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Choline Chloride, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-13

Change to read:

Choline Chloride, $HOCH_2CH_2N(CH_3)_3Cl$—**139.62**

■[*67-48-1*]■1S (*USP30*)
—White crystals or crystalline powder. Very soluble in water. Is hygroscopic. Store in tight containers.

Assay—Transfer about 100 mg, previously dried at 105° for 2 hours and accurately weighed, to a beaker, add 20 mL of water and 1 drop of aluminum chloride solution (1 in 10), and mix. Add slowly 20 mL of a freshly prepared, filtered sodium tetraphenylborate solution (1 in 50), and allow the mixture to stand for 30 minutes with occasional swirling. Pass through a medium-porosity, sintered-glass filter, and wash the beaker and the precipitate with four 10-mL portions of water. The weight of the precipitate, determined after drying at 105° for 2 hours, and multiplied by 0.3298, gives the equivalent weight of $C_5H_{14}ClNO$. Not less than 99.5% is found.

Residue on ignition ⟨281⟩: not more than 0.1%.

BRIEFING

Chromium Trioxide, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-14

Change to read:

Chromium Trioxide, CrO_3—**99.99**

■[*1333-82-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Chromotropic Acid, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-15

Change to read:

Chromotropic Acid *(4,5-Dihydroxy-2,7-naphthalenedisulfonic Acid),* $C_{10}H_8O_8S_2 \cdot 2H_2O$—**356.33**

■[*148-25-4*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Chromotropic Acid Disodium Salt, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43748-1

Change to read:

Chromotropic Acid Disodium Salt *(4,5-Dihydroxy-2,7-naphthalenedisulfonic Acid, Disodium Salt),* $C_{10}H_6O_8Na_2S_2 \cdot 2H_2O$—**400.29**

■[*129-96-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Cinchonidine, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-16

Change to read:

Cinchonidine, $C_{19}H_{22}N_2O$—**294.39**

■[*485-71-2*]■1S (*USP30*)
—White crystals, crystalline or granular powder. Soluble in alcohol and in chloroform; practically insoluble in water.

Assay—Dissolve about 125 mg, accurately weighed, in 50 mL of glacial acetic acid. Add a few drops of *p*-naphtholbenzein TS, and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 14.72 mg of $C_{19}H_{22}N_2O$. Not less than 99.0% is found.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 1.0% of its weight.

Melting range ⟨741⟩: between 200° and 205°.

Specific rotation ⟨781⟩: between –105° and –115°, calculated on the dried basis, determined in a solution in alcohol containing 10 mg per mL.

In-Process Revision

BRIEFING

Cinchonine, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-17

Change to read:

Cinchonine, $C_{19}H_{22}N_2O$—**294.39**

■[*118-10-5*]■1S (*USP30*)
—White crystals, crystalline or granular powder. Slightly soluble in chloroform, sparingly soluble in alcohol, and practically insoluble in water.

Assay—Dissolve about 125 mg, accurately weighed, in 50 mL of glacial acetic acid. Add a few drops of *p*-naphtholbenzein TS, and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 14.72 mg of $C_{19}H_{22}N_2O$. Not less than 99.0% is found.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 1.0% of its weight.

Melting range ⟨741⟩*:* between 255° and 261°.

Specific rotation ⟨781⟩*:* between +219° and +229°, calculated on the dried basis, determined in a solution in alcohol containing 50 mg per 10 mL.

BRIEFING

Citric Acid, Anhydrous, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-18

Change to read:

Citric Acid, Anhydrous—

■[*77-92-9*]■1S (*USP30*)
—Use *Anhydrous Citric Acid* (USP monograph).

BRIEFING

Cobalt Chloride, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-19

Change to read:

Cobalt Chloride *(Cobaltous Chloride),* $CoCl_2 \cdot 6H_2O$—**237.93**

■[*7646-79-9*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Cobalt Nitrate, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43375-20

Change to read:

Cobalt Nitrate, $Co(NO_3)_2 \cdot 6H_2O$—**291.03**

■[*10141-05-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Cobaltous Acetate, *USP 29* page 3121—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-1

Change to read:

Cobaltous Acetate *(Cobalt Acetate),* $Co(C_2H_3O_2)_2 \cdot 4H_2O$—**249.08**

■[*71-48-7*]■1S (*USP30*)
—Red, needlelike crystals. Soluble in water and in alcohol. Use ACS reagent grade.

BRIEFING

Congo Red, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-1

Change to read:

Congo Red, $C_{32}H_{22}N_6Na_2O_6S_2$—**696.67**

■[*573-58-0*]■1S *(USP30)*
—A dark red or reddish-brown powder. ▲▲*USP29* Decomposes on exposure to acid fumes. Its solutions have a pH of about 8 to 9.5. One g dissolves in about 30 mL of water. Is slightly soluble in alcohol.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 3.0% of its weight.

Residue on ignition—Accurately weigh about 1 g, previously dried at 105° for 4 hours, and place it in a porcelain dish or crucible. Carefully ignite until well charred, cool, add 2 mL of sulfuric acid, and carefully ignite until the residue is white or practically so. Cool, add 0.5 mL of sulfuric acid and 1 mL of nitric acid, evaporate, and again ignite to constant weight: the weight of the sodium sulfate so obtained is between 20.0% and 24.0% of the weight of the dried specimen taken.

Sensitiveness—To 50 mL of carbon dioxide-free water add 0.1 mL of congo red solution (1 in 1000). The red color of the solution is changed to violet by the addition of 0.05 mL of 0.10 N hydrochloric acid and is restored by the subsequent addition of 0.05 mL of 0.10 N sodium hydroxide.

BRIEFING

Coomassie Brilliant Blue R-250, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-2

Change to read:

Coomassie Brilliant Blue R-250, $C_{45}H_{44}N_3O_7S_2Na$—**825.97**

■[*6104-58-1*]■1S *(USP30)*
—Brown powder.

BRIEFING

Copper, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-3

Change to read:

Copper, Cu—**At. Wt. 63.546**

■[*7440-50-8*]■1S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Cortisone, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-4

Change to read:

Cortisone, $C_{21}H_{28}O_5$—**360.44**

■[*53-06-5*]■1S *(USP30)*
—White, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Melts at about 220°, with decomposition.

Absorption maximum—The UV absorption spectrum of a 1 in 100,000 solution in alcohol shows a maximum at about 238 nm.

Specific rotation ⟨781⟩: about +209°, determined in a 1 in 100 solution in alcohol.

BRIEFING

***m*-Cresol Purple,** *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-5

Change to read:

***m*-Cresol Purple,** $C_{21}H_{18}O_5S$—**382.43**

■[*2303-01-7*]■1S *(USP30)*
—Use a suitable grade.

BRIEFING

Cupric Acetate, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-6

Change to read:

Cupric Acetate, $Cu(C_2H_3O_2)_2 \cdot H_2O$—**199.65**

■[*142-71-2*]■1S *(USP30)*
—Use ACS reagent grade.

In-Process Revision

BRIEFING

Cupric Chloride, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-7

Change to read:

Cupric Chloride, $CuCl_2 \cdot 2H_2O$—**170.48**

■[*7447-39-4*]■1S (*USP30*)
—Bluish-green deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether. Use ACS reagent grade.

BRIEFING

Cupric Citrate, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-8

Change to read:

Cupric Citrate ([*Citrato*(*4-*)]*dicopper*), $Cu_2C_6H_4O_7$—**315.18**

■[*866-82-0*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Cupric Sulfate, Anhydrous, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-9

Change to read:

Cupric Sulfate, Anhydrous, $CuSO_4$—**159.61**

■[*7758-98-7*]■1S (*USP30*)
—A white or grayish-white powder free from a blue tinge. Upon the addition of a small quantity of water, it becomes blue. Soluble in water. Store in tight containers.

Chloride (Reagent test)—One g shows not more than 0.02 mg of Cl (0.002%).

Substances not precipitated by hydrogen sulfide—Determine as directed for ACS reagent grade of *Cupric Acetate:* the residue weighs not more than 6 mg (0.15%).

BRIEFING

Cyanoacetic Acid, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-10

Change to read:

Cyanoacetic Acid, $C_3H_3NO_2$—**85.06**

■[*372-09-8*]■1S (*USP30*)
—White to light yellow, crystalline solid. Very soluble in water.

Assay—Dissolve about 300 mg, accurately weighed, in 25 mL of water and 25 mL of alcohol. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary corrections. Each mL of 0.1 N sodium hydroxide is equivalent to 85.06 mg of $C_3H_3NO_2$. Not less than 99% is found.

BRIEFING

Cyanogen Bromide, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-11

Change to read:

Cyanogen Bromide, BrCN—**105.92**

■[*506-68-3*]■1S (*USP30*)
—Colorless crystals. Volatilizes at room temperature. Its vapors are highly irritating and *very toxic*. Melts at about 52°. Freely soluble in water and in alcohol. Store in tight containers in a cold place.

Solubility—Separate 1-g portions dissolve completely in 10 mL of water and in 10 mL of alcohol, respectively, to yield colorless solutions.

BRIEFING

Cyclohexane, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-12

Change to read:

Cyclohexane, C_6H_{12}—**84.16**

■[*110-82-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Cyclohexanol, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-13

Change to read:

Cyclohexanol, $C_6H_{12}O$—**100.16**

■[*108-93-0*]■1S (*USP30*)
—A clear liquid. ▲▲*USP29* Freely soluble in water. Miscible with alcohol, with ethyl acetate, and with aromatic hydrocarbons.

Assay—When examined by gas-liquid chromatography, using suitable gas chromatographic apparatus and conditions, it shows a purity of not less than 98%.

Melting temperature: about 23°.

Specific gravity: about 0.962, at 20°.

BRIEFING

L-Cystine, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-14

Change to read:

L-Cystine, $C_6H_{12}N_2O_4S_2$—**240.30**

■[*58-89-3*]■1S (*USP30*)
—A white, crystalline powder. Very slightly soluble in water; soluble in dilute mineral acids and in solutions of alkali hydroxides; insoluble in alcohol and in other organic solvents.

Specific rotation ⟨781⟩: between –215° and –225°, determined in a 2 in 100 solution of test specimen, previously dried over silica gel for 4 hours, in dilute hydrochloric acid (1 in 10) at a temperature of 20°.

Loss on drying ⟨731⟩—Dry it over silica gel for 4 hours: it loses not more than 0.2% of its weight.

Residue on ignition (Reagent test): not more than 0.1%.

BRIEFING

Decanol, *USP 29* page 3122—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-15

Change to read:

Decanol *(n-Decyl Alcohol),* $C_{10}H_{22}O$—**158.28**

■[*25339-17-7*]■1S (*USP30*)
—A clear, viscous liquid. Specific gravity: about 0.83 at 20°. Solidifies at about 6.5°. Insoluble in water; soluble in alcohol and in ether.

Assay—When examined by gas-liquid chromatography, using suitable gas chromatographic apparatus and conditions, it shows a purity of not less than 99%.

BRIEFING

Deuterium Oxide, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-16

Change to read:

Deuterium Oxide, D_2O—**20.032**

■[*7789-20-0*]■1S (*USP30*)
—Use a suitable grade having a minimum isotopic purity of 99.8 atom % of deuterium.

BRIEFING

Devarda's Alloy, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-17

Change to read:

Devarda's Alloy *(Devarda's Metal),*

■[*8049-11-4*]■1S (*USP30*)
—A gray powder composed of 50 parts of copper, 45 parts of aluminum, and 5 parts of zinc.

BRIEFING

Dextran, High Molecular Weight, *USP 29* page 3123 and page 186 of *PF* 32(1) [Jan.–Feb. 2006]—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-18

In-Process Revision

Change to read:

Dextran, High Molecular Weight—

■[*9004-54-0*]■1S (*USP30*)
—A dextran molecular weight standard having a weight-average molecular weight, M_W, of 1 to 2×10^6 Da and a weight-average molecular weight to number-average molecular weight ratio, M_W / M_N, of 1.0 to 1.8.

[NOTE—A suitable grade is available from ~~Sigma-Aldrich, www.sigma-aldrich.com.~~]

▲American Polymer Standards Corporation, www.ampolymer.com.]▲*USP30*

BRIEFING

Dextrin, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-19

Change to read:

Dextrin, $(C_6H_{10}O_5)_n \cdot xH_2O$—

■[*9004-53-9*]■1S (*USP30*)
—A white amorphous powder. Slowly soluble in cold water; more readily soluble in hot water; insoluble in alcohol.

Insoluble matter—Boil 1 g with 30 mL of water in a small flask: the solution is colorless and clear, or not more than opalescent.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 10.0% of its weight.

Residue on ignition (Reagent test)—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 5 mg (0.5%).

Chloride (Reagent test)—Dissolve 3 g in 75 mL of boiling water, cool, dilute with water to 75 mL, and filter if necessary. To 25 mL of the filtrate add 2 mL of nitric acid and 1 mL of silver nitrate TS, and allow to stand for 5 minutes: any turbidity produced is not greater than that of a control containing 0.02 mg of added Cl (0.002%).

Sulfate (Reagent test, *Method I*)—To a 25-mL portion of the filtrate from the preceding test add 0.5 mL of diluted hydrochloric acid and 2 mL of barium chloride TS, and allow to stand for 10 minutes: any turbidity produced is not greater than that of a control containing 0.2 mg of added SO_4 (0.02%).

Alcohol-soluble substances—Boil 1 g with 20 mL of alcohol for 5 minutes under a reflux condenser, and filter while hot. Evaporate 10 mL of the filtrate on a steam bath, and dry at 105°: the residue weighs not more than 5 mg (1%).

Reducing sugars—Shake 2 g with 100 mL of water for 10 minutes, and filter until clear. To 50 mL of the filtrate add 50 mL of alkaline cupric tartrate TS, and boil for 3 minutes. Filter through a tared filtering crucible, wash with water, then with alcohol, and finally with ether, and dry at 105° for 2 hours: the precipitate of cuprous oxide weighs not more than 115 mg (corresponding to about 5% of reducing sugars as dextrose).

BRIEFING

3,3′-Diaminobenzidine Hydrochloride, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43379-20

Change to read:

3,3′-Diaminobenzidine Hydrochloride, $(NH_2)_2C_6H_3C_6H_3(NH_2)_2 \cdot 4HCl$—**360.11**

■[*7411-49-6*]■1S (*USP30*)
—White to yellowish–tan (occasionally purple), needle-shaped crystals. Soluble in water. Stable in organic solvents but unstable in aqueous solution at room temperature. Store aqueous solutions in a refrigerator.

Insoluble matter—Dissolve 2 g in 100 mL of water, without heating, and filter immediately: the insoluble residue does not exceed 1 mg (0.05%).

Residue on ignition (Reagent test): not more than 1 mg, from 2 g (0.05%).

Suitability test for detection of selenium—Dissolve 1.633 g of selenious acid (H_2SeO_3) in water, and dilute with water to 1 L. Dilute 10 mL of this solution with water to 1 L, to make a solution containing 0.010 mg of Se per mL. Place 1 mL of the resulting solution in a 100-mL beaker, add 2 mL of formic acid solution (1 in 7), and dilute with water to 50 mL. Add 2 mL of 3,3′-diaminobenzidine hydrochloride solution (1 in 200), and allow to stand for 30 to 50 minutes. Adjust with 6 N ammonium hydroxide to a pH between 6 and 7. Transfer to a 125-mL separator, add 10.0 mL of toluene, and shake vigorously for 30 seconds: a distinct yellow color is produced in the toluene layer. A blank containing diaminobenzidine hydrochloride but no selenium standard, treated in the same manner, shows no color in the toluene layer.

BRIEFING

2,3-Diaminonaphthalene, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-1

Change to read:

2,3-Diaminonaphthalene, $C_{10}H_{10}N_2$—**158.20**

■[*771-97-1*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Diatomaceous Earth, Flux-Calcined, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-2

Change to read:

Diatomaceous Earth, Flux-Calcined—

■[*91053-39-3*]■1S (*USP30*)
—Use a suitable grade.
[NOTE—A suitable grade is "Chromosorb W, AW-DMCS," available from Alltech, www.alltechweb.com.]

BRIEFING

Diatomaceous Earth, Silanized, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-3

Change to read:

Diatomaceous Earth, Silanized

■[*91053-39-3*]■1S (*USP30*)
—Use a suitable grade.
[NOTE—Suitable grades are available commercially as "Anachrome Q," "Gas-Chrom Q," and "Varaport 30."]

BRIEFING

Diatomaceous Silica, Calcined, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-4

Change to read:

Diatomaceous Silica, Calcined—

■[*68855-54-9*]■1S (*USP30*)
—A form of silica (SiO_2) consisting of fused frustules and fragments of diatoms. It is an amorphous, fine, light pink or white powder. Insoluble in water, in acids, and in dilute solutions of alkali hydroxides.

Loss on ignition—Accurately weigh about 4 g, and ignite to constant weight: it loses not more than 10.0% of its weight.

Organic impurities—It does not darken appreciably upon ignition.

Loss on drying ⟨731⟩—Dry it at 110° for 2 hours: it loses not more than 2.0% of its weight.

[NOTE—Suitable grades are "Chromosorb P" and "Chromosorb W," available from Alltech, www.alltechweb.com.]

BRIEFING

2,6-Dibromoquinone-chlorimide, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-5

Change to read:

2,6-Dibromoquinone-chlorimide (*2,6-Dibromo-N-chloro-p-benzoquinone Imine; DBQ Reagent*), $C_6H_2Br_2ClNO$—**299.35**

■[*537-45-1*]■1S (*USP30*)
—A yellow, crystalline powder. Insoluble in water; soluble in alcohol and in dilute alkali hydroxide solutions.

Melting range ⟨741⟩: between 82° and 84°.

Solubility in alcohol—A solution of 100 mg in 10 mL of alcohol is not more than faintly turbid.

Residue on ignition (Reagent test)—Ignite 500 mg with 0.5 mL of sulfuric acid: the residue weighs not more than 1 mg (0.2%).

Sensitiveness—To 10 mL of a water solution containing 0.01 mg of phenol add 0.3 mL of a sodium borate buffer (made by dissolving 2.84 g of crystallized sodium borate in 90 mL of warm water, adding 8.2 mL of 1 N sodium hydroxide, and diluting with water to 100 mL) and 0.1 mL of a solution of 10 mg of the test specimen in 20 mL of alcohol: a distinct blue color develops within 10 minutes.

BRIEFING

Dibutylamine, *USP 29* page 3123—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-6

Change to read:

Dibutylamine, $C_8H_{19}N$—**129.24**

■[*111-92-2*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 200°; the detector temperature is maintained at 300°; and the column temperature is maintained at 100° and programmed to rise 10° per minute to 200°. The area of the $C_8H_{19}N$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.415 and 1.419 at 20°.

BRIEFING

Dibutyl Phthalate, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-7

Change to read:

Dibutyl Phthalate, $C_{16}H_{22}O_4$—**278.34**

■[*84-74-2*]■1S (*USP30*)
—Clear, colorless liquid.

Assay—Accurately weigh about 2 g into a suitable flask, add 25.0 mL of 1 N sodium hydroxide and 30 mL of isopropyl alcohol, and mix. Digest the mixture at a temperature near boiling for 30 minutes, then cool in a water bath to room temperature. Add phenolphthalein TS, and titrate with 1 N sulfuric acid VS to the disappearance of the pink color. Perform a complete blank determination, and make any necessary correction. Each mL of 1 N sulfuric acid consumed is equivalent to 139.2 mg of $C_{16}H_{22}O_4$. Not less than 98% is found.

Refractive index ⟨831⟩: between 1.491 and 1.493 at 20°.

Acid content—Accurately weigh about 10 g, and dissolve in 100 mL of an alcohol-ether mixture (1 : 1). Add phenolphthalein TS, and titrate immediately with 0.05 N alcoholic potassium hydroxide VS. Each mL of 0.05 N alcoholic potassium hydroxide is equivalent to 4.15 mg of phthalic acid: not more than 0.02% is found.

BRIEFING

2,5-Dichloroaniline, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-8

Change to read:

2,5-Dichloroaniline, $Cl_2C_6H_3NH_2$—**162.02**

■[*95-82-9*]■1S (*USP30*)
—White, needle-like crystals. Slightly soluble in water; soluble in alcohol and in ether.

Melting range, Class I ⟨741⟩: between 49° and 50°.

BRIEFING

2,6-Dichloroaniline, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-9

Change to read:

2,6-Dichloroaniline, $C_6H_5Cl_2N$—**162.02**

■[*608-31-1*]■1S (*USP30*)
—Off-white powder.

Melting range ⟨741⟩: between 38° and 41°.

BRIEFING

***o*-Dichlorobenzene,** *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-10

Change to read:

***o*-Dichlorobenzene,** $C_6H_4Cl_2$—**147.00**

■[*95-50-1*]■1S (*USP30*)
—Clear liquid, having a light yellowish-brown tint (about APHA 20). ▲*USP29* Practically insoluble in water. Miscible with alcohol and with ether. Boils at about 180°.

Assay—When examined by gas–liquid chromatography, with the use of suitable apparatus and conditions, it shows a purity of not less than 98%.

Density: between 1.299 and 1.301.

Refractive index ⟨831⟩: between 1.548 and 1.550 at 25°.

Residue on evaporation—Evaporate 80 mL on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 50 mg (0.005%).

Acidity—Add phenolphthalein TS to 25 mL of methanol, and titrate with 0.02 N alcoholic potassium hydroxide VS until a faint pink color persists for 15 seconds. Pipet 25 mL of test specimen into the solution; mix, avoiding exposure to the atmosphere; and titrate with 0.02 N alcoholic potassium hydroxide VS: not more than 2.2 mL is required to restore the pink color (about 0.005%).

BRIEFING

Dichlorofluorescein, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-11

Change to read:

Dichlorofluorescein, $C_{20}H_{10}Cl_2O_5$—**401.20**

■[*76-54-0*]■1S (*USP30*)
—[NOTE—This specification covers both the 4,5- and 2,7-isomers of dichlorofluorescein, either of which is suitable for the preparation of dichlorofluorescein TS.] A weak orange-colored, crystalline powder. Sparingly soluble in water; soluble in alcohol and in solutions of alkali hydroxides.

Residue on ignition (Reagent test)—Ignite 200 mg with 5 drops of sulfuric acid: the residue weighs not more than 1 mg (0.5%).

Sensitiveness—Dissolve 100 mg in 60 mL of alcohol, add 2.5 mL of 0.1 N sodium hydroxide, and dilute with water to 100 mL. Add 1 mL of this solution to a solution of potassium iodide prepared by dissolving 100 mg of potassium iodide, previously dried at 105° to constant weight and accurately weighed, in 50 mL of water containing 1 mL of glacial acetic acid, and titrate with 0.1 N silver nitrate VS until the color of the precipitate changes from pale yellowish orange to pink. The volume of 0.1 N silver nitrate consumed is not more than 0.10 mL greater than the calculated volume, the calculated volume being based upon the KI content of the dried specimen as determined in the *Assay* under *Potassium Iodide* (USP monograph).

BRIEFING

Dichlorofluoromethane, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-12

Change to read:

Dichlorofluoromethane, $CHCl_2F$—**102.92**

■[*75-43-4*]■1S (*USP30*)
—Colorless gas.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography*⟨621⟩) equipped with a thermal-conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.53-mm × 30-m capillary column coated with a 5-µm layer of phase G2; the injection port temperature is maintained at 200°; the detector temperature is maintained at 200°; and the column temperature is maintained at 0° and programmed to rise 5° per minute to 40°, and then to rise 10° per minute to 180°. The area of the $CHCl_2F$ peak is not less than 98% of the total peak area.

BRIEFING

2,4-Dichloro-1-naphthol, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-13

Change to read:

2,4-Dichloro-1-naphthol, $C_{10}H_6OCl_2$—**213.06**

■[*2050-76-2*]■1S (*USP30*)
—Light tan powder.

Melting range ⟨741⟩: between 103° and 107°, but the range between beginning and end of melting does not exceed 2°.

BRIEFING

2,6-Dichlorophenol-indophenol Sodium, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-15

Change to read:

2,6-Dichlorophenol-indophenol Sodium *(2,6-Dichloro-indophenol Sodium),* $O:C_6H_2Cl_2:NC_6H_4ONa$ with about $2H_2O$—**290.08** (anhydrous)

■[*620-45-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

2,6-Dichlorophenylacetic Acid, *USP 29* page 3124—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-16

Change to read:

2,6-Dichlorophenylacetic Acid, $C_8H_6Cl_2O_2$—**205.04**

■[*6575-24-2*]■1S (*USP30*)
—White powder.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°;

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and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the $C_8H_6Cl_2O_2$ peak is not less than 97% of the total peak area.

BRIEFING

Dicyclohexylamine, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-18

Change to read:

Dicyclohexylamine, $(C_6H_{11})_2NH$—**181.32**

■[*101-83-7*]■1S (*USP30*)
—Clear, strongly alkaline liquid. ▲▲*USP29* Sparingly soluble in water. Miscible with common organic solvents. Density: 0.9104. Solidifies at –0.1°; melts at about 20°.

Assay—Accurately weigh about 400 mg in a tared, small weighing bottle equipped with a well-fitting closure. Transfer the stoppered bottle to a 250-mL beaker, add sufficient glacial acetic acid TS to cover the bottle, and open the bottle under the surface of the acid. Add crystal violet TS, and titrate with 0.1 N perchloric acid VS. Each mL of 0.1 N perchloric acid is equivalent to 18.13 mg of $(C_6H_{11})_2NH$. Not less than 98% is found.

Specific gravity ⟨841⟩: between 0.911 and 0.917.

Boiling range (Reagent test): between 255° and 257°.

Water, *Method I* ⟨921⟩: not more than 0.5%.

BRIEFING

Diethylamine, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-19

Change to read:

Diethylamine, $(C_2H_5)_2NH$—**73.14**

■[*109-89-7*]■1S (*USP30*)
—Colorless, flammable, strongly alkaline liquid. Miscible with water and with alcohol. Forms a hydrate with water. *May be irritating to skin and mucous membranes.* Store in well-closed containers. Use ACS reagent grade.

BRIEFING

***N,N*-Diethylaniline,** *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43381-20

Change to read:

***N,N*-Diethylaniline,** $C_6H_5N(C_2H_5)_2$—**149.23**

■[*91-66-7*]■1S (*USP30*)
—Light yellow to amber liquid.

Assay—Inject an appropriate specimen (about 0.2 µL) into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas flowing at about 40 mL per minute. The following conditions have been found suitable: a 3-mm × 1.8-m stainless steel column containing 20% phase G16 on support S1A; the injection port temperature is maintained at 250°; the column temperature is maintained at 140° and programmed to rise 6° per minute to 200°. The detector temperature is maintained at 310°. The area of the *N*,*N*-diethylaniline peak having a retention time of about 4.9 minutes is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.5405 and 1.5425 at 20°.

BRIEFING

Diethylene Glycol, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-1

Change to read:

Diethylene Glycol, $C_4H_{10}O_3$—**106.12** ~~[*111-46-6*]~~

■[*111-46-6*]■1S (*USP30*)
—A colorless to faintly yellow, viscous, hygroscopic liquid. Miscible with water, with alcohol, with ether, and with acetone. Insoluble in benzene and in carbon tetrachloride.

Specific gravity ⟨841⟩: between 1.117 and 1.120 at 20°.

Distilling range ⟨721⟩: between 240° and 250°.

Acidity—Transfer 54 mL (60 g) to a 250-mL conical flask, add phenolphthalein TS, and titrate with 0.02 N alcoholic potassium hydroxide VS to the production of a pink color that is stable for at least 15 seconds: not more than 2.5 mL is consumed (0.005% as CH_3COOH).

Water ⟨921⟩: not more than 0.2%.

Residue on ignition ⟨281⟩—Transfer 50 g to a tared platinum dish, heat the dish gently until the vapors ignite, and allow the specimen to burn completely. Ignite the residue at 800 ± 25°, cool, and weigh: the residue weighs not more than 2.5 mg (0.005%).

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BRIEFING

Diethylene Glycol Succinate Polyester, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-2

Change to read:

Diethylene Glycol Succinate Polyester, $(OCH_2CH_2OCH_2CH_2OOCCH_2CH_2COO)_n$

■—[*26183-02-8*]■1S (*USP30*)
—Clear, viscous liquid. Soluble in chloroform. Is stabilized by modification of the diethylene glycol succinate polyester, to render it suitable for use in gas–liquid chromatography to a temperature of 200°.
[NOTE—A suitable grade is available from Alltech, www.alltech-web.com.]

BRIEFING

Diethylenetriamine, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-3

Change to read:

Diethylenetriamine, $C_4H_{13}N_3$—**103.17**

■[*111-40-0*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G2. The injection port temperature is maintained at 200°; the column temperature is maintained at 100° and programmed to rise 10° per minute to 250° and held there for 5 minutes; and the detector temperature is maintained at 300°. The area of the main peak is not less than 95% of the total peak area.

Refractive index ⟨831⟩: between 1.4815 and 1.4845 at 20°.

BRIEFING

Di(2-ethylhexyl)phthalate, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-4

Change to read:

Di(2-ethylhexyl)phthalate *[Bis(2-ethylhexyl)phthalate],* $C_{24}H_{38}O_4$—**390.56**

■[*117-81-7*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Digitonin, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-5

Change to read:

Digitonin, $C_{56}H_{92}O_{29}$—**1229.31**

■[*11024-24-1*]■1S (*USP30*)
—White, crystalline powder. Almost insoluble in water; soluble in warm alcohol, and in glacial acetic acid and in 75% acetic acid; insoluble in chloroform and in ether. Melts at about 230°, with decomposition.

Specific rotation ⟨781⟩: between –47° and –49°, determined in a solution in 75% acetic acid containing 100 mg per mL.

Solubility in alcohol—A solution of 500 mg in 20 mL of warm alcohol is colorless and complete.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 6% of its weight.

Residue on ignition (Reagent test): not more than 0.3%.

BRIEFING

10,11-Dihydrocarbamazepine, *USP 29* page 3125. It is proposed to delete this reagent. It will be available as a USP Reference Standard.

(HDQ: M. Marques) RTS—43908-1

Delete the following:

~~■**10,11-Dihydrocarbamazepine,** $C_{15}H_{14}N_2O$ **238.28** White crystals.~~

~~*Assay*—When tested by thin-layer chromatography, with the use of plates coated with chromatographic silica gel mixture, a developing system consisting of toluene and methanol (80:20), and examined visually and under long-wavelength UV light, a single spot is exhibited.~~■1S (*USP30*)

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BRIEFING

Dihydroquinidine Hydrochloride, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-7

Change to read:

Dihydroquinidine Hydrochloride, $C_{20}H_{27}ClN_2O_2$—**362.89**

■[*1476-98-8*]■1S (*USP30*)
—Rhombic plates. Freely soluble in methanol and in chloroform.

Assay—

MOBILE PHASE—Prepare a mixture of water, acetonitrile, diethylamine, and methanesulfonic acid (860 : 100 : 20 : 20).

PROCEDURE—Inject about 20 µL into a suitable liquid chromatograph (see *Chromatography* ⟨621⟩) equipped with a 235-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The area of the $C_{20}H_{27}ClN_2O_2$ peak is not less than 97.5% of the total peak area.

BRIEFING

Dihydroquinine, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-8

Change to read:

Dihydroquinine *(Hydroquinine),* $C_{20}H_{26}N_2O_2$—**326.43**

■[*522-66-7*]■1S (*USP30*)
—Freely soluble in acetone, in alcohol, and in chloroform; almost insoluble in water.

Assay—

MOBILE PHASE—Prepare a mixture of water, acetonitrile, diethylamine, and methanesulfonic acid (860 : 100 : 20 : 20) and methanol (82 : 18).

PROCEDURE—Inject about 20 µL into a suitable liquid chromatograph (see *Chromatography* ⟨621⟩) equipped with a 235-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The area of the $C_{20}H_{26}N_2O_2$ peak is not less than 97.5% of the total peak area.

BRIEFING

2,5-Dihydroxybenzoic Acid, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-9

Change to read:

2,5-Dihydroxybenzoic Acid, $C_7H_6O_4$—**154.12**

■[*303-07-1*]■1S (*USP30*)
—Off-white powder. Freely soluble in alcohol yielding a clear, very pale yellow solution.

Assay—Dissolve about 75 mg, accurately weighed, in 30 mL of methanol. Slowly add 40 mL of water. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 15.41 mg of $C_7H_6O_4$. Not less than 99% is found.

Melting range ⟨741⟩: about 207°, with decomposition.

BRIEFING

Diiodofluorescein, *USP 29* page 3125—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-10

Change to read:

Diiodofluorescein, $C_{20}H_{10}I_2O_5$—**584.10**

■[*31395-16-1*]■1S (*USP30*)
—Orange-red ▲*USP29* powder. Slightly soluble in water; soluble in alcohol and in solutions of alkali hydroxides.

Residue on ignition—Ignite 200 mg with 5 drops of sulfuric acid: the weight of the residue does not exceed 1.0 mg (0.5%).

Sensitiveness—Accurately weigh about 100 mg of potassium iodide, previously dried at 105° to constant weight, and dissolve it in 50 mL of water. Add 1 mL of diiodofluorescein TS prepared from the test specimen and 1 mL of glacial acetic acid, and titrate with 0.1 N silver nitrate VS until the color of the precipitate changes from brownish-red to a bluish-red. The volume of 0.1 N silver nitrate consumed is not in excess of 0.10 mL over the calculated volume, based on the KI content of the dried potassium iodide determined as follows. Dissolve about 500 mg of potassium iodide, accurately weighed, in about 10 mL of water, and add 35 mL of hydrochloric acid and 5 mL of chloroform. Titrate with 0.05 M potassium iodate VS until the purple color of iodine disappears from the chloroform. Add the last portions of the iodate solution dropwise, agitating vigorously and continuously. After the chloroform has been decolorized, allow the mixture to stand for 5 minutes. If the chloroform develops a purple color, titrate further with the iodate solution. Each mL of 0.05 M potassium iodate is equivalent to 16.60 mg of KI.

BRIEFING

Diisodecyl Phthalate, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-11

Change to read:

Diisodecyl Phthalate [*Bis*(*isodecyl*)*phthalate*], $C_{28}H_{46}O_4$—**446.66**

■[*26761-40-0*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Diisopropyl Ether, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-12

Change to read:

Diisopropyl Ether *(Isopropyl Ether),* $[(CH_3)_2CH]_2O$—**102.17**

■[*108-20-3*]■1S (*USP30*)
—Colorless, mobile liquid. Slightly soluble in water. Miscible with alcohol and with ether. *[Caution—It is highly flammable. Do not use where it may be ignited. Do not evaporate to the point of near dryness, since it tends to form explosive peroxides.]*

Specific gravity: between 0.716 and 0.720.

Distilling range, Method II ⟨721⟩—Not less than 95% distills between 65° and 70°.

Peroxides—To 10 mL, contained in a clean, glass-stoppered cylinder previously rinsed with a portion of the ether under examination, add 1 mL of freshly prepared potassium iodide solution (1 in 10). Shake, and allow to stand for 1 minute: no yellow color is observed in either layer (about 0.001% as H_2O_2).

Residue on evaporation—[NOTE—If peroxide is present, do not carry out this procedure.] Evaporate 14 mL (10 g) from a tared shallow dish, and dry at 105° for 1 hour: the residue weighs not more than 1 mg (0.01%).

Acidity—Add 2 drops of bromothymol blue TS to 10 mL of water in a glass-stoppered, 50-mL flask, and titrate with 0.010 N sodium hydroxide until a blue color persists after vigorous shaking. Add 5 mL of diisopropyl ether, and titrate with 0.010 N sodium hydroxide: not more than 0.30 mL is required to restore the blue color (0.005% as CH_3COOH).

[NOTE—For spectrophotometric determinations, use diisopropyl ether that meets the following additional requirement.]

Absorbance—Its absorbance at 255 nm, in a 10-mm quartz cell, does not exceed 0.2, water being used as the blank.

BRIEFING

Diisopropylamine, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-13

Change to read:

Diisopropylamine, $[(CH_3)_2CH]_2NH$—**101.19**

■[*108-18-9*]■1S (*USP30*)
—Colorless liquid.

Assay—Not less than 98% of $C_6H_{15}N$ is found, a suitable gas chromatograph equipped with a flame-ionization detector being used. The following conditions have been found suitable: a 3.2-mm × 1.83-m stainless steel column is packed with a cross-linked polystyrene support; the injection port temperature is maintained at 250° and the detector temperature at 310°; the column temperature is programmed to rise at 10° per minute from 50° to 220°.

Refractive index ⟨831⟩: between 1.3915 and 1.3935, at 20°.

BRIEFING

Diisopropylethylamine, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-14

Change to read:

Diisopropylethylamine *(N,N-Diisopropylethylamine),* $C_8H_{19}N$—**129.24**

■[*7087-68-5*]■1S (*USP30*)
—Clear, colorless liquid. Soluble in glacial acetic acid.

Assay—Accurately weigh about 500 mg, dissolve in 50 mL of glacial acetic acid, mix, add crystal violet TS, and titrate with 0.1 N perchloric acid VS. Each mL of 0.1 N perchloric acid is equivalent to 12.92 mg of $C_8H_{19}N$. Not less than 98% is found.

Refractive index ⟨831⟩: between 1.4125 and 1.4145 at 20°.

BRIEFING

2,5-Dimethoxybenzaldehyde, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-15

In-Process Revision

Change to read:

2,5-Dimethoxybenzaldehyde, $C_9H_{10}O_3$—**166.17**

■[*93-02-7*]■1S (*USP30*)
—Off-white crystals.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, nitrogen being used as the carrier gas. The following conditions have been found suitable: a 0.3-mm × 30-m capillary column coated with phase G1; the injection port temperature is maintained at 270°; the detector temperature is maintained at 300°; the column temperature is maintained at 150° and programmed to rise 10° per minute to 270°. The area of the main peak is not less than 97% of the total peak area.

Melting range ⟨741⟩: between 50° and 52°.

BRIEFING

1,2-Dimethoxyethane, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-16

Change to read:

1,2-Dimethoxyethane, $C_4H_{10}O_2$—**90.12**

■[*110-71-4*]■1S (*USP30*)
—Clear, colorless liquid. ▲*USP29* Miscible with water and with alcohol. Soluble in hydrocarbon solvents. *May form peroxides on standing*.

Boiling range (Reagent test)—Not less than 95% distills between 83° and 86°.

Refractive index ⟨831⟩: between 1.379 and 1.381, at 20°.

Acidity—To 20 mL add bromophenol blue TS, and titrate with 0.020 N sodium hydroxide: not more than 2.0 mL is consumed (about 0.015% as CH_3COOH).

Water, *Method I*⟨921⟩: not more than 0.2%.

BRIEFING

(3,4-Dimethoxyphenyl)acetonitrile, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-17

Change to read:

(3,4-Dimethoxyphenyl)acetonitrile *(Homoveratronitrile),* $C_{10}H_{11}NO_2$—**177.20**

■[*93-17-4*]■1S (*USP30*)
—Off-white fibers.

Melting range ⟨741⟩: between 65° and 67°.

BRIEFING

Dimethyl Phthalate, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-18

Change to read:

Dimethyl Phthalate, $C_{10}H_{10}O_4$—**194.19**

■[*131-11-3*]■1S (*USP30*)
—Viscous, colorless liquid.

Assay—

MOBILE PHASE—Prepare a filtered and degassed mixture of chromatographic *n*-heptane and *n*-propyl alcohol (HPLC grade) (97 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

STANDARD SOLUTION—Dissolve a suitable quantity of dimethyl phthalate in *Mobile phase* to obtain a solution having a known concentration of about 0.26 mg per mL.

PROCEDURE—Inject about 20 µL into a suitable liquid chromatograph (see *Chromatography* ⟨621⟩) equipped with a 238-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 1.0 mL per minute. The area of the dimethyl phthalate peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.514 and 1.518 at 20°.

BRIEFING

Dimethyl Sulfone, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-19

Change to read:

Dimethyl Sulfone *(Methyl Sulfone),* $(CH_3)_2SO_2$—**94.13**

■[*67-71-0*]■1S (*USP30*)
—White crystals.

Melting range ⟨741⟩: between 109° and 111°.

BRIEFING

Dimethyl Sulfoxide, Spectrophotometric Grade, *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43382-20

Change to read:

Dimethyl Sulfoxide, Spectrophotometric Grade—

■[*67-68-5*]■1S *(USP30)*
—Use methyl sulfoxide ACS spectrophotometric reagent grade.

BRIEFING

***N,N*-Dimethylacetamide,** *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-2

Change to read:

***N,N*-Dimethylacetamide,** C_4H_9NO—**87.12**

■[*127-19-5*]■1S *(USP30)*
—Clear, colorless liquid. Miscible with water and with many organic solvents.

Assay—When examined by gas–liquid chromatography, with the use of suitable apparatus and conditions, it shows a purity of not less than 99%.

Distilling range ⟨721⟩: between 164.5° and 167.5°.

Residue on evaporation—Evaporate 215 mL on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 2 mg (0.001%).

pH of 20% solution—Weigh 20 g of it into a 100-mL volumetric flask, and dilute with carbon dioxide-free water to volume: the solution shows a pH between 4.0 and 7.0.

Ultraviolet absorbance—Determine its absorbance throughout the range 270 to 400 nm, using a 1-cm cell, a suitable spectrophotometer, and water to set the instrument: the absorbance does not exceed 1.00 at 270 nm, 0.30 at 280 nm, 0.15 at 290 nm, 0.05 at 310 nm, 0.03 at 320 nm, and 0.01 at 360 to 400 nm.

Water, Method I ⟨921⟩: not more than 0.05%.

BRIEFING

***p*-Dimethylaminoazobenzene,** *USP 29* page 3126—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-3

Change to read:

***p*-Dimethylaminoazobenzene** *(Methyl Yellow, Butter Yellow),* $C_{14}H_{15}N_3$—**225.29**

■[*60-11-7*]■1S *(USP30)*
—Yellow leaflets or yellow, crystalline powder.

Solubility—Insoluble in water; sparingly soluble in chloroform, in ether, or in fatty oils. Dissolve 100 mg in 20 mL of alcohol: the solution is complete or practically so and clear.

Melting range ⟨741⟩: between 115° and 117°.

Residue on ignition ⟨281⟩: not more than 0.1%.

Sensitiveness—Add 0.05 mL of an alcohol solution (1 in 200) and 2 g of ammonium chloride to 25 mL of carbon dioxide-free water: the lemon-yellow color of the solution is changed to orange by the addition of 0.05 mL of 0.1 N hydrochloric acid and restored on the subsequent addition of 0.05 mL of 0.1 N sodium hydroxide.

BRIEFING

***p*-Dimethylaminobenzaldehyde,** *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-4

Change to read:

***p*-Dimethylaminobenzaldehyde,** $(CH_3)_2NC_6H_4CHO$—**149.19**

■[*100-10-7*]■1S *(USP30)*
—Use ACS reagent grade.

BRIEFING

2,6-Dimethylaniline, *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-5

Change to read:

2,6-Dimethylaniline, $C_8H_{11}N$—**121.18**

■[*87-62-7*]■1S *(USP30)*
—Yellow liquid.

Refractive index ⟨831⟩: about 1.5609 at 20°.

BRIEFING

***N,N*-Dimethylaniline,** *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-6

Change to read:

***N,N*-Dimethylaniline,** $C_6H_5N(CH_3)_2$—**121.18**

■[*121-69-7*]■1S *(USP30)*
—Light yellow liquid. Clear, colorless liquid when freshly distilled, but acquiring a reddish to reddish-brown color. Specific gravity: about 0.960. Freezing point about 2°. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in dilute mineral acids.

In-Process Revision

Assay—Inject an appropriate specimen (about 0.2 µL) into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas flowing at about 40 mL per minute. The following conditions have been found suitable: a 3-mm × 1.8-m stainless steel column containing 20% phase G16 on support S1A; the injection port temperature is maintained at 250°; the column temperature is maintained at 50° and programmed to rise 10° per minute to 200°. The detector temperature is maintained at 310°. The area of the *N,N*-dimethylaniline peak having a retention time of about 11.5 minutes is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.5571 and 1.5591 at 20°.

Boiling range (Reagent test)—Distill 100 mL: the difference between the temperatures observed, when 1 mL and 95 mL have distilled, is not more than 2.5°. Its boiling temperature at a pressure of 760 mm of mercury is 194.2°.

Hydrocarbons—Dissolve 5 mL in a mixture of 10 mL of hydrochloric acid and 15 mL of water: a clear solution results and it remains clear on cooling to about 10°.

Aniline or monomethylaniline—Place 5 mL in a glass-stoppered flask, add 5 mL of a solution of acetic anhydride in benzene (1 in 10), mix, and allow to stand for 30 minutes. Add 30.0 mL of 0.5 N sodium hydroxide VS, shake the mixture, add phenolphthalein TS, and titrate with 0.5 N hydrochloric acid VS. Perform a blank determination, and make any necessary correction. Not more than 0.30 mL of 0.5 N sodium hydroxide is consumed by the test specimen.

BRIEFING

3,4-Dimethylbenzophenone, *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-7

Change to read:

3,4-Dimethylbenzophenone, $C_{15}H_{14}O$—**210.27**

■[*2571-39-3*]■1S (*USP30*)
—White chunks melting at about 45°.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with phase G1: the detector temperature and the injection port temperature are maintained at 300°; the column temperature is maintained at 180° and programmed to rise at the rate of 10° per minute to 280° and held at that temperature for 10 minutes. The area of the main peak is not less than 99% of the total peak area.

BRIEFING

5,5-Dimethyl-1,3-cyclohexanedione, *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-8

Change to read:

5,5-Dimethyl-1,3-cyclohexanedione, $C_8H_{12}O_2$—**140.18**

■[*126-81-8*]■1S (*USP30*)
—White, crystalline solid. Slightly soluble in water; soluble in alcohol, in methanol, in chloroform, and in acetic acid.

Melting range ⟨741⟩: between 148° and 150°.

BRIEFING

Dimethylformamide, *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-9

Change to read:

Dimethylformamide *(N,N-Dimethylformamide),* $HCON(CH_3)_2$—**73.09**

■[*68-12-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

***N,N*-Dimethylformamide Diethyl Acetal,** *USP 29* page 3127. It is proposed to delete this reagent. It will be available as a USP Reference Standard.

(HDQ: M. Marques) RTS—43908-3

Delete the following:

~~■***N,N*-Dimethylformamide Diethyl Acetal** **147.22** [*1188-33-6*]
Use a suitable grade.
[NOTE—A suitable grade is available from Sigma-Aldrich, www.sigma-aldrich.com.]■1S (*USP30*)~~

BRIEFING

***N, N*-Dimethyl-1-naphthylamine,** *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-10

In-Process Revision

Change to read:

***N,N*-Dimethyl-1-naphthylamine,** $C_{12}H_{13}N$—**171.24**

■[*86-56-6*]■1S (*USP30*)
—Pale yellow to yellow, aromatic liquid. Soluble in alcohol and in ether.

Assay—Transfer about 250 mg, accurately weighed, to a suitable beaker, add 100 mL of glacial acetic acid, and dissolve by stirring. When solution is complete, titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 17.12 mg of $C_{12}H_{13}N$. Not less than 98% is found.

Refractive index ⟨831⟩: between 1.6210° and 1.6230° at 20°, sodium light being used.

Sulfanilamide test—Dissolve 20 mg of USP Sulfanilamide RS in 100 mL of water to obtain the *Sulfanilamide solution*. Into two 150-mL beakers pipet 1.0 mL and 2.5 mL of the *Sulfanilamide solution,* respectively. Dilute with water to 90 mL. To provide a blank, place 90 mL of water in a third beaker. To each beaker add 8.0 mL of trichloroacetic acid solution (3 in 20) and 1.0 mL of sodium nitrite solution (1 in 1000). Stir the solutions for 5 minutes, then add 10 mL of acetate buffer TS, and 1.0 mL of a 1 in 1000 solution of *N,N*-dimethyl-1-naphthylamine in alcohol. The pH is about 5 to 6, using pH paper. Stir for an additional 5 minutes, then add 20 mL of glacial acetic acid. The pH is about 3 to 4, using pH paper. In comparison with the blank, the beaker containing 1.0 mL of the *Sulfanilamide solution* shows a pink color, while the other beaker shows a deep pink to red color.

BRIEFING

***N,N*-Dimethyloctylamine,** *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-11

Change to read:

***N,N*-Dimethyloctylamine,** $C_{10}H_{23}N$—**157.30**

■[*7378-99-6*]■1S (*USP30*)
—Colorless liquid.

Refractive index ⟨831⟩: 1.4243 at 20°.

BRIEFING

2,6-Dimethylphenol, *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-12

Change to read:

2,6-Dimethylphenol, $(CH_3)_2C_6H_3OH$—**122.16**

■[*576-26-1*]■1S (*USP30*)
—White to pale yellow crystalline solid.

Assay—Inject a 1 in 3 solution of it in xylene into a suitable gas chromatograph equipped with a flame-ionization detector, helium being used as the carrier gas at a flow rate of about 40 mL per minute. The following conditions have been found suitable: a 3.2-mm × 1.83-m stainless steel column packed with 10% phase G25 on support S1A; the injection port temperature is maintained at about 250° and the detector temperature at about 310°; the column temperature is programmed to rise at 8° per minute from 100° to 200°. Similarly inject a specimen of xylene. The area of the $C_8H_{10}O$ peak is not less than 98% of the total peak area corrected for xylene.

Melting range ⟨741⟩: between 44° and 46°.

BRIEFING

***N,N*-Dimethyl-*p*-phenylenediamine Dihydrochloride,** *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-13

Change to read:

***N,N*-Dimethyl-*p*-phenylenediamine Dihydrochloride,** $(CH_3)_2NC_6H_4NH_2 \cdot 2HCl$—**209.12**

■[*99-89-9*]■1S (*USP30*)
—Nearly white, fine, crystalline, hygroscopic solid that may have a pinkish cast. Freely soluble in water; soluble in alcohol.

Assay—Transfer about 400 mg, accurately weighed, to a 250-mL beaker, and dissolve in about 75 mL of water. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Each mL of 0.1 N sodium hydroxide is equivalent to 10.46 mg of $C_8H_{12}N_2 \cdot 2HCl$. Not less than 98% is found.

Solubility—A solution of 1 g in 10 mL of water produces not more than a slight haze.

BRIEFING

***m*-Dinitrobenzene,** *USP 29* page 3127—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-14

Change to read:

***m*-Dinitrobenzene,** $C_6H_4(NO_2)_2$—**168.11**

■[*99-65-0*]■1S (*USP30*)
—Pale yellow crystals or crystalline powder. Almost insoluble in cold water; slightly soluble in hot water. Soluble in chloroform and in benzene; sparingly soluble in alcohol. Is volatile in steam.

Melting range ⟨741⟩: between 89° and 92°.

Residue on ignition (Reagent test): not more than 0.5%.

In-Process Revision

BRIEFING

3,5-Dinitrobenzoyl Chloride, *USP 29* page 3128—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-15

Change to read:

3,5-Dinitrobenzoyl Chloride, $C_7H_3ClN_2O_5$—**230.56**

■[*74367-78-5*]■1S (*USP30*)
—Pale yellow, crystalline powder. Freely soluble in dilute sodium hydroxide solutions; soluble in alcohol. *[Caution—Corrosive, moisture-sensitive, lachrymator, and possible mutagen. Store under nitrogen.]*

Melting range ⟨741⟩: between 69° and 71°.

Solubility in sodium hydroxide—A solution of 500 mg in 25 mL of 1 N sodium hydroxide is clear or not more than faintly turbid.

Residue on ignition—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 1 mg (0.1%).

BRIEFING

2,4-Dinitrochlorobenzene, *USP 29* page 3128—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-16

Change to read:

2,4-Dinitrochlorobenzene, $C_6H_3(NO_2)_2Cl$—**202.55**

■[*97-00-7*]■1S (*USP30*)
—Yellow to brownish-yellow crystals. Insoluble in water; soluble in hot alcohol, in ether, and in benzene.

Melting range ⟨741⟩: between 51° and 53°.

Residue on ignition—Ignite 500 mg with 5 drops of sulfuric acid: the residue weighs not more than 1 mg (0.2%).

BRIEFING

2,4-Dinitrofluorobenzene, *USP 29* page 3128—See briefing under *Acetaldehyde.*

(HDQ: M. Marques) RTS—43402-17

Change to read:

2,4-Dinitrofluorobenzene *(1-Fluoro-2,4-dinitrobenzene),* $C_6H_3FN_2O_4$—**186.10**

■[*70-34-8*]■1S (*USP30*)
—Light yellow solid. Use a suitable grade.

BRIEFING

***n*-Heptane, Chromatographic,** *USP 29* page 3133. It is proposed to include a *Procedure* for the *Residue on evaporation* test.

(HDQ: M. Marques) RTS—43923-1

Change to read:

***n*-Heptane, Chromatographic**—Clear, colorless, volatile, flammable liquid consisting essentially of C_7H_{16}. ▲▲*USP29* Practically insoluble in water; soluble in absolute alcohol. Miscible with ether, with chloroform, with benzene, and with most fixed and volatile oils. [NOTE—*n*-Heptane may require purification by passage through a column of silica gel, a ratio of about 25 g of the gel for each 100 mL of *n*-heptane being used, and subsequent fractional distillation.]

Boiling range (Reagent test): between 94.5° and 99.0°.

Spectral purity—Measure in a 1-cm cell at 250 nm, with a suitable spectrophotometer, against water as the blank: its absorbance is not more than 0.10.

Residue on evaporation—~~It meets the requirements of the test for *Residue on evaporation* under *Hexane, Solvent.*~~

■Evaporate 150 mL (100 g) on a steam bath, and dry at 105° for 30 minutes: the residue weighs not more than 1 mg (0.001%).■1S (*USP30*)

BRIEFING

Iminostilbene, *USP 29* page 3134. It is proposed to delete this reagent. It will be available as a USP Reference Standard.

(HDQ: M. Marques) RTS—43908-2

Delete the following:

■~~**Iminostilbene,** $C_{14}H_{11}N$ **193.24** Yellow-orange powder. Sparingly soluble in ethyl acetate.~~

~~*Melting range* ⟨741⟩: between 197° and 201°.~~■1S (*USP30*)

BRIEFING

***N*-Methylpyrrolidine,** *USP 29* page 3139. It is proposed to correct the information regarding the quality grade of this reagent.

(HDQ: M. Marques) RTS—43854-1

In-Process Revision

Change to read:

***N*-Methylpyrrolidine** *(1-Methylpyrrolidine),* $C_4H_8NCH_3$—**85.15** [*120-94-5*]~~—Use ACS reagent grade.~~

■Use a suitable grade.■1S (*USP30*)

BRIEFING

Phenylhydrazine Hydrochloride, *USP 29* page 3145. It is proposed to revise the specifications for this reagent by replacing the tests for *Melting range, Solubility,* and *Residue on ignition* with an updated specification for a suitable grade.

(HDQ: M. Marques) RTS—43999-1

Change to read:

Phenylhydrazine Hydrochloride, $C_6H_5NHNH_2 \cdot HCl$—**144.60**—White or yellowish crystals or powder. Soluble in water and in alcohol. Store in tight containers, protected from light.

~~*Melting range* ⟨741⟩: between 242° and 246°, with slight darkening.~~

~~*Solubility*—Separate 500-mg portions dissolve in 10 mL of water and in 10 mL of alcohol, respectively, to yield solutions that are clear and complete or practically so.~~

~~*Residue on ignition* (Reagent test)—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 1 mg (0.1%).~~

■Use a suitable grade with a content of not less than 99%.■1S (*USP30*)

BRIEFING

Silica Gel, Octadecylsilanized Chromatographic, *USP 29* page 3151. It is proposed to update the supplier information for this reagent.

(HDQ: M. Marques) RTS—43926-1

Change to read:

Silica Gel, Octadecylsilanized Chromatographic—Use a suitable grade.

[NOTE—A suitable grade is available commercially as "Reversed Phase Uniplates" from ~~Analtech, Inc., Newark, DE 19711.~~

■Analtech, www.analtech.com.]■1S (*USP30*)

Volumetric Solutions

BRIEFING

Volumetric Solutions, *USP 29* page 3175 and page 1489 of *PF* 31(5) [Sept.–Oct. 2005]. It is proposed to make a correction in the formula used to calculate the normality of *Potassium Hydroxide, Normal (1 N)*.

(HDQ: M. Marques) RTS—43855-1

Change to read:

Potassium Hydroxide, Normal (1 N)
KOH, **56.11**

56.11 g in 1000 mL

Dissolve 68 g of potassium hydroxide in about 950 mL of water. Add a freshly prepared saturated solution of barium hydroxide until no more precipitate forms. Shake the mixture thoroughly, and allow it to stand overnight in a stoppered bottle. Decant the clear liquid, or filter the solution in a tight, polyolefin bottle, and standardize by the procedure set forth for *Sodium Hydroxide, Normal (1 N).*

~~$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH}}$$~~

■$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL KOH}}$$■1S (*USP30*)

Change to read:

Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)
NaOH, **40.00**

To 250 mL of alcohol add 2 mL of a 50% ~~(w/w)~~

■(w/v)■2S (*USP29*)
solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced.

$$N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL sodium hydroxide}}$$

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 29* page 3184 and page 187 of *PF* 32(1) [Jan.–Feb. 2006].

(HDQ) RTS—43284-1

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Add the following:	
▲Benazepril Hydrochloride Tablets	W ▲*USP30*
Add the following:	
■Citalopram ~~Hydrobromide~~ Tablets	W ■2S (*USP29*)
Add the following:	
■Black Cohosh Tablets	T, LR ■2S (*USP29*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W ■2S (*USP29*)
Add the following:	
■Diclofenac Potassium Tablets	T, LR ■2S (*USP29*)
Add the following:	
■Didanosine Tablets	T ■2S (*USP29*)
Add the following:	
▲Estradiol Vaginal Tablets	T ▲*USP30*
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W ■2S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Fexofenadine Hydrochloride Tablets	W ■2S (*USP29*)
Add the following:	
■Fluvoxamine Maleate Tablets	T ■1S (*USP29*)
Add the following:	
■Fosinopril Sodium Tablets	T ■2S (*USP29*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T ■2S (*USP29*)
Add the following:	
■Ginkgo Capsules	T, LR ■2S (*USP29*)
Add the following:	
■Ginkgo Tablets	T, LR ■2S (*USP29*)
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ■ ■2S (*USP29*)
Add the following:	
▲Glipizide and Metformin Hydrochloride Tablets	W ▲*USP30*
Add the following:	
■Glyburide and Metformin Hydrochloride Tablets	T, LR ■1S (*USP29*)
Add the following:	
■Irbesartan Tablets	W ■2S (*USP29*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W ■2S (*USP29*)
Add the following:	
■Isosorbide Mononitrate Tablets	T ■2S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■2S (*USP29*)
Add the following:	
■Ketoprofen Capsules, Extended-Release	T■2S (*USP29*)
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■2S (*USP29*)
Add the following:	
■Modafinil Tablets	T■2S (*USP29*)
Add the following:	
■Nefazodone Hydrochloride Tablets	T■2S (*USP29*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■2S (*USP29*)
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	T, LR■2S (*USP29*)
Add the following:	
■Quinapril Tablets	W■2S (*USP29*)
Add the following:	
■Tizanidine Tablets	T■2S (*USP29*)
Add the following:	
■Valerian Capsules	T, LR■2S (*USP29*)
Add the following:	
■Valganciclovir Tablets	T■1S (*USP30*)
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■2S (*USP29*)

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 29* page 3191, page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 812 of *PF* 29(3) [May–June 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 2183 of *PF* 30(6) [Nov.–Dec. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], page 1193 of *PF* 31(4) [July–Aug. 2005], page 1491 of *PF* 31(5) [Sept.–Oct. 2005], page 1703 of *PF* 31(6) [Nov.–Dec. 2005], and page 188 of *PF* 32(1) [Jan.–Feb. 2006].

(HDQ) RTS—42654-1; 43284-1; 43401-1; 43513-1

Add the following:

■**Coconut Oil:** Clear, white to light yellow-tan, viscous liquid. Freely soluble in methylene chloride and in light petroleum (bp: 65° to 70°); very slightly soluble in alcohol; practically insoluble in water. *NF category:* Coating agent; emulsifying and/or solubilizing agent.■1S (*NF25*)

Add the following:

■**Dantrolene Sodium:** Fine orange to orange-brown powder. Sparingly soluble in acetone, in dimethyformamide, and in glycerine.■1S (*USP30*)

Add the following:

■**Polyvinyl Acetate:** Colorless to light yellow granules or beads. Freely soluble in ethyl acetate; soluble in alcohol, in acetone, and in chloroform; practically insoluble in water. *NF category:* Coating agent; desiccant; tablet binder.■1S (*NF25*)

Add the following:

■**Valganciclovir Hydrochloride:** White to off-white powder. Very soluble in 2-propanol; freely soluble in alcohol; slightly soluble in hexane; practically insoluble in acetone or in ethyl acetate.■1S (*USP30*)

In-Process Revision

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 32(1) through 32(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF.*

Title and Proposal	***PF Volume, Issue, and Page Numbers of Pending Proposals***		
	Vol.	***No.***	***Page(s)***
General Notices—*Tests and Assays—Foreign Substances and Impurities; Preservation, Packaging, Storage, and Labeling—Storage Temperature and Humidity; Repackaging Instructions; Guidelines for Packaging and Storage Statements in USP–NF Monographs* (*Controlled Cold Temperature*-added)	31	3	718
<u>*USP Monographs*</u>			
Acetaminophen—*Packaging and storage*	31	4	1024
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetazolamide Oral Solution (new)	32	1	43
Acetazolamide Oral Suspension (new)	32	1	44
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Medical Air—*Definition, Packaging and storage*	31	4	1024
Albendazole Oral Suspension—*Labeling*	32	1	46
Alprazolam Oral Suspension (new)	32	1	46
Albumin Human—*Definition, Packaging and storage, Expiration date, Labeling, USP Reference standards* (add), *Identification A, B* (add), *Bacterial endotoxins* (add), *Safety* (add), *Sterility* (add), *pH* (add), *Molecular size distribution* (add), *Heat stability* (add), *Incubation* (add) *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add)	31	5	1338
Albuterol Tablets—*Assay*	31	3	726
Alendronate Sodium—*Packaging and storage*	31	5	1344
Allopurinol—*USP Reference standards, Assay*	28	5	1386
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Amantadine Hydrochloride—*Chromatographic purity*	31	5	1344
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—*Dissolution*	31	4	1025

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Amitriptyline Hydrochloride—*USP Reference standards, Identification, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	31	6	1606
Amoxicillin Capsules—*Labeling* (add), *Dissolution*	32	1	47
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water* (delete)	31	4	1026
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Aspartic Acid—*Chloride*	31	5	1345
Aspirin Boluses—*Dissolution*	31	4	1026
Atenolol—*Assay*	31	5	1345
Azathioprine Oral Suspension (new)	32	1	48
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Oral Solution (new)	32	1	49
Baclofen Oral Suspension (new)	32	1	51
Benazepril Hydrochloride (new)	31	4	1027
Benazepril Hydrochloride Tablets (new)	32	1	52
Benzonatate Capsules—*Dissolution* (add)	32	1	55
Betamethasone Oral Solution—*Thin-layer chromatographic identification test*	31	4	1032
Bethanechol Chloride Oral Solution (new)	32	1	55
Bethanechol Chloride Oral Suspension (new)	32	1	57
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	31	3	741
Bromocriptine Mesylate—*Chromatographic purity*	31	5	1346
Bromocriptine Mesylate Capsules—*Dissolution*	32	1	58
Budesonide (new)	30	6	1978
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butorphanol Tartrate Nasal Solution (new)	31	5	1346
Calcitonin Salmon (new)	31	4	1036
Calcitonin Salmon Nasal Solution (new)	30	4	1178
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	32	1	58
Calcitriol Injection (new)	32	1	61
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate—*USP Reference standards* (add), *Identification*	31	6	1608
Calcium Lactate Tablets—*Identification*	31	6	1609
Calcium Pantothenate—*USP Reference standards, Ordinary impurities*	32	1	62
Camphor—*Water*	31	3	742
Captopril Oral Solution (new)	32	1	63
Captopril Oral Suspension (new)	32	1	64
Carbamazepine—*USP Reference standards, Chromatographic purity (Related compounds), Assay*	32	1	65
Carbamazepine Tablets—*Dissolution*	31	4	1044
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium—*Heavy metals*	31	5	1349
Carboxymethylcellulose Sodium Paste—*Heavy metals*	31	5	1349
Cefaclor Tablets (new)	29	6	1858
Cefadroxil for Oral Suspension—*Water*	31	4	1045
Cefonicid for Injection—*Assay*	32	1	67
Ceftazidime—*USP Reference standards, Assay*	32	1	67

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(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Ceftazidime Injection—*USP Reference standards*	32	1	68
Ceftazidime for Injection—*USP Reference standards*	32	1	68
Chlorthalidone—*USP Reference standards, Limit of 4'-chloro-3'-sulfamoyl-2-benzophenone carboxylic acid (CCA) (Limit of chlorthalidone related compound A), Assay*	32	1	68
Cilostazol (new)	32	1	69
Cimetidine Tablets—*Dissolution*	32	1	72
Citalopram Hydrobromide (new)	31	3	742
Citalopram Tablets (new)	31	4	1046
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid (delayed implementation to January 1, 2009)*	31	2	394
Cladribine (new)	31	2	395
Cladribine—*Specific rotation, Related compounds, Limit of residual solvents*	31	6	1609
Clindamycin Hydrochloride Oral Solution—*pH*	31	5	1350
Clonazepam Oral Suspension (new)	32	1	73
Clopidogrel Bisulfate—*Related compounds, Assay*	32	1	74
Clopidogrel Tablets—*Related compounds, Assay*	32	1	76
Clotrimazole Lozenges—*Dissolution*	32	1	78
Cloxacillin Benzathine—*Assay*	31	4	1050
Cloxacillin Benzathine Intramammary Infusion—*Assay*	31	4	1051
Cyanocobalamin—*Pseudo cyanocobalamin*	31	5	1350
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Diclofenac Potassium (new)	31	5	1350
Diclofenac Potassium Tablets (new)	31	5	1352
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Didanosine (new)	31	5	1355
Didanosine for Oral Solution (new)	31	5	1357
Didanosine Tablets (new)	31	5	1359
Digoxin Oral Solution—*Assay*	31	5	1361
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diltiazem Hydrochloride Oral Solution (new)	32	1	79
Diltiazem Hydrochloride Oral Suspension (new)	32	1	80
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1612
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1614
Diphtheria Toxin for Schick Test (delete)	31	6	1616
Dipyridamole Oral Suspension (new)	32	1	81
Divalproex Sodium (new)	31	5	1362
Docusate Calcium—*Limit of bis(2-ethylhexyl)maleate*	31	3	752
Docusate Potassium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Docusate Sodium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Dolasetron Mesylate Oral Solution (new)	32	1	83

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Dolasetron Mesylate Oral Suspension (new)	32	1	84
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Dronabinol—*USP Reference standards, Identification, Limit of* Δ^8*-tetrahydrocannabinol* (delete), *Related compounds* (add), *Assay*	32	1	86
Drospirenone (new)	31	3	754
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Ensulizole—*USP Reference standards, Assay*	31	6	1617
Estradiol and Norethindrone Acetate Tablets (new)	31	5	1364
Estradiol Transdermal System (new)	31	4	1063
Estradiol Vaginal Tablets (new)	31	6	1617
Conjugated Estrogens—*Definition*	30	3	840
Synthetic Conjugated Estrogens (new)	31	6	1620
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add), *Related compounds*	31	4	1067
Ethyl Chloride—*Alcohol* (delete)	31	5	1368
Etidronate Disodium—*Limit of phosphite*	31	6	1625
Felodipine Extended-Release Tablets—*Labeling* (add), *Dissolution*	32	1	89
Fenofibrate (new)	31	3	763
Fentanyl (new)	31	6	1626
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Fluconazole—*Definition, Labeling* (add), *USP Reference standards, Melting range* (delete), *Related compounds*	31	5	1368
Flucytozine Oral Suspension (new)	32	1	92
Flumazenil—*USP Reference standards, Related compounds, Assay*	32	1	94
Fluorometholone Acetate (new)	31	5	1371
Flurazepam Hydrochloride—*Identification*	31	3	766
Flurbiprofen—*Identification*	31	4	1069
Fluticasone Propionate—*Chemical information, Definition, Content of acetone, Assay*	32	1	95
Fluticasone Propionate Nasal Spray (new)	32	1	97
Fluvastatin Sodium—*Packaging and storage, USP Reference standards, Identification, Loss on drying* (add), *Water* (delete), *Chromatographic purity*	32	1	103
Fluvastatin Capsules—*USP Reference standards, Identification, Chromatographic purity*	32	1	105
Fluvoxamine Maleate Tablets (new)	30	5	1622
Formoterol Fumarate (new)	32	1	106
Fosinopril Sodium (new)	32	1	110
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Ganciclovir Oral Suspension (new)	32	1	113
Gemcitabine for Injection—*USP Reference standards, Chromatographic purity*	31	6	1630
Gemcitabine Hydrochloride—*USP Reference standards*	32	1	114
Glipizide and Metformin Hydrochloride Tablets (new)	31	6	1631
Glucagon—*Assay*	31	6	1635
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Dissolution*	29	2	418
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Glycopyrrolate Tablets—*Identification*	31	4	1077
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	31	6	1637
Helium—*USP Reference standards* and *Assay* (postponed indefinitely)	31	4	1014

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Helium—*Definition, Packaging and storage*	31	4	1077
Hepatitis B Virus Vaccine Inactivated (delete)	31	6	1641
Hydrocodone Bitartrate—*USP Reference standards* *Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hydroxyzine Hydrochloride—*USP Reference standards, Chromatographic purity*	32	1	114
Hyoscyamine Sulfate—*USP Reference standards, Identification, Melting temperature* (delete), *Loss on drying* (delete), *Water* (add), *Residue on ignition, Other alkaloids* (delete), *Readily carbonizable substances* (delete), *Chromatographic purity* (add), *Assay*	31	4	1078
Hyoscyamine Sulfate Elixir—*Identification*	31	5	1372
Hyoscyamine Sulfate Injection—*Identification*	31	5	1373
Hyoscyamine Sulfate Oral Solution—*Identification*	31	5	1373
Hyoscyamine Sulfate Tablets—*Identification*	31	5	1374
Hypromellose Ophthalmic Solution—*Identification*	31	3	771
Ibuprofen—*Assay*	31	5	1374
Insulin—*USP Reference standards*	31	5	1375
Insulin Human—*USP Reference standards*	31	5	1375
Sodium Iodide I 123 Capsules—*Definition*	31	6	1642
Sodium Iodide I 123 Solution—*Definition, Radionuclidic purity, Bacterial endotoxins, pH*	31	6	1642
Sodium Iodide I 131 Solution—*pH*	31	6	1643
Iodoform—*Molecular weight*	32	1	115
Irbesartan—*Limit of azide*	32	1	115
Irbesartan Tablets (new)	31	4	1080
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isopropyl Alcohol—*USP Reference standards* (add), *Identification*	31	5	1375
Isosorbide Dinitrate Tablets—*Dissolution, Assay*	31	5	1375
Isosorbide Dinitrate Chewable Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Extended-Release Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Sublingual Tablets—*Assay*	31	5	1377
Diluted Isosorbide Mononitrate—*USP Reference standards, Identification, pH* (delete), *Water* (delete), *Residue on ignition* (delete), *Related compounds, Assay*	31	6	1643
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082
Ivermectin—*Specific rotation, Limit of alcohol and formamide*	31	6	1645
Ketoprofen—*Assay*	31	3	772
Ketoprofen Extended-Release Capsules (new)	31	5	1378
Labetalol Hydrochloride Oral Solution (new)	32	1	116
Labetalol Hydrochloride Oral Suspension (new)	32	1	117
Leflunomide (new)	31	5	1380
Leflunomide Tablets (new)	31	5	1383
Leuprolide Acetate (new)	30	3	882
Levocabastine Hydrochloride (new)	31	6	1647
Lidocaine and Prilocaine Cream (new)	31	4	1087
Lindane—*Definition, Assay*	31	6	1648
Lipid Injectable Emulsion (new)	31	2	416
Lisinopril Tablets—*Dissolution*	31	4	1090
Lovastatin—*Assay*	32	1	118
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	419
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	31	5	1386
Magnesium Chloride—*Identification*	31	2	420

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	421
Magnesium Oxide—*Labeling, Bulk density* (add)	31	4	1091
Mangafodipir Trisodium—*Limit of residual solvents*	31	6	1650
Mebendazole Oral Suspension—*Labeling*	32	1	119
Megestrol Acetate Oral Suspension—*Dissolution*	31	5	1387
Meloxicam (new)	31	1	57
Metformin Hydrochloride—*Related compounds*	31	4	1092
Metformin Hydrochloride Tablets—*Identification, Related compounds*	31	4	1093
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
Methoxyflurane—*Foreign odor* (delete)	31	5	1388
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Metolazone Oral Suspension (new)	32	1	119
Metoprolol Tartrate Oral Solution (new)	32	1	121
Metoprolol Tartrate Oral Suspension (new)	32	1	122
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Miconazole Nitrate Cream—*Identification*	32	1	123
Miconazole Nitrate Vaginal Suppositories—*Assay*	31	5	1389
Mirtazapine—*Heavy metals*	31	6	1650
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Morphine Sulfate Extended-Release Capsules—*Packaging and storage* (add)	32	1	124
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage* (add)	32	1	124
Narasin Granular—*Molecular weight, Assay*	32	1	124
Narasin Premix—*Assay*	32	1	126
Nefazodone Hydrochloride (new)	31	4	1094
Nefazodone Hydrochloride Tablets (new)	31	4	1096
Nitrous Oxide—*USP Reference standards, Identification,* and *Assay* (postponed indefinitely)	31	4	1014
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate—*USP Reference standards, Limit of residual solvents, Chromatographic purity, Assay*	31	5	1390
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole—*Chromatographic purity*	31	4	1100
Omeprazole Delayed-Release Capsules—*Identification, Chromatographic purity*	31	5	1392
Ondansetron Hydrochloride—*Limit of ondansetron related compound D, Assay*	32	1	126
Ondansetron Hydrochloride Oral Suspension (new)	32	1	127
Ondansetron Injection—*Chromatographic purity*	31	6	1651
Ondansetron Oral Solution—*Packaging and storage* (add), *Limit of ondansetron related compound D, Related compounds*	32	1	128
Ondansetron Orally Disintegrating Tablets (new)	31	4	1101
Orphenadrine Citrate Injection—*Assay*	31	6	1651
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete), *Related compounds* (add), *Assay*	31	1	64
Oxaprozin—*Packaging and storage* (add)	32	1	130
Oxaprozin Tablets—*Packaging and storage* (add)	32	1	130

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Oxybutynin Chloride Extended-Release Tablets (new)	31	6	1652
Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxygen—*Definition, Packaging and storage*	31	4	1107
Oxygen 93 Percent—*Definition, Packaging and storage*	31	4	1107
Pamidronate Disodium (new)	31	4	1108
Pamidronate Disodium for Injection (new)	31	4	1111
Pancuronium Bromide (new)	32	1	130
Paricalcitol—*Identification, Chromatographic purity, Assay*	32	1	132
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital Sodium—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piroxicam Cream (new)	32	1	134
PEG 3350 and Electrolytes for Oral Solution—*Title* (name change—*delayed implementation to February 1, 2009*), *Definition, Assay for potassium and sodium*	31	5	1393
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay (delayed implementation to January 1, 2009)*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Pravastatin Sodium (new)	31	5	1394
Prednicarbate (new)	31	5	1398
Prednicarbate Cream (new)	31	6	1655
Prednicarbate Ointment (new)	31	6	1657
Pseudoephedrine Sulfate—*Ordinary impurities*	32	1	135
Quinapril Tablets—*Packaging and storage*	29	4	1071
Quinidine Sulfate Oral Suspension (new)	32	1	136
Ramipril—*Definition, Assay*	31	3	787
Ranitidine Hydrochloride—*USP Reference standards, Chromatographic purity, Assay*	30	6	2033
Oral Rehydration Salts—*USP Reference standards* (add), *Identification F* (delete), *Assay for citrate (delayed implementation to January 1, 2009)*	31	5	1399
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Risperidone (new)	31	6	1659
Ritonavir (new)	31	3	788
Rubella and Mumps Virus Vaccine Live (delete)	31	6	1662
Saccharin Calcium (new)—*Harmonization*	31	2	607
Saccharin Sodium (new)—*Harmonization*	31	4	1225
Saquinavir Mesylate—*Identification*	31	5	1400
Schick Test Control (delete)	31	6	1662
Senna—*Title, Definition, Packaging and storage, Labeling* (add), *USP Reference standards* (add), *Botanic characteristics, Identification, Microbial enumeration* (add) *Loss on drying* (add), *Total ash* (add), *Assay* (add)	32	1	137
Senna Pods (new)	32	1	140

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Sennosides—*Definition, Packaging and storage, Residue on ignition*	32	1	141
Sevoflurane (new)	30	1	178
Simvastatin—*Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	32	1	141
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	31	3	795
Sodium Bicarbonate Injection—*Packaging and storage*	31	5	1401
Sodium Chloride—*Identification, Loss on drying, Limit of phosphates, Limit of potassium*	31	5	1401
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate (delayed implementation to April 1, 2009)*	31	3	797
Sodium Lactate Injection—*Identification B* (delete)	31	5	1402
Sodium Phosphates Rectal Solution—*Assay*	31	5	1403
Sodium Salicylate Tablets—*USP Reference standards* (add)	31	4	1116
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Stavudine Capsules—*Assay*	31	5	1403
Succinylcholine Chloride—*Limit of ammonium salts* (delete), *Chromatographic purity*	31	5	1404
Sulfamethazine Granulated—*Assay*	31	3	797
Sumatriptan Succinate Oral Suspension (new)	32	1	144
Talc—*Packaging and storage* (new), *Limit of iron, Limit of calcium, Limit of aluminum*	31	6	1662
Tazobactam (new)	31	4	1116
Technetium Tc 99m Fanolesomab Injection (new)—*Packaging and storage* (add)	31	5	1405
Temazepam—*Identification*	32	1	145
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Thalidomide—*Microbial limits, Chromatographic purity*	32	1	146
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thimerosal—*Identification*	32	1	147
Thioridazine Hydrochloride—*Identification*	31	3	798
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Titanium Dioxide—*Definition, Packaging and storage, Labeling, Loss on ignition, Water-soluble substances, Acid-soluble substances, Limit of lead* (add), *Limit of antimony* (add), *Limit of mercury* (add), *Organic volatile impurities* (delete), *Assay*	30	4	1301
Tizanidine Tablets (new)	32	1	147
Tolazamide—*Chromatographic purity*	31	4	1118
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Travoprost (new)	31	4	1119
Travoprost Ophthalmic Solution (new)	31	4	1121
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800
Tricitrates Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	465
Triclosan—*USP Reference standards; Limit of monochlorophenols and 2,4-dichlorophenol; Limit of 1,3,7-trichlorodibenzo-p-dioxin, 2,8-dichlorodibenzo-p-dioxin, 2,8-dichlorodibenzofuran, and 2,4,8-trichlorodibenzofuran; Assay*	31	5	1408
Trimethoprim—*Packaging and storage*	31	5	1409
Tryptophan—*Chloride, Sulfate*	31	5	1410
Tylosin Tartrate (new)	31	5	1410
Ursodiol Capsules—*Dissolution*	31	3	800
Valsartan (new)	32	1	150
Valsartan and Hydrochlorothiazide Tablets (new)	31	4	1123
Valproic Acid Injection (new)—*Title (delayed implementation to October 1, 2007)*	31	5	1412
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add)	30	6	2055
Vasopressin—*Identification*	31	4	1127

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Verapamil Hydrochloride Injection—*USP Reference standards, Related compounds*	32	1	154
Verapamil Hydrochloride Oral Solution (new)	32	1	155
Verapamil Hydrochloride Oral Suspension (new)	32	1	156
Verapamil Hydrochloride Tablets—*USP Reference standards, Related compounds*	32	1	158
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins*	31	2	468
Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Sterile Purified Water—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Zidovudine Tablets—*USP Reference standards, Related compounds, Assay*	32	1	158
<u>*Dietary Supplements Monographs*</u>			
Ademetionine Disulfate Tosylate (new)	31	2	469
Acesulfame Potassium—*Packaging and storage* (add), *Limit of fluoride*	31	3	811
Black Cohosh (new)	28	5	1455
Powdered Black Cohosh (new)	28	5	1460
Powdered Black Cohosh Extract (new)	28	5	1461
Black Cohosh Tablets (new)	28	5	1462
Ethylcellulose Aqueous Dispersion—*Identification*	31	3	811
Ethylparaben—*Identification*	31	3	812
Gamma Cyclodextrin (new)	31	3	812
Ginger—*Packaging and storage, Labeling, USP Reference standards, Identification, Microbial enumeration, Alcohol-soluble extractives, Limit of shogaols, Content of gingerols and gingerdiones*	32	1	160
Powdered Ginger—*Packaging and storage, USP Reference standards*	32	1	162
Ginger Capsules—*USP Reference standards, Content of gingerols, gingerdiones, and shogaols*	32	1	163
Ginger Tincture—*USP Reference standards, Thin-layer chromatographic identification test, Microbial enumeration, Content of gingerols*	32	1	163
Ginkgo—*Definition, Packaging and storage, USP Reference standards, Thin-layer chromatographic identification test, Microbial enumeration, Content of terpene lactones*	32	1	164
Powdered Ginkgo Extract (new)	32	1	166
Ginkgo Capsules (new)	32	1	172
Ginkgo Tablets (new)	32	1	174
Lutein—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1133
Lutein Preparation—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1134
Tomato Extract Containing Lycopene—*Microbial enumeration, Limit of aflatoxins*	30	2	578
Maleic Acid—*Identification*	31	3	815
Maltose—*Water*	31	3	815
Fish Oil Containing Omega-3 Acids (new)	31	2	474
Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481

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Olive Oil—*Definition, Labeling* (add), *Teaseed oil*	31	3	815
Phenoxyethanol—*Chromatographic purity, Assay*	31	3	816
Polyethylene Glycol (new)—*Harmonization*	31	3	897
Polyoxyl 10 Oleyl Ether—*Free ethylene oxide*	31	3	816
Polyoxyl 20 Oleyl Cetostearyl Ether—*Free ethylene oxide*	31	3	817
Pygeum Extract—*Packaging and storage*	30	3	956
Sodium Benzoate—*USP Reference standards* (add), *Identification*	31	3	818
Sucrose (new)—*Harmonization*	31	3	902
Sugar Spheres—*Identification, Specific rotation*	31	3	819
Tagatose (new)	31	3	819
Thymol—*USP Reference standards* (add), *Identification*	31	3	821
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Xanthan Gum—*Assay*	31	3	821
USP General Test Chapters			
⟨1⟩ Injections—*Labels and Labeling, Packaging*	31	5	1428
⟨1⟩ Injections—*Packaging—Printing on Ferrules and Cap Overseals* (postponed indefinitely)	31	6	1599
⟨1⟩ Injections *(Harmonization)—Packaging*	31	1	192
⟨11⟩ USP Reference Standards—	26	4	1101
	27	1	1832
	27	6	3348
	28	2	433
	28	3	839
	28	5	1468
	29	3	710
	29	5	1601
	29	6	2022
	30	2	613
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
	31	3	822
	31	4	1154
	31	5	1433
	31	6	1680
	32	1	181
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests *(Harmonization)—Title, Introduction, General Procedures, Enumeration Methods, Growth Promotion Test and Suitability of the Counting Method, Testing of Products*	29	5	1714
⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) *(Harmonization)—Title, Introduction, General Proce dures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
⟨121⟩ Insulin Assays—*Appendix* (add)	30	5	1675
⟨231⟩ Heavy Metals—*Method II*	32	1	182
⟨267⟩ Porosimetry by Mercury Intrusion (new)—*Harmonization*	31	3	905
⟨281⟩ Residue on Ignition—*Harmonization*	31	5	1526
⟨345⟩ Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514
⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures (delayed implementation to January 1, 2006)*	30	1	220
⟨401⟩ Fats and Fixed Oils—*Acid Value (Free Fatty Acids)*	31	4	1157

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⟨429⟩ Light Diffraction Measure of Particle Size (new)—*Harmonization*	31	4	1234
⟨467⟩ Organic Volatile Impurities—*Title (delayed implementation to January 1, 2007); Residual Solvents Limits; Identification, Control, and Quantification of Residual Solvents; Other Analytical Procedures* (delete); *Appendix 1*	31	5	1435
⟨616⟩ Bulk Density and Tapped Density—*Harmonization*	31	3	909
⟨621⟩ Chromatography—*Interpretation of Chromatograms, System Suitability, Glossary of Symbols, Chromatographic reagents*	31	6	1681
⟨644⟩ Conductivity (new)	31	3	841
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨699⟩ Density of Solids (new)—*Harmonization*	31	3	912
⟨711⟩ Dissolution—*Introduction, Procedure, Interpretation*	31	6	1691
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	31	5	1448
⟨730⟩ Inductively-Coupled Plasma—*References* (add)	30	3	1022
⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	31	3	845
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *(Harmonization)*	31	1	228
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
⟨941⟩ X-Ray Diffraction (new)—*Harmonization*	31	4	1241
General Information Chapters			
⟨1058⟩ Analytical Instrument Qualification (new)	31	5	1453
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	30	5	1706
⟨1072⟩ Disinfectants and Antiseptics (new)	30	6	2108
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients—*Background* (delete), *General Guidance* (delete), *Excipient Quality Systems* (delete), *Appendix 1* (delete), *Appendix* (delete), *Background* (add), *General Guidance* (add), *Quality Management System—Excipient Quality Systems* (add), *Management Responsibility* (add), *Resource Management* (add), *Product Realization* (add), *Measurement, Analysis, and Improvement* (add), *Appendix 1* (add), *Appendix 2* (add)	28	5	1504
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	31	4	1167
⟨1082⟩ Genotoxicity Testing (new)	30	1	264
⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1092⟩ The Dissolution Procedure: Development and Validation (new)	31	5	1463
⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products—*Introduction (Tables 1 and 2)*	29	5	1733
⟨1112⟩ Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new)	30	5	1709

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⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add),*Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding—*Basic Pharmaceutical Calculations*	31	3	847
⟨1184⟩ Sensitization Testing (new)	30	1	289
⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)	31	4	1180
⟨1208⟩ Sterility Testing—Validation of Isolator Systems—*Introduction, Isolator Design and Construction, Validation of the Isolator System, Package Integrity Verification, Maintenance of Asepsis Within the Isolator Environment, Interpretation of Sterility Test Results, Training and Safety*	30	6	2162
⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1217⟩ Tablet Breaking Force (new)	31	6	1695
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1223⟩ Validation of Alternative Microbiological Methods (new)	31	5	1475
⟨1225⟩ Validation of Compendial Methods—*Title, Introduction, Submissions to the Compendia, Validation*	31	2	549
⟨1226⟩ Verification of Compendial Procedures (new)	31	2	555
⟨1230⟩ Water for Health Applications—*Microbial Considerations*	31	5	1486
⟨1232⟩ Instrumentation for Analysis of High Purity Pharmaceutical Waters (new)	30	5	1806
⟨2030⟩ Supplemental Information for Articles of Botanical Origin (new)	31	2	555
⟨2040⟩ Disintegration and Dissolution of Dietary *Supplements—Disintegration, Rupture Test for Soft Gelatin Capsules* (add)	32	1	184
Reagent Specifications			
2-Aminophenol	31	5	1487
3-Aminopropionic Acid	31	4	1189
3-Aminosalicylic Acid	31	5	1487

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L-Arabinitol (delete)	31	5	1487
Bacterial Alkaline Protease Preparation	30	2	644
Barbituric Acid (new)	29	1	265
Benzaldehyde	31	2	574
1-Butaneboronic Acid (delete)	31	4	1189
Butyl Methacrylate (new)	31	4	1189
n-Butylboronic Acid	31	4	1189
Deuterated Methanol (new)	29	6	2054
Dextran, High Molecular Weight	32	1	186
2,8-Dichlorodibenzo-*p*-dioxin (delete)	30	6	2168
2,8-Dichlorodibenzofuran (delete)	30	6	2168
2,4-Dichlorophenol (delete)	30	6	2168
Dicyclohexyl	31	3	858
DEAE-Agarose (new)	29	1	265
2-Dimethylaminoethyl Methacrylate (new)	31	4	1190
N,N-Dimethyldodecylamine-*N*-oxide (new)	27	4	2837
Docusate Sodium (new)	31	4	1190
Dodecyltrimethylammonium Bromide (new)	31	3	859
Erythritol (delete)	31	5	1487
Ethylene Oxide in Methylene Chloride (50 mg/mL) (new)	31	3	859
Furfural	31	4	1190
Galactitol (delete)	31	5	1488
Geneticin (new)	31	6	1700
Hexadimethrine Bromide (new)	29	1	265
Hydrazine Hydrate, 85% in Water	32	1	186
Hydroxypropyl-β-cyclodextrin (new)	31	6	1701
Isoferulic Acid (new)	27	4	2837
Isopropyl Iodide	31	6	1701
Lead Standard Solution (new)	31	5	1488
Magnesium Matrix Modifier (new)	31	5	1488
1-Naphthol	32	1	186
Nitric Acid, 65 Percent (new)	31	5	1488
Palladium Matrix Modifier (new)	31	5	1488
Anion-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Cation-Exchange Resin, Styrene-Divinylbenzene	30	3	1043
Thrombin Human (new)	29	6	2055
p-Toluenesulfonyl-L-arginine Methyl Ester Hydrochloride	32	1	186
2,4,8-Trichlorodibenzofuran (delete)	30	6	2169
1,3,7-Trichlorodibenzo-*p*-dioxin (delete)	30	6	2169
Saccharin Calcium	31	2	607
Saccharin Calcium—*Harmonization*	31	2	609
Saccharin Sodium	31	2	612
Saccharin Sodium—*Harmonization*	31	2	613
Sodium Carbonate, Monohydrate (new)	31	6	1701
1-Vinyl-2-pyrrolidone	31	6	1701
Zinc Sulfate Heptahydrate (new)	26	2	504
Test Solutions			
Phenol TS (new)	31	3	859
Sodium Citrate TS, Alkaline (new)	31	3	859
Sodium Tetraphenylboron TS	31	5	1489
Volumetric Solutions			
Iodine, Hundreth-Normal (0.01 N)	31	5	1489
Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)	31	5	1490
Reference Tables			
Container Specifications for Capsules and Tablets	32	1	187
Excipients, USP and NF Excipients, Listed by Category	31	6	1664
Description and Solubility	25	4	8589
	25	6	9254
	26	4	1135
	27	1	1908

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
	28	2	554
	28	6	1953
	29	1	266
	29	3	812
	29	5	1684
	30	4	1405
	30	5	1822
	31	1	122
	31	2	591
	31	3	861
	31	4	1193
	31	5	1491
	31	6	1703
	32	1	188
NF Monographs			
Acetyltributyl Citrate—*Assay*	32	1	177
Acetyltriethyl Citrate—*Assay*	32	1	178
Amino Methacrylate Copolymer (new)	31	4	1137
Calcium Silicate—*Definition, USP Reference standards* (add), *pH, Lead* (delete), *Limit of lead* (add), *Limit of fluoride, Assay for silicon dioxide, Assay for calcium oxide, Ratio of silicon dioxide to calcium oxide*	31	5	1417
Canola Oil (new)	31	6	1667
Carboxymethylcellulose Calcium—*Heavy metals*	31	5	1420
Carboxymethylcellulose Sodium 12—*Labeling, Viscosity, Heavy metals*	31	5	1420
Cellaburate—*Packaging and storage* (add)	31	5	1420
Cellacefate—*USP Reference standards*	32	1	179
Microcrystalline Cellulose—*Labeling, Identification, Particle size distribution estimation by analytical sieving*	31	5	1421
Powdered Cellulose—*Identification B*	31	5	1421
Corn Syrup (new)	28	2	403
High Fructose Corn Syrup (new)	28	2	408
Corn Syrup Solids (new)	28	6	1894
Crospovidone—*Monograph*	28	4	1257
Cyclomethicone—*Identification*	31	4	1140
Dibutyl Sebacate—*Saponification value*	31	4	1140
Diethanolamine—*USP Reference standards* (add), *Identification*	31	5	1422
Diisopropanolamine (new)	31	4	1140
Erythritol (new)	31	5	1422
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion (new)	31	4	1141
Ethylcellulose Aqueous Dispersion—*Labeling, Identification*	31	6	1668
Glyceryl Monostearate—*Labeling, USP Reference standards* (delete), *Assay for monoglycerides*	31	6	1669
Hydroxyethyl Cellulose (new)—*Harmonization*	30	2	709
Hydroxypropyl Cellulose—*USP Reference standards* (add), *Identification*	31	5	1425
Low-Substituted Hydroxypropyl Cellulose—*Harmonization*	30	1	338
Isobutane—*Limit of sulfur compounds* (delete)	31	5	1425
Lactitol—*Related compounds*	31	4	1143
Magnesium Stearate—*Microbial limits*	29	6	2018
Magnesium Stearate—*Harmonization*	30	1	340
Maltitol (new)	31	4	1143
Maltol—*Packaging and storage*	31	5	1425
Monoethanolamine—*USP Reference standards* (add), *Identification* (add)	31	5	1425
Nitrogen—*Definition, Packaging and storage, Assay*	31	4	1145
Nitrogen 97 Percent—*Definition, Packaging and storage, Assay*	31	4	1146
Oleyl Oleate (new)	31	6	1670
Paraffin—*Readily carbonizable substances*	31	5	1426

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Polacrilin Potassium—*CAS number, Chemical name*	31	6	1671
Polyethylene Glycol—*Harmonization*	31	3	897
Polyoxyl 35 Castor Oil—*Viscosity*	31	6	1671
Potassium Alginate (new)	31	5	1426
Saccharin	31	2	616
Saccharin (new)—*Harmonization*	31	2	618
Sesame Oil—*USP Reference standards* (add), *Triglyceride composition*	30	5	1668
Silicon Dioxide (new)—*Harmonization*	31	4	1229
Colloidal Silicon Dioxide (new)—*Harmonization*	31	4	1233
Sodium Starch Glycolate—*Harmonization*	31	5	1523
Sodium Sulfite—*Identification*	31	4	1146
Sorbitol Sorbitan Solution—*Title statement*	31	6	1671
Rice Starch (new)—*Harmonization*	30	2	721
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706
Sucralose—*Limit of hydrolysis products*	31	4	1146
Sucrose—*Harmonization*	31	3	902
Compressible Sugar—*Loss on drying*	31	4	1147
Confectioner's Sugar—*Identification*	31	4	1147
Strawberry Syrup (new)	32	1	179
Tagatose (new)	30	5	1672
Tetrafluoroethane (new)	31	6	1672
Tributyl Citrate—*Assay*	32	1	179
Triethyl Citrate—*Assay*	32	1	180
Trolamine—*USP Reference standards* (add), *Identification*	31	5	1427
Xylitol—*USP Reference standards, Limit of other polyols, Assay*	31	4	1147

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
USP Monographs			
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albuterol Tablets—			
Dissolution	30	1	50
Dissolution	31	1	40
†Allopurinol—*Chromatographic purity, Related compounds*	28	5	1386
Alprazolam Tablets—*Dissolution*	30	5	1582
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Baclofen Tablets—*Dissolution*	30	1	61
Betamethasone Tablets—*Dissolution*	30	1	62
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Carboxymethylcellulose Sodium Suspension (entire submission)	30	3	812
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Colchicine Tablets—*Dissolution*	30	1	91
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add)	29	6	1870
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Estradiol Transdermal System (new)—*Drug release*	30	4	1201
Ethinyl Estradiol Tablets—*Related compounds*	31	2	402
Ethosuximide Capsules—*Dissolution*	30	1	102
Fluticasone Propionate—*Content of acetone (Procedure)*	31	4	1070
Gabapentin Capsules (new) (entire submission)	28	2	298
Glycopyrrolate Tablets—*Dissolution*	30	1	105
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Indocyanine Green—*Definition, Assay*	29	6	1905

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Irbesartan Tablets (new)—*Dissolution*	29	4	1035
Isosorbide Dinitrate Sublingual Tablets—*Dissolution*	30	1	113
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Levothyroxine Sodium Oral Solution (new)—*Preview*	31	3	938
Lisinopril Tablets—*Dissolution*	30	1	121
Loperamide Hydrochloride Tablets—*Dissolution*	30	5	1633
Magnesium Oxide—*Bulk density* (add)	29	4	1047
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Meprobamate Tablets—*Dissolution*	30	1	129
Methenamine Tablets—*Dissolution*	30	1	130
Methocarbamol Tablets—*Dissolution*	30	1	130
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Ondansetron Orally Disintegrating Tablets (new)—*Disintegration, Dissolution*	30	6	2024
Oxybutynin Chloride Extended-Release Tablets (new) (entire submission)	30	4	1276
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
Penicillamine Capsules—*Dissolution*	30	1	153
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036
Spironolactone Oral Suspension (new) (entire submission)	30	3	929
Spironolactone and Hydrochlorothiazide Oral Suspension (new) (entire submission)	30	3	930
Terbutaline Sulfate Tablets—*Dissolution*	31	1	76
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Timolol Maleate Tablets—*Dissolution*	30	1	191
Titanium Dioxide (new) (entire submission)	30	4	1304
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Vecuronium Bromide for Injection (new)—*Preview*	25	4	8449
Dietary Supplements Monographs			
Ginkgo Capsules (new)—*Disintegration and dissolution*	27	2	2238
Ginkgo Tablets (new)—*Disintegration and dissolution*	27	2	2240
Asian Ginseng Capsules (new)—*Dissolution*	30	2	571
American Ginseng Capsules (new)—*Dissolution*	30	2	565
American Ginseng Tablets—*Dissolution*	30	2	567
Valerian Capsules (new)—*Disintegration and dissolution*	27	1	1825
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
USP Fluvastatin for System Suitability RS (add)	31	1	99
USP Polyoxyl 35 Castor Oil RS	30	5	1674
†⟨41⟩Weights and Balances (entire submission)	31	2	508

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
⟨386⟩ Environmentally Sensitive Preparations (new) (entire submission)	30	5	1680
⟨429⟩ Light Diffraction Measure of Particle Size (new) (entire submission)	28	3	895
⟨621⟩ Chromatography—*System Suitability (All revisions after the first two paragraphs, through the end up to Glossary)*	30	6	2094
⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets* (delete), *Interpretation*	30	1	234
USP General Information Chapters			
⟨1089⟩ In Vitro, Absorption-Indicating Cell Culture System (new)—*Preview*	25	5	8733
Reagents, Indicators, and Solutions			
1,4-Butanediol (add)—*Preview*	25	5	8747
1-Vinyl-2-pyrrolidone	31	1	108
Reference Tables			
Container Specifications			
Citalopram Hydrobromide Tablets (add)	31	3	859
Description and Relative Solubility			
Magnesium Oxide	29	4	1262
Titanium Dioxide (add)	30	4	1405
NF Monographs			
Alfadex—*Packaging and storage*	30	1	202
Sodium Caprylate—*Packaging and storage*	30	3	990

†New cancellations in *PF* 32(2).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

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

BRIEFING

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

(DSN: L. Evans) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in the *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

All manuscripts are subject to review by USP headquarters staff, Committee members, or qualified outside referees, and if accepted for publication will be subject to editing by USP staff. Accepted manuscripts become the property of the USP Convention (USPC) and may not be published elsewhere without written permission from the USPC. Authors are also responsible for obtaining permission for reprinting any illustrations that have been published elsewhere.

Abstract—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

References—Consult a current copy of the *Pharmacopeial Forum* and the *ACS Style Guide* for assistance with reference style.

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Contact Person—When submitting a manuscript, designate one author of the article as correspondent and include that author's full address, telephone number, fax number, and e-mail address.

Submission Instructions—Manuscripts must be submitted both as an electronic file and as a printed copy of the electronic file. Submit the text in Microsoft® Word or another current word-processing application. The preferred format for graphics submitted electronically is tagged image file format (TIFF). Graphics that cannot be submitted electronically must be camera-ready, of easily reproducible quality and size, and clearly labeled. Photocopies are not acceptable. Manuscripts submitted for publication should be addressed to:

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The Role of Container–Closure Systems in Stability Testing For Climate Zone IV*

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ABSTRACT The authors suggest that designation of long-term stability test conditions must include the effect of barrier packaging on the atmosphere inside the package. In December 2004, the Association of South East Asian Nations (ASEAN) proposed to the World Health Organization (WHO) that the standard for long-term stability testing for markets in Climate Zone IV be changed from 30 °C, 65% relative humidity (RH) to 30 °C, 75% RH. The argument for this proposal was based on the effect of absolute humidity on drug products. It did not take into account the effect of barrier packaging on control of the absolute humidity inside the package. The authors stipulate that selection of stability test conditions must include consideration of package permeation, storage temperature, and the permeation driving force, i.e., partial pressure for water vapor. The authors show that for challenge of the packaged drug product, relative humidities lower than 75% at 30 °C would adequately represent the ASEAN countries' Climate Zone average condition of 27 °C, 79% RH. Laboratory testing is advised.

INTRODUCTION

Some questions have been raised during international discussions of test conditions for stability testing for Climate Zone IV (*1–5*). The current ASEAN Climate Zone IV is 30 °C, 66% RH. At the ''Consultation to Discuss Stability Studies in a Global Environment'' on 13–14 December 2004 at WHO Headquarters in Geneva, it was proposed by the ASEAN countries that stability test conditions for Climate Zone IV should be changed to 30 °C and 75% RH. This would result in a change to the WHO Guidelines for stability testing. The ''Recommendations Agreed To by the Meeting'' (*1*) recognized three options available to WHO. The options are the following: 1) revert to 30 °C, 70% RH; 2) change to 30 °C, 75% RH; or 3) add a new Climate Zone IVb (30 °C, 75% RH), making the present 30 °C, 65% RH the stability test condition for Climate Zone IVa. Delegates were charged with the task of providing feedback and recommendations from their constituencies to WHO about the options.

Two items in the discussions during the Consultation deserve comment. First, the presenters favoring 30 °C, 75% RH based their arguments on the assumption that absolute humidity is the governing atmospheric condition for permeation of moisture into a container–closure system. This is not so. The atmospheric driving force for moisture permeation into a container is the pressure differential for water vapor between the inside and the outside of the container–closure system.

Second, two presenters (*3,4*) and one author (*5*) stated that glass bottles and high-density polyethylene (HDPE) bottles are impermeable to moisture when they have metal caps or high-density polyethylene caps. This, also, is not true.

This *Stimuli* article is intended to serve as feedback to WHO on the subject of the function of the container–closure system during stability testing. It addresses the questions of impermeability and the forces that drive permeation.

MOISTURE PERMEATION MECHANISM OF CONTAINER–CLOSURE SYSTEMS

Nearly all container–closure systems are permeable to water vapor (moisture). Only a few are not. Among the moisture-permeable container–closure systems commonly used in the pharmaceutical industry are the following: HDPE containers with any metal or plastic screw closures, low-density polyethylene (LDPE) containers with any metal or plastic closures, glass containers with any metal or plastic closure, polyvinyl chloride (PVC) blisters with lidding, PVC/polyvinylidene chloride (PVdC) blisters with lidding, and PVC/Aclar blisters with lidding.

Examples of moisture-impermeable container–closure systems include flame-sealed glass ampuls, and possibly aluminum (Al/Al) blisters. These Al/Al blisters usually test at or near zero permeation, but given a long enough time of exposure to test conditions, a low permeation rate may be found. Permeation into Al/Al blisters may happen through the seal or through pinholes in the aluminum foil.

Bottle container–closure systems have a container and a closure. The closure consists of two parts, the cap and the cap liner. The closure's moisture seal is the cap liner, which consists of the facing, which is a barrier material, and a resilient backing material. The backing material serves to keep the facing (the barrier) in close contact with the top of the container finish (the threaded neck).

Permeation into glass containers varies depending on the kind of material in the liner and the size (area) of the liner. The larger the area, the greater is the permeation. In *Table 1,* the 90-mL bottle with a 38-mm diameter cap size has a much larger area of liner facing than does the 30-mL bottle with only a 28-mm diameter cap size. The permeation for the metal cap with pulp/vinyl/wax liner is correspondingly higher for the 90-mL bottle than it is for the 30-mL bottle.

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Table 1. Water Vapor Transmission Rate (WVTR) at 37 °C, 85% RH for Glass Containers with a Variety of Closures (*6*)

Container Size	Cap Size*	Cap Material	Cap Liner Material	WVTR, mg/day
30 mL	28/400	Polystyrene	Pulp/vinyl/wax	5.4
		Polypropylene	Pulp/vinyl/wax	7.9
		Metal	Pulp/vinyl/wax	3.6
45 mL	33/400	Polystyrene	Pulp/foil/PVdC/wax	0.0
			Pulp/foil/vinyl/wax	3.6
		Metal	Pulp/foil/PVdC/wax + glassine innerseal	0.2
60 mL	33/400	Metal	Pulp/foil/vinyl	3.5
90 mL	38/400	Metal	Pulp/vinyl/wax	16.3
			Pulp/Aclar	0.43

* Cap size numbers: diameter of the thread in mm/style number of thread.

Also in *Table 1,* within each size class the permeation is different for different liners. For the 45-mL bottle, the foil/PVdC liner facing was so effective that this test produced a 0.0 permeation result. Foil/vinyl is a much less effective barrier, and that is shown in the WVTR of 3.6 mg/day.

The cap material often does not appreciably participate in the promotion or limitation of permeation. Note that in *Table 1* for the 45-mL bottle differences in permeation are explained by the difference in liner materials, not by the material of which the cap is made. Polystyrene is known to be a very poor barrier to water, and metal is known to be a good barrier. Yet the metal cap shows a permeation value and the polystyrene cap shows none. The difference is that a waxed glassine paper innerseal was incorporated in the metal cap's liner system.

Permeation of moisture into plastic containers is the result of ingress of water vapor through the wall of the container and the ingress of water vapor through the liner in the cap (see *Tables 2* and *3*). All that was said above about the effect of cap size and liner material is true for the caps used on plastic containers. During any test, permeation through the cap liner is confounded by permeation through the bottle wall. The two permeations can be separated. When a plastic bottle container–closure system is exposed to test conditions, the permeation of the bottle alone can be measured by making a hermetic wax seal on the closures of additional bottles and exposing the bottles to the same test conditions. The information presented in *Table 3* is the result of conducting such a test and then subtracting the bottle wall permeation from the whole-package permeation to get the closure permeation.

Table 2. WVTR at 37 °C, 85% RH for HDPE Containers with a Variety of Closures (*6*)

Container Size	Cap Size	Cap Material	Cap Liner Material	WVTR, mg/day
45 mL	28/400	Metal	Pulp/foil/PVdC/wax	0.93
			Pulp/vinyl/wax	4.0
160 mL	38/400	Metal	Pulp/foil/PVdC/wax	1.7
		Polystyrene	Pulp/foil/PVdC/wax	1.2
		Polypropylene	Pulp/foil/ vinyl/wax	9.6
480 mL	43/400	Metal	Pulp/foil/PVdC/wax	3.3

Table 3. WVTR at 37 °C, 85% RH for HDPE Containers and Various Closures, Showing Each Separately (*6*)

Container Size	Cap Size	Cap Material	Cap Liner Material	WVTR, mg/day
90 mL	38/400	Metal	Pulp/foil/PVdC/wax	1.5
	Permeation through container wall*			1.3
	Permeation through closure**			0.2
90 mL	38/400	Metal	Pulp/wax	8.3
	Permeation through container wall*			1.3
	Permeation through closure**			7.0
160 mL	38/400	Metal	Pulp/foil/PVdC/wax	1.4
	Permeation through container wall*			1.1
	Permeation through closure**			0.3
160 mL	38/400	Polypropylene	Pulp/foil/PVC/wax	9.6
	Permeation through container wall*			1.2
	Permeation through closure**			8.4

* Closure sealed with wax to form a hermetic seal, giving container wall permeation.
** Closure permeation obtained by subtracting wall permeation from container–closure permeation.

One of the most widely used container–closure systems is an HDPE bottle with induction heat sealed liner. Typical moisture permeation for a 50-mL bottle with 28/400 closure is 1.34 mg/d when tested at 40 °C, 75% RH. The bottle material is HDPE, the cap is polypropylene (PP), and the liner material is pulp/wax/Al foil/PE. This permeation value can be compared with 0.93 mg/d for the 45-mL, 28/400 bottle at the top of *Table 2*. The cap liners are the same size, the 50-mL bottle is slightly larger in surface area, and the test temperature is 3 °C higher for the 50-mL bottle than for the 45-mL bottle. The driving force (the pressure differential for water) is higher [41.5 mm Hg (55.3 mbar)] at 40 °C, 75% RH than at 37 °C, 85% RH [40.0 mm Hg (53.3 mbar)]. These factors all serve to explain why the induction heat sealed aluminum foil barrier system has a slightly higher permeation rate than does the PVdC barrier system. Temperature and water vapor pressure differential are the forces that drive permeation of moisture into container–closure systems. The theory is explained in the following section.

WATER VAPOR TRANSMISSION INTO PACKAGES

As discussed, water vapor can transfer from the storage environment into sealed packages by several mechanisms. One mechanism is convective mass transfer through channel or pinhole defects in the package. This mechanism will not be considered further because such packages have gross defects that should be identified through normal quality control systems. The remaining mechanisms are diffusion of water vapor through microscopic imperfections in the container seal or the container wall, and bulk diffusion of water vapor through semipermeable materials such as plastics.

Both of these types of transport of permeants through packages are well described by Fick's first and second laws of diffusion:

$$F = -D\frac{\partial C}{\partial x} \quad (1)$$

and

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \quad (2)$$

where F is the rate of mass transfer for the permeating substance per unit area, D is the diffusion coefficient, C is the concentration of the diffusing substance (within the material in question), x is the spatial coordinate in the direction of transfer, and t is time (*7–9*).

To make this equation more useful for calculating permeation through packages, it is necessary to relate C, the concentration of the substance within the package material, to the storage conditions and the conditions within the package headspace. This is commonly done using Henry's law, which relates partial pressure of a component in the gas phase to concentration of the substance in the solid or liquid phase that is in equilibrium with that gas phase:

$$C = Sp \quad (3)$$

where S is the Henry's law constant, or solubility coefficient, of the permeating substance in the solid or liquid phase, C is the concentration of the diffusing substance in the solid or liquid phase, and p is the partial pressure of the permeating sub-

stance in the gas phase (*8*). This relationship holds well for most substances dissolving in polymers, including water vapor, when the concentration of the permeant is low.

Putting these relationships together and assuming steady-state transfer gives us the classic equation describing permeation that holds when D and S are independent of concentration:

$$P = DS = \frac{q\ell}{At\Delta p} \quad (4)$$

where P is the permeability coefficient, D is the diffusion coefficient, S is the solubility coefficient, q is the amount of permeant transferred through the material during time t, A is the area available for permeation, ℓ is the thickness of the material being permeated (assumed constant), and Δp is the difference in partial pressure of the permeating substance in the gas phase in contact with the two surfaces of the material (*8*). It is important to note that the difference in partial pressure is required in this equation, not the difference in relative humidity (RH) nor the difference in either mass fraction or volume fraction of water vapor in the air. Of course, the partial pressure can be calculated if temperature is known, along with either RH, mass fraction, or volume fraction of water vapor.

The assumption that D and S are independent of concentration is generally accurate for water vapor permeating through polymers that do not strongly interact with water, such as polyolefins (e.g., polyethylene and polypropylene). It is not accurate for interacting systems, such as permeation of hydrocarbons through polyolefins, or permeation of water through ethylene vinyl alcohol. Such cases require a more complex analysis than the one that follows.

When the mass transfer is not at steady state, equation (4) still holds for differential times t and can be integrated over time. When water vapor is permeating into a package that is maintained at constant temperature and relative humidity and the package contains a desiccant, steady-state permeation usually can be assumed, because the desiccant maintains the partial pressure of water vapor inside the package at a uniform low value (near zero). The time to reach steady state depends on the thickness of the material, its initial condition, and its barrier characteristics but generally is short in relation to desired shelf life.

When water vapor is permeating into a package that is maintained at constant temperature and relative humidity but does not contain a desiccant, the water vapor partial pressure inside the package changes with time, so steady state usually cannot be assumed. In such cases, the moisture sorption isotherm for the product can be used to relate the moisture content of the product to the partial pressure inside the package. This assumes that moisture in the product and the package headspace equilibrate relatively rapidly in comparison to the rate of transfer of moisture through the package and that chemical consumption of water is negligible. In most cases of pharmaceutical packaging, these are good assumptions.

When the thickness of a material varies, equation (4) still holds for differential areas, A, of the material and can be integrated over the entire area. More commonly, measurements of the permeability coefficient are simply made for the whole package, and the equation is written as:

$$P^* = \frac{q}{t\Delta p} \quad (5)$$

where P^* is the per-package permeability coefficient for the specific package, with thickness and area incorporated. As is the case for equation (4), equation (5) can be written for a differential time t and integrated if permeation is not at steady state.

Measurements for moisture permeation through package materials or packages frequently are reported as a WVTR, determined at specified conditions, rather than as a permeability coefficient. For use in calculations, WVTR can be transformed into a permeability coefficient by dividing by the partial pressure difference at which the WVTR was determined, as follows:

$$P = \frac{WVTR}{\Delta p_{test}} \quad (6)$$

where Δp_{test} is the difference in water vapor partial pressure on the two sides of the material. If the WVTR is reported for a whole package, then use of equation (6) will yield a whole-package permeability coefficient.

PERMEABILITY COEFFICIENT

The permeability coefficient for a specific permeant/material combination depends, in theory, only on the type of permeant, the type of material, and on temperature. It does not depend on the concentration of the permeant, the thickness of the material, or other characteristics. In practice, there is likely to be some dependence of the permeability coefficient on the permeant concentration if there is interaction between the permeant and the material (*9, 10*).

For example, interaction of polyethylene with hydrocarbons can result in swelling of the polymer matrix and therefore in an increase in the diffusion coefficient, resulting in an increase in the permeability coefficient. Also, there may be some influence of thickness and, more generally, processing conditions, especially for semicrystalline polymers. Sorption and diffusion in semicrystalline polymers occurs predominantly in the amorphous regions. Therefore, if processing conditions result in an increase in crystallinity, the permeability coefficient will be decreased. If processing conditions result in a decrease in crystallinity, the permeability coefficient will increase. Other processing conditions that decrease free volume without necessarily increasing crystallinity have a similar effect. This is why orientation of polymers generally results in an improved barrier. Thickness plays a role because thickness affects heat transfer, which in turn affects the time during which a polymer remains at conditions that allow crystallization to occur.

A permeability coefficient for a whole package system depends, by its nature, on that particular package. However, the PQRI Working Group has shown that permeation behavior of a particular container can be generalized to provide useful information about the ability of other containers to provide sufficient moisture protection when rates are expressed on a per-unit-product basis (*11*).

The relationship between the permeability coefficient and temperature is somewhat complex. Both solubility and diffusion are affected by temperature. Diffusion increases with increasing temperature, following an Arrhenius relationship. Solubility may either increase or decrease with increasing temperature. For volatile substances, it is common for solubility to decrease as temperature increases, but for solids and liquids, solubility generally increases as temperature increases. Over reasonably small temperature ranges (and provided the temperature range does not span a polymer's glass transition temperature, T_g), the permeability coefficient typically exhibits an Arrhenius dependence on temperature:

$$P = Ae^{\frac{-E_a}{RT}} \quad (7)$$

where A is the pre-exponential term, E_a is the activation energy (determined by a best fit of P values at different temperatures), T is the absolute temperature, and R is the gas constant (8.314 J mol^{-1} K^{-1}) (*9*).

For ease of calculation, this formula is generally rewritten using a known value of P at one temperature, along with the activation energy, to calculate P at another temperature:

$$P_2 = P_1 e^{\frac{E_a}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)} \quad (8)$$

Here P_2 is the value to be determined at temperature T_2, and P_1 is the known value at temperature T_1. The negative sign in the original exponent has now been incorporated into the temperature difference term.

DETERMINATION OF ZONE IV STABILITY TEST CONDITIONS BASED ON WATER VAPOR PERMEATION

The primary determinants of moisture-related product failure are the amount of water uptake by the product, time, and temperature. The amount and timing of water uptake are themselves determined by the barrier characteristics of the package, the storage conditions, and the conditions internal to the package (e.g., water vapor partial pressure in the package headspace).

The goal of stability testing is to provide some degree of certainty that the product will remain efficacious during its labeled shelf life. Currently there is debate about the appropriateness of real-time test conditions for Zone IV countries. ASEAN has proposed test conditions of 30 °C and 75% RH rather than the current conditions of 30 °C and 65% RH adopted in 2003. They argue that these conditions more accurately reflect the hot and humid conditions that characterize ASEAN countries, along with other areas such as Brazil, Cuba, China, and India. Their argument is that absolute humidity (kg water/kg dry air) is the best guideline for determining the conditions to be used for long-term stability testing. Average values of absolute humidity are reported to range from 0.0175 to 0.0186 kg water/kg dry air, depending on the methods used to determine the average. Average temperature and RH values for ASEAN nations are reported as 27 °C and 79% RH (*2, 3*).

ASEAN considered only the absolute humidity and temperature in determining appropriate test conditions. However, it is the moisture inside the package that actually affects product stability, not the moisture in the environment. Further, although the absolute humidity of the package headspace may or may not be useful in determining the effect of water on the product, it is not useful in determining the amount of moisture that will permeate into a package. The difference in partial pressure of water vapor inside and outside the package is, along with temperature, the determining factor in how much moisture will permeate into the package. The rate of permeation and the moisture uptake characteristics of the product determine the partitioning of the permeating moisture between the product and the package headspace, thus determining the equilibrium vapor pressure of water in the package headspace and hence the absolute humidity inside the package.

In cases when the product absorbs all or nearly all of the permeating moisture (e.g., in packaging desiccant), the package usually reaches steady state relatively quickly compared to the product's shelf life. Steady-state moisture gain can be calculated easily from equation (4) or (5). As an example, assume use of a polypropylene (PP) vial with a surface area of 7.13×10^{-3} m^2 and an average wall thickness of 0.001 m; for simplicity, further assume no permeation through the closure. A typical WVTR for PP is 200 g μm/m^2 d at the standard conditions of 37.8 °C, 90% RH (*12*). The activation energy for water vapor permeation for PP has been tabulated as 42 kJ/mol (*10*).

The steady-state water vapor permeation rate for this vial at any given set of conditions can be calculated from equation (4) rearranged as follows:

$$\frac{q}{t} = \frac{P A \Delta p}{\ell} \quad (9)$$

The first step is to calculate the permeability coefficient for water vapor for PP, from the reported WVTR value for the material and the conditions at which it was determined, using the saturation vapor pressure of water at 37.8 °C of 42.175 mm Hg:

$$P = \frac{WVTR}{\Delta p_{test}} = \frac{200\ g\ \mu m}{m^2\ d\ 0.90(42.175\ mm\ Hg)} = \frac{5.269\ g\ \mu m}{m^2\ d\ mm\ Hg} \quad (10)$$

If desired, we can also calculate the per-package permeability coefficient:

$$P^* = P \times \frac{Area}{Thickness} = 5.269 \frac{g\,\mu m}{m^2\,d\,mm\,Hg} \times \frac{0.00713\ m^2}{1000\ \mu m} = 3.7568 \times 10^{-5} \frac{g}{d\ pkg\ mm\,Hg} \quad (11)$$

If we assume that *P* does not vary with temperature, we can obtain the values in *Table 4* for WVTR at various conditions. *Table 4* also shows absolute humidity calculated by the following equation:

$$AH = \frac{0.018\,p_D}{0.029(p - p_D)} \quad (12)$$

where *AH* is absolute humidity, in kg water/kg dry air; p_D is the partial pressure, in mbar, of water; *p* is total atmospheric pressure, in mbar; 0.018 is the molar mass of water, in kg; and 0.029 is the molar mass of dry air, in kg *(13)*. Saturation vapor pressures are obtained from Perry and Chilton (*14*). These tabulated values are more accurate than values calculated using Wexler's equation.

Table 4. WVTR for the Example PP Vial at Various Conditions, Assuming *P* Does Not Vary with Temperature

T, °C	p_{sat}, mm Hg	*RH,* %	p_D, mm Hg (mbar)	*AH,* kg water/ kg dry air	WVTR, g/day
25	23.756	80	19.004 (25.338)	0.01592	0.0007140
27	26.739	79	21.124 (28.163)	0.01774	0.0007936
27.8	28.021	79	22.137 (29.513)	0.01862	0.0008316
30	31.824	60	19.094 (25.457)	0.01600	0.0007173
30	31.824	65	20.386 (27.579)	0.01737	0.0007771
30	31.824	70	22.277 (29.700)	0.01874	0.0008369
30	31.824	75	23.868 (31.821)	0.02012	0.0008967

From the values above it can be seen that, even assuming that *P* does not increase as temperature increases, it can be calculated that more water vapor will permeate into a container at 30 °C and 70% RH than at 27 °C and 79% RH or even at 27.8 °C and 79% RH. This holds true regardless of the container characteristics because the WVTR for a given container will be proportional to partial pressure difference.

Of course, assuming that *P* does not increase with increasing temperature is a poor assumption. The increase in permeation with temperature provides an additional safety margin when test conditions of 30 °C and 70% RH are used to determine stability in Zone IV countries.

For the vial above, we can calculate *P* for water vapor at other desired temperatures from the value of *P* at 37.8 °C, using equation (8), obtaining the values shown in *Table 5*.

Table 5. Water Vapor Permeability Coefficients for PP

Temperature, °C	*P* for Water Vapor, g μm/m² d mm Hg
37.8	5.269
23	2.340
25	2.623
27	2.937
27.8	3.071
30	3.469
37.8	5.269

We can now use these values to calculate a more accurate steady-state water vapor transmission rate for the vial at various storage conditions, resulting in the values shown in *Table 6*.

Table 6. WVTR for the Example PP Vial at Various Conditions, Correcting for Variation in *P* with Temperature

T, °C	*P,* g μm/ m² d mm Hg	*RH,* %	WVTR, g/day
25	2.623	80	0.0003554
27	2.937	79	0.0004424
27.8	3.071	79	0.0004847
30	3.469	60	0.0004723
30	3.469	65	0.0005116
30	3.469	70	0.0005510
30	3.469	75	0.0005904

It can be seen that in this case the WVTR even at 30 °C and 60% RH will be higher than the WVTR at 27 °C and 79% RH, although not as high as the WVTR at 27.8 °C and 79% RH. The WVTR at 30 °C and 65% RH will be higher than the WVTR at either 27 °C or 27.8 °C and 79% RH. The WVTR at 30 °C and 70% RH is even larger and, for this vial, will be 13.7% higher than at 27.8 °C and 79% RH.

The magnitude of these differences depends on the activation energy of permeation for the container in question but not on its surface area or thickness. For example, if this vial were LDPE, instead of PP, a typical WVTR would be 440 g μm/m² d at the standard conditions of 37.8 °C, 90% RH

(Selke, 1997), resulting in a value for P of 11.59 g μm/m² d mm Hg. The activation energy is 34 kJ/mol (*10*). *Table 7* shows the calculated WVTRs.

Table 7. WVTR for the Example Vial Made from LDPE, Correcting for Variation in *P* with Temperature

T, °C	*P*, g μm/ m² d mm Hg	*RH,* %	WVTR, g/day
25	6.590	80	0.000893
27	7.221	79	0.001088
27.8	7.487	79	0.001182
30	8.263	60	0.001125
30	8.263	65	0.001219
30	8.263	70	0.001312
30	8.263	75	0.001407

For the LDPE vial, moisture gain at 30 °C and 65% RH will be 3% higher than at 27.8 °C and 79% RH.

The situation is more complicated when the water vapor partial pressure inside the package increases during the storage period, because the contents absorb some but not all of the permeating moisture. The permeation rate is governed by the difference between the water vapor pressure inside and outside of the package, so it can be affected by the package contents. In such cases, permeation is not at steady state, and a more complex analysis is required and must take into consideration the moisture sorption isotherm of the package contents.

CONCLUSION

This paper presents the theory to support using the effect of climate on package permeation as the basis for designating stability test conditions for Climate Zone IV. It demonstrates that temperature, partial pressure for water vapor, and package permeation control the amount of water that becomes available to the product. Absolute humidity does not enter the equation at all. The selection of stability test conditions to represent Climate Zone IV can be made only through consideration of storage temperature, partial pressure for water vapor, and moisture permeability of the package.

The theoretical argument suggests that the current WHO Zone IV real-time stability conditions of 30 °C, 65% RH are adequate. This has not been tested by direct experimentation. Laboratory studies are now being designed to gather data for appropriate stability test conditions. These studies will focus on the permeation behavior of drug product packaging materials at temperatures and relative humidities characteristic of Zone IV conditions.

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NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

USP Dictionary of USAN and International Drug Names
2005 USP DICTIONARY SUPPLEMENT 6

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2005 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2005) edition will be included in the next complete edition of the Dictionary.

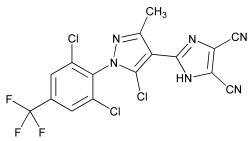
Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

Fampronil

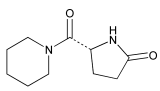
Change the chemical information and structure to read:

$C_{16}H_6Cl_3F_3N_6$. 445.61. 2-{5-Chloro-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-3-methyl-1*H*-pyrazol-4-yl}-1*H*-imidazole-4,5-dicarbonitrile. *CAS-134183-95-2.* INN.



Fasoracetam

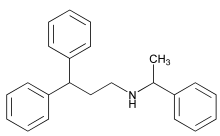
Change the chemical structure to read:



Fendiline

Change the chemical information and structure to read:

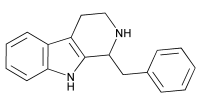
$C_{23}H_{25}N$. 315.45. *N*-(3,3-Diphenylpropyl)-α-methylbenzylamine. *CAS-13042-18-7.* INN; MI.



Fenharmane

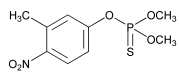
Change the chemical information and structure to read:

$C_{18}H_{18}N_2$. 262.35. 1-Benzyl-2,3,4,9-tetrahydro-1*H*-pyrido[4,3-*b*]indole. *CAS-3851-30-7.* INN.



Fenitrothion

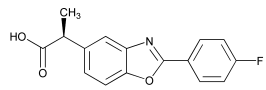
Change the chemical structure to read:



Flunoxaprofen

Change the chemical information and structure to read:

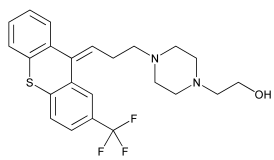
$C_{16}H_{12}FNO_3$. 285.27. (*S*)-(+)-2-(*p*-Fluorophenyl)-α-methyl-5-benzoxazoleacetic acid. *CAS-66934-18-7.* INN; MI.



Flupentixol

Change the chemical information and structure to read:

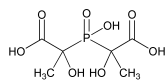
$C_{23}H_{25}F_3N_2OS$. 434.52. (*Z*)-2-Trifloromethyl-9-[3-[4-(2-hydroxyethyl)piperazin-1-yl]propylidene]thioxanthene. *CAS-2709-56-0.* INN; BAN; DFC; MI. *[Name previously used: Flupenthixol.]* ✧*N-7009; LC 44.*



Foscolic Acid

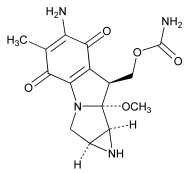
Change the chemical formula and structure to read:

$C_6H_{11}O_8P$.



Mitomycin

Change the chemical structure to read:



Nomenclature

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This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

[*Note—This index covers Vol. 32 No. 1, pp. 1–224, Vol. 32 No. 2, pp. 225–704*]

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PHARMACOPEIAL FORUM VOL. 32 NO. 3 MAY–JUNE 2006

* The *USP–NF* (*USP 30–NF 25*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

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

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

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

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

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

STANDARDS DEVELOPMENT

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

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

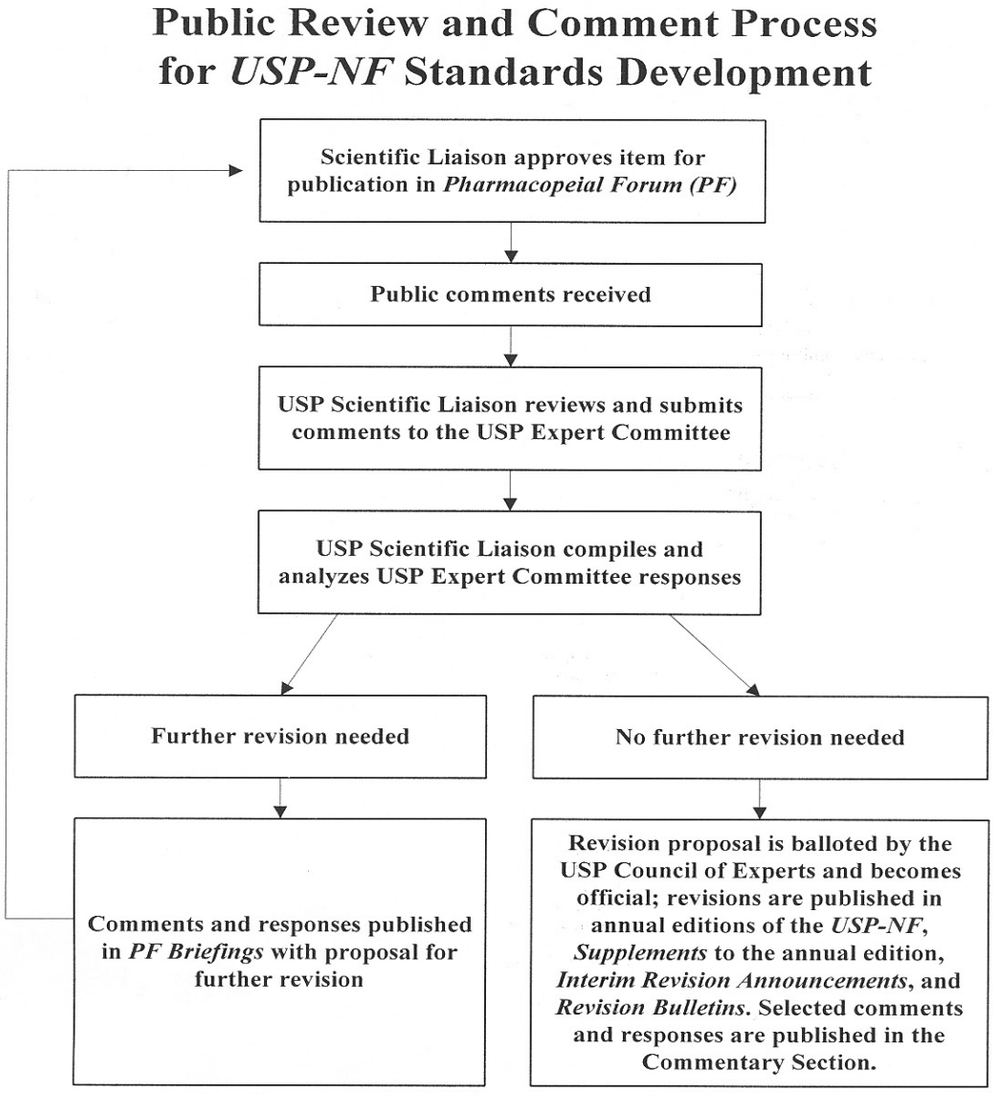
PF includes the following:

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

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

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

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



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@usp.org).

HOW TO USE *PF*

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

The content of the different sections of *PF* is briefly described below. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a *Request for Revision* is available in the *Guideline for Submitting Requests for Revision to the USP–NF* on the USP website (www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP–NF*

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

Other Sections

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

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

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

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

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

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Cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

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

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

EXPERT COMMITTEE DESIGNATIONS*

2005–2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell, Gene, and Tissue Therapies
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding
RMI	Radiopharmaceuticals and Medical Imaging Agents
RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics
VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005–2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

STAFF	E-MAIL	PHONE	ASSIGNMENT
Clydewyn M. Anthony, Ph.D., Scientist	cma@usp.org	(301) 816-8139	Monograph Development—Cough, Cold, and Analgesics (MD-CCA)
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STAFF DIRECTORY *(continued)*

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Tina S. Morris, Ph.D., Director, Biologics and Biotechnology	tsm@usp.org	(301) 816-8397	B&B Vaccines and Virology (BB-VV)
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STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
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Stefan P. Schuber, Ph.D., Director, Scientific Reports	sps@usp.org	(301) 816-8551	
Maged H. M. Sharaf, Ph.D., Senior Scientist	mhs@usp.org	(301) 816-8318	Dietary Supplements—Botanicals (DSB); Dietary Supplements—General Chapters (DS-GC)
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Kahkashan Zaidi, Ph.D., Senior Scientist	kxz@usp.org	(301) 816-8269	Aerosols (AER); General Chapters (GC)

POLICIES AND ANNOUNCEMENTS

This section includes information about general scientific and policy issues that may have an impact on *USP–NF* standards and processes and announcements about issues being considered by USP. This section also includes publication and comment schedules.

STANDARDS DIVISION REORGANIZED. USP has recently made changes in support of the work of the Council of Experts and its Expert Committee members. These changes cap a series of previous efforts to improve service to the Council, all with the goal of assuring both the USP Board of Trustees and the Council of Experts and its Expert Committees that they are getting the best possible support from USP staff. The key change now is the creation of a new Standards Division that ties together all of USP's Council of Experts support into one area to be headed by a Chief Standards Officer (CSO). Dr. Roger Williams will serve as the CSO on an interim basis until a suitable candidate can be hired. The Division is one of four in the organization, the others being Legal, Finance and Accounting, and Business.

A matrix management approach will be used in the new Division, which consists of five departments and one group. These are: the Department of Standards Development (DSD—Todd Cecil, Vice President); the Department of Patient Safety (DPS—Diane Cousins, Vice President); the Information Development Group (IDG—Deborah Perfetto, Group Director); the Department of International Affairs (IA—Nancy Blum, Vice President); the Department of Volunteer and Organizational Affairs (VOA—Angela Long, Vice President); and the Department of Monograph and Reference Standards Development (MRSD—Ronald Manning, Vice President). The first four Departments and Groups work "vertically" in the matrix to support the Council of Experts. The final two (VOA and MRSD) provide support "laterally," together with other units outside the organization.

A key to the success of the new Division will be the creation of staff Teams, headed by Group Directors, who will manage the many activities for a specific area, both from within the Division and from other Divisions, needed to achieve success on behalf of the Council of Experts. As part of these changes and in response to recent Board decisions, other USP staff will refocus their energies in support of the organization. As an example, Dr. Eric Sheinin, who has provided distinguished support to the Council of Experts over the last several years, will focus on implementing, with Mr. John Fowler, USP's new verification programs for pharmaceutical ingredients, approved for development by the USP Board of Trustees at their December 2005 meeting. The need for Dr. Sheinin's assistance here is based on his many years at FDA doing similar work.

USP has high hopes that this re-organization will greatly improve the delivery of standards-setting services to the Council of Experts and its Expert Committees and, in turn, facilitate their work in making USP's products and services available to direct customers and healthcare constituencies throughout the world.

Staff Promotions Announced. In support of this reorganization, Dr. Williams announced the following staff appointments:

- *Ian DeVeau* has been appointed as Director, Veterinary Drugs and Radiopharmaceuticals Group. In his new role he will oversee the revision and expansion of the *USP–NF* in the area of veterinary drugs and radiopharmaceuticals and the revision and development of information monographs concerning the clinical uses of these products.
- *Gabriel Giancaspro* has been appointed as Director, Dietary Supplements. In his new role he will oversee the revision and expansion of the *USP–NF* in the area of Dietary Supplements and the development of information concerning these products.
- *Tina Morris* has been promoted to Director, Biologics and Biotechnology Group. In this role she coordinates the activities of the four core Expert Committees in the B&B area, as well as cross-cutting B&B standards-setting activities. She also directs the development of new lines of B&B reference standards at USP, including procedural standards, ancillary materials standards, DNA & genetic testing standards, and reagent Reference Standards.
- *Karen Russo* has been promoted to Director, Small Molecules and Monograph Acquisition Group. In this position, she serves a coordinating role with the pharmaceutical industry for monograph development and acquisition efforts. Dr. Russo oversees a staff of scientific liaisons working with the USP Council of Experts to provide the scientific content for monographs.
- *Catherine Sheehan* has been promoted to Director, Excipients. In this role she coordinates the activities of the three core Expert Committees in the excipient area, as well as excipient standards-setting activities. She also coordinates the development of new excipient Reference Standards at USP, including procedural standards.

David A. Porter will continue as Director, General Chapters, rounding out the six group directors in DSD.

- *Joy Chacon* is VOA's new Director of Compendial Operations. In her new role, Ms. Chacon will oversee the project management approaches for the new Standards Development Teams and will lead a group of Project Managers and administrative staff. She will support the Team Leader (DSD Group Director) in the facilitation of Team activities.
- *Jennifer Payette* is VOA's new Director of Stakeholder and Organizational Affairs. Her new responsibilities include directing the activities and collaborating on strategy for USP's program of domestic and international Stakeholder Forums and Project Teams, and directing and seeking opportunities for organizational outreach including developing special programs and building relations with scientific, trade, and standards-setting organizations.

COORDINATION OF OFFICIAL NEW MONOGRAPHS, REVISIONS, AND USP REFERENCE STANDARDS. USP is pleased to announce a change in the way that we coordinate the adoption of official new monographs and revisions with the release of the required Reference Standards. Beginning with the *Second Supplement* to *USP 29–NF 24,* new monographs and revisions to existing monographs will not be published as official standards until the required USP Reference Standards are available. Monographs may be made available on a case-by-case basis without USP Reference Standards availability, but this should be a rare occasion. This effort will temporarily slow the presentation of new monographs that are published in the *USP–NF,* but will ultimately lead to better public standards.

USP OPENS FACILITY IN INDIA. In February the U.S. Pharmacopeia established its first overseas site in its 185-year history—with the inauguration of its state-of-the-art laboratory and office at ICICI Knowledge Park, Shameerpet, in Hyderabad. Dr. Darrell R. Abernethy, President, USP, inaugurated the facility in the presence of a distinguished gathering of USP-India Board members, senior management, advisory group members, stakeholders, and other invitees. The setting-up of the site was a significant step forward for USP, which, over the years, has worked with the Indian national and state governments and Indian manufacturers on many scientific and policy initiatives. With the new site in India, USP will now be physically closer to these groups so that it can expand this cooperation. Outside the U.S., India has the largest number of U.S. FDA-approved plants. USP will be working closely with the Indian Pharmacopeia.

The inauguration of the site was preceded by meetings of the USP-India Board of Directors, the USP-India Advisory Group, and the India Stakeholder Forum. The establishment of USP-India is in line with fulfilling USP's global public health strategy and its primary goal of providing "Good Pharmaceutical Care for All." Working with many constituencies and stakeholders around the world, USP supports the availability of safe and effective good quality therapeutic products for consumers everywhere.

The USP also held its 5th Annual Scientific Meeting in Hyderabad with a joint symposium sponsored by USP, the Parenteral Drug Association, and the Indian Stakeholder Forum. The meeting discussed matters of interest to industry scientists engaged in the manufacture, analysis, and quality control of pharmaceutical and biotechnology products; exporters of bulk pharmaceuticals; and regulatory agencies.

USP ISSUES INTERIM REVISION ANNOUNCEMENT FOR GENERAL CHAPTER ⟨231⟩ HEAVY METALS. In response to comments from industry, USP is reverting back to the Heavy Metals text that appeared in *USP 28–NF 23* for *Heavy Metals, Method II*. The *USP 28–NF 23* test has been used in industry for some time. The search continues for a more robust and practical method.

Should you have any questions, please contact Kahkashan Zaidi, Ph.D., Senior Scientist, General Chapters (301-816-8269 or kxz@usp.org).

COMMENTS ON RESIDUAL SOLVENTS DUE JUNE 1, 2006. The June 1 deadline is approaching to send comments to USP regarding the *Residual Solvents* test, following the retraction notice that was included on page 14 of the *USP 29–NF 24:*

"*Residual Solvents* ⟨467⟩: *meet the requirements." is hereby withdrawn from all monographs in the USP and the NF. This retraction is made to allow the USP Council of Experts further time to evaluate the most appropriate manner to implement the Residual Solvents test. The General Notices statement concerning the application of Residual Solvents to all monographs is unaffected by this retraction.*

This notice also serves as an additional request for comments on this issue from all users of the USP. Please forward your comments to:

Todd Cecil, Ph.D.
Vice President
Department of Standards Development
USP
12601 Twinbrook Parkway
Rockville, MD 20852

Comments must be received by June 1, 2006 to ensure consideration.

EXPERT COMMITTEE SUMMARIES AVAILABLE ON THE USP WEB SITE. Summaries of the first meetings of the cycle for the 2005–2010 Standards Expert Committees are now posted and available at http://www.usp.org/USPNF/meetingSummaries/.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, other scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2006 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

Calendar of Forthcoming Pharmacopeial Education Courses as of May 2006 (open to public, not on-site at a company)

Date	Name of Course	Location	Price
2-May-06	Effectively Using the *USP–NF*—Sessions I & II	Istanbul, Turkey	*
3-May-06	Analytical Method Validation	Istanbul, Turkey	*
24-May-06	Effectively Using the *USP–NF*—Sessions I & II	Chicago, IL	$595
31-May-06	Effectively Using the *USP–NF*—Sessions I & II	Toronto, Canada	**
6-Jun-06	Analytical Method Validation (in Spanish)	Barcelona, Spain	***
6-Jun-06	Analytical Method Validation	Montreal, Canada	****

*Registration handled by:
Ekin Kimya Ticaret Limited Sirketi
Bulgurlu Mahallesi
Sarigazi Caddesi No: 29
Post code: 34696
Uskudar-Istanbul
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Tel: (90) 216-524-12-24
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**Registration handled by:
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3780 14th Ave, Suite 210
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Tel 905-513-7743
FAX 905-513-7786
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Fax: (514) 336-1768
E-mail: custserv@acamchem.com

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

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

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

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

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

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

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

NEW *PHARMACOPEIAL FORUM* PUBLIC REVIEW AND COMMENT PERIOD DEADLINES. The full year's listing of comment period deadlines and the targeted official publications appears below. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts*, USP is implementing the 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing.

The listing of comment period deadlines and the targeted official publications appears below.

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Publication Date	Official Date
PF 31(6)	April 17, 2006	*USP 30–NF 25*	November 2006	January 2007
PF 32(1)	April 17, 2006			
PF 32(2)	June 15, 2006	*USP 30–NF 25 1st Supplement*	February 2007	April 2007
PF 32(3)	August 15, 2006			
PF 32(4)	October 16, 2006	*USP 30–NF 25 2nd Supplement*	June 2007	August 2007
PF 32(5)	December 15, 2006			
PF 32(6)	February 15, 2007	*USP 31–NF 26*	November 2007	January 2008
PF 33(1)	April 16, 2007			
PF 33(2)	June 15, 2007	*USP 31–NF 26 1st Supplement*	February 2008	April 2008

* ***Section 9.04(b) of the Rules and Procedures of the 2005–2010 Council of Experts***
A period of at least ninety (90) days from the date of publication will be allowed for public review and comment. The time allowed for public comments shall be noted in the publication in the PF. For good cause shown, the Chairperson may alter the time specified.

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, official revisions are published in *PF* in the *Interim Revision Announcement;* these revisions are also incorporated in the upcoming *Supplement.* The official publication in which an *IRA* is incorporated will depend upon publication deadlines. The 5th *IRA* and the 6th *IRA* will not appear until *Supplement 1*. See table below. The electronic version of *USP–NF* is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement.* The new table below outlines the publications and their release and official dates, and the book or supplement which supersedes them.

Publication Schedules

Publication	Release Date	Official Date	Superseded by
USP 29–NF 24	Nov. 1, 2005	Jan. 1, 2006	*1st Supplement*
1st Supplement	Feb. 1, 2006	Apr. 1, 2006	*2nd Supplement*
1st *IRA* [*PF* 32(1)]	Jan. 1, 2006	Feb. 1, 2006	*2nd Supplement*
2nd *IRA* [*PF* 32(2)]	Mar. 1, 2006	Apr. 1, 2006	*2nd Supplement*
3rd *IRA* [*PF* 32(3)]	May 1, 2006*	June 1, 2006*	*USP 30–NF 25*
2nd Supplement	June 1, 2006*	Aug. 1, 2006*	*USP 30–NF 25*
4th *IRA* [*PF* 32(4)]	July 1, 2006*	Aug. 1, 2006*	*USP 30–NF 25*
5th *IRA* [*PF* 32(5)]	Sept. 1, 2006*	Oct. 1, 2006*	*1st Supplement USP 30–NF 25*
6th *IRA* [*PF* 32(6)]	Nov. 1, 2006*	Dec. 1, 2006*	*1st Supplement USP 30–NF 25*
USP 30–NF 25	Nov. 1, 2006*	Jan. 1, 2007*	

*Tentative

PRIORITY NEW MONOGRAPH ITEMS. USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monographs are marked received upon receipt of monograph proposal. Received monographs are removed from this list upon publication in *Pharmacopeial Forum.* (This list has been updated as of March 6, 2006.) For additional information, contact Karen A. Russo, Ph.D., kar@usp.org. Monograph sponsors should consult USP's Guideline for Submitting Requests for Revision to the *USP–NF.*

Noncomplex Actives (Drug Substances)

Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Amlodipine Besylate ***(Received)***	Anagrelide Hydrochloride	Arsenic Trioxide
Azelaic Acid	Balsalazide Disodium	Bentoquatam
Bepridil Hydrochloride	Bivalirudin	Cabergoline
Calcipotriene	Calcium Trisodium Pentetate	Calfactant
Candesartan Cilexetil	Carmustine ***(Received)***	Carvedilol
Cefdinir ***(Received)***	Cefditoren Pivoxil	Ceftibuten
Cetrorelix	Cevimeline	Chloroxine
Colfosceril	Cytarabine Liposome	Dalfopristin
Dapirazole Hydrochloride	Desirudin	Desonide ***(Received)***
Dexrazoxane	Difloxacin Hydrochloride	Docosanol
Entacapone	Epoprostenol	Erythromycin Phosphate
Erythromycin Thiocyanate	Esmolol	Esomeprazole Magnesium ***(Received)***
Estazolam	Estradiol Benzoate	Estramustine Phosphate Sodium
Ethanolamine Oleate	Etomidate	Etoposide Phosphate
Exemestane	Felbamate	Fluoromethane F 18
Foscarnet Sodium	Fosfomycin Tromethamine	Gadobenate Dimeglumine
Gadopentetic Acid	Galantamine Hydrobromide	Gallium Nitrate
Ganirelix	Glyceryl Aminobenzoate	Granisetron
Halobetasol Propionate	Haloperidol Decanoate ***(Received)***	Hydrocodone Polistirex
Ibandronate Sodium	Imipramine Pamoate	Imiquimod
Irinotecan	Isosulfan Blue	Itraconazole
Lamotrigine ***(Received)***	Latanoprost	Lawsone
Levetriacepam	Levobetaxolol	Levomethadyl Acetate
Lomustine	Lopinavir	Metipranolol Hydrochloride
Midazolam Hydrochloride	Mifepristone	Miglitol

Noncomplex Actives (Drug Substances) *(Continued)*

Misoprostol ***(Received)***	Mivacurium	Moexipril
Nalbuphine Hydrochloride	Nalmefene Hydrochloride	Nateglinide ***(Received)***
Nedocromil Sodium	Nicardipine Hydrochloride	Nilutamide
Nisoldipine	Olopatadine	Olsalazine Sodium
Orbifloxacin	Orlistat Received	Oxcarbazepine ***(Received)***
Pantoprazole Sodium ***(Received)***	Pemoline	Pentamidine Isethionate
Piperonyl Butoxide	Pirbuterol Acetate	Poractant Alpha
Prednicarbate ***(Received)***	Proguanil	Quetiapine Fumarate
Rose Bengal	Salmeterol Xinafoate	Sertraline Hydrochloride ***(Received)***
Sodium Phenylbutyrate	Sterile Methotrexate Sodium	Streptozocin
Sulfacytine	Tacrolimus	Terbinafine Hydrochloride
Terconazole	Tiludronate Disodium	Tiopronin
Tranexamic Acid	Trimipramine Maleate ***(Received)***	Trovafloxacin Mesylate
Voriconazole	Zinc Tridosium Pentetate	

Noncomplex Actives (Drug Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate, and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol for Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Suppository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Aminopterin Sodium Tablets	Amlodipine and Benazepril Hydrochloride Capsules
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Metered-Dose Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Bivalirudin Injection
Brompheniramine Maleate, Dextromethorphan Hydrobromide, and Pseudoephedrine Hydrochloride Oral Solution	Budesonide Inhalation Aerosol	Budesonide Metered-Dose Inhalation Aerosol
Bupivacaine and Lidocaine Hydrochlorides Injection	Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules
Butalbital and Acetaminophen Tablets	Butorphanol Tartrate Nasal Solution ***(Received)***	
Cabergoline Tablets	Calcipotriene Cream	
Calcipotriene Ointment	Calcipotriene Topical Solution	Calcitriol Capsules
Calcitriol Oral Solution	Calcium Acetate Capsules	Calcium Trisodium Pentetate Injection
Calfactant Intratracheal Suspension	Carbidopa and Levodopa Extended-Release Tablets	Carbidopa and Levodopa Tablets for Oral Suspension
Carbidopa, Levidopa, and Entacapone Tablets	Carmustine for Injection	Carmustine Implant
Carvedilol Tablets	Cefdinir Tablets	Cefditoren Pivoxil Tablets
Ceftibuten Capsules	Ceftibuten for Oral Suspension	Ceftiofur Hydrochloride Oral Suspension
Cetirizine Hydrochloride Oral Solution	Cetirizine Hydrochloride Tablets	Cetrorelix Injection
Cevimeline Hydrochloride Capsules	Chloroxine Cream	Chlorpromazine Hydrochloride Extended-Release Capsules
Choline and Magnesium Salicylates Oral Solution	Choline and Magnesium Salicylates Tablets	Choline Salicylate Oral Solution
Ciclopirox Shampoo	Ciclopirox Topical Gel	Ciclopirox Topical Solution

Noncomplex Actives (Drug Products) *(Continued)*		
Cilostazol Tablets ***(Received)***	Cimetidine Oral Solution	Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension
Ciprofloxacin Otic Solution	Citalopram Hydrobromide Oral Solution	Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation
Cladribine Injection	Clemastine Fumarate Syrup	Clobetasol Propionate Gel
Clonazepam Orally Disintegrating Tablets	Clorazepate Dipotassium Capsules	Clorazepate Dipotassium Extended-Release Tablets
Clotrimazole and Betamethasone Dipropionate Lotion	Colestipol Hydrochloride Tablets	Colfosceril and Tyloxapol Suspension
Compound Undecylenic Acid Cream	Compound Undecylenic Acid Topical Powder	Conjugated Estrogens and Medroxyprogesterone Acetate Tablets
Cromolyn Sodium Metered-Dose Nasal Solution	Cyclosporine Modified Capsules	Cyclosporine Modified Oral Solution
Cyclosporine Ointment	Cyclosporine Topical Solution	Cysteamine Bitartrate Capsules
Cytarabine Liposome Injection	Dalfopristin and Quinupristin Injection	Dantrolene Sodium Capsules ***(Received)***
Dantrolene Sodium for Injection ***(Received)***	Dantrolene Sodium Oral Suspension	Dapiprazole for Ophthalmic Solution
Desirudin for Injection	Desonide Cream	Dexrazoxane for Injection
Dextroamphetamine Sulfate Extended-Release Capsules	Dextromethorphan Polistirex Extended-Release Oral Suspension	Diazepam Injectable Emulsion
Diclofenac Sodium Ophthalmic Solution	Diethylpropion Hydrochloride Extended-Release Tablets	Difenoxin and Atropine Tablets
Difloxacin Hydrochloride Tablets	Dihydroergotamine Mesylate Metered Spray	Diltiazem Malate Extended-Release Tablets
Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets	Divalproex Sodium Delayed-Release Capsules
Dorzolamide and Timolol Ophthalmic Solution	Dorzolamide Ophthalmic Solution	Doxacurium Chloride Injection
Doxepin Hydrochloride Cream	Doxycycline Oral Gel	Econazole Nitrate Cream
Edrophonium Chloride and Atropine Sulfate Injection	Enalapril Maleate and Diltiazem Malate Extended-Release Tablets	Enalapril Maleate and Felodipine Extended-Release Tablets
Enalaprilat Injection	Entacapone Tablets	Ephedrine Sulfate and Guaifenesin Tablets
Epoprostenol for Injection	Epoprostenol Injection	Esmolol Hydrochloride Injection
Esomeprazole Magnesium Capsules	Estazolam Tablets	Estramustine Phosphate Sodium Capsules
Ethanolamine Oleate Injection	Etidronate Disodium Injection Concentrate	Etomidate Injection
Exemestane Tablets	Famotidine Orally Disintegrating Tablets	Felbamate Oral Suspension
Felbamate Tablets	Fentanyl Lozenges	Fentanyl Transdermal System ***(Received)***
Ferrous Fumarate and Docusate Sodium Extended-Release Capsules	Flavoxate Hydrochloride	Flavoxate Hydrochloride Tablets
Fluconazole Injection	Fluconazole Tablets	Flunisolide Inhalation Aerosol
Flunisolide Nasal Spray	Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution
Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***	Fluticasone Propionate Inhalation Powder
Fluticasone Propionate Ointment ***(Received)***	Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection
Fosfomycin for Oral Solution	Gabapentin Oral Solution	Gabapentin Tablets ***(Received)***
Gadobenate Dimeglumine Injection	Galantamine Hydrobromide Tablets ***(Received)***	Gallium Nitrate Injection
Ganciclovir Capsules	Ganirelix Acetate Injection	Gatifloxacin Injection
Gatifloxacin Tablets	Gentamicin Sulfate Oral Solution	Gentamicin Sulfate Soluble Powder
Glimepiride Tablets ***(Received)***	Glipizide Extended-Release Tablets	Granisetron Injection
Granisetron Tablets	Guaifenesin and Salts Of Dextromethorphan and Pseudoephedrine Oral Solution	Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets
Guanidine Hydrochloride	Guanidine Hydrochloride Tablets	Halobetasol Propionate Cream
Halobetasol Propionate Ointment	Haloperidol Decanoate Injection	Haloperidol Lactate Injection
Haloperidol Lactate Oral Concentrate	Hydralazine Hydrochloride and Hydrochlorothiazide Capsules	Hydrochlorothiazide Capsules
Hydrochlorothiazide Oral Solution Concentrate	Hydrocodone Bitartrate and Acetaminophen Oral Solution	Hydrocodone Bitartrate and Aspirin Tablets
Hydrocodone Bitartrate and Guaifenesin Oral Solution	Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrocodone Bitartrate and Homatropine Methylbromide Tablets

Noncomplex Actives (Drug Products) *(Continued)*

Hydrocortisone Acetate Dental Paste	Hydrocortisone Acetate Rectal Foam Aerosol	Hydrocortisone Butyrate Lotion
Hydroflumethiazide and Reserpine Tablets	Hydromorphone Hydrochloride Oral Solution	Hydroquinone Lotion
Ibandronate Sodium Tablets	Ibuprofen Capsules	Idarubicin Hydrochloride Injection
Imipramine Pamoate Capsules	Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol
Ipratropium Bromide Inhalation Solution	Irinotecan Hydrochloride Injection	Isosulfan Blue Injection
Isradipine Extended-Release Tablets	Itraconazole Injection	Itraconazole Oral Solution
Ketoconazole Cream	Ketoconazole Shampoo	Ketoprofen Capsules
Ketoprofen Extended-Release Capsules	Ketoprofen Tablets	Ketotifen Fumarate
Ketotifen Fumarate Ophthalmic Solution	Lactic Acid Lotion	Lamivudine Tablets
Latanoprost Ophthalmic Solution	Leucovorin Calcium for Injection	Levetriacepam Tablets
Levobetaxolol Ophthalmic Suspension	Levocabastine Ophthalmic Suspension	Levofloxacin Solution
Levomethadyl Acetate Hydrochloride Oral Concentrate	Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder	Liothyronine Injection
Lisinopril and Hydrochlorothiazide Tablets	Lomustine Capsules	Lopinavir and Ritonavir Solution
Lopinavir Capsule	Lopinavir Solution	Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***
Loratadine Orally Disintegrating Tablets	Losartan Potassium Tablets	Mefloquine Hydrochloride Tablets
Melphalan for Injection	Mesalamine Suppositories	Mesoridazine Besylate Concentrate
Metaraminol Bitartrate Injection	Methacholine Chloride for Inhalation Solution	Methadone Hydrochloride Oral Concentrate
Methocarbamol and Aspirin Tablets	Methoxsalen Softgels	Methyclothiazide and Deserpidine Tablets
Methylphenidate Hydrochloride Chewable Tablets	Metipranolol Ophthalmic Solution	Metronidazole Capsules
Metronidazole Cream	Metronidazole Extended-Release Tablets	Metronidazole Hydrochloride for Injection
Metronidazole Lotion	Miconazole Nitrate Topical Aerosol	Midazolam Hydrochloride Injection ***(Received)***
Mifepristone Tablets	Miglitol Tablets	Milrinone Injection
Misoprostol Tablets ***(Received)***	Mivacurium in Dextrose Injection	Mivacurium Injection
Moexipril Hydrochloride and Hydrochlorothiazide Tablets	Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution
Morphine Sulfate for Injection Concentrate	Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate
Morphine Sulfate Tablets	Mycophenolate Mofetil Capsules	Mycophenolate Mofetil Oral Solution
Mycophenolate Mofetil Tablets	Nalbuphine Hydrochloride Injection	Nalmefene Hydrochloride Injection
Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution		Naproxen Extended-Release Tablets
Nateglinide Tablets	Nedocromil Sodium Inhalation Aerosol	Neomycin Sulfate Oral Powder
Nevirapine Oral Suspension ***(Received)***	Nevirapine Tablets ***(Received)***	Nicardipine Hydrochloride Capsules
Nilutamide Tablets	Nimodipine Capsules	Nisoldipine Extended-Release Tablets
Nitroglycerin Solution in Acrylic Adhesive	Nizatidine Tablets	Ofloxacin in Dextrose Injection
Ofloxacin Injection	Ofloxacin Tablets ***(Received)***	Olopatadine Ophthalmic Solution
Olsalazine Sodium Capsules	Ondansetron Oral Solution ***(Received)***	Ondansetron Tablets
Orbifloxacin Tablets	Orlistat Capsules ***(Received)***	Orphenadrine Citrate Extended-Release Tablets
Orphenadrine Citrate, Aspirin, and Caffeine Tablets	Oxcarbazepine Suspension	Oxcarbazepine Tablets
Oxiconazole Cream	Pancuronium Bromide Injection ***(Received)***	Pantoprazole Sodium for Injection
Pantoprazole Sodium Tablets	Paroxetine Hydrochloride Extended-Release Tablets	Paroxetine Oral Suspension
Pemirolast Potassium Ophthalmic Solution	Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution
Pentaerythritol Tetranitrate Extended-Release Capsules	Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation
Pentamidine Isethionate for Injection	Pentazocine Hydrochloride and Acetaminophen Tablets	Phendimetrazine Tartrate Extended-Release Capsules
Phenobarbital Capsules	Phentermine Resin Complex	Phentermine Resin Complex Capsules

Noncomplex Actives (Drug Products) *(Continued)*		
Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules	Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pilocarpine Hydrochloride Ophthalmic Gel
Pilocarpine Hydrochloride Ophthalmic Ointment	Pilocarpine Hydrochloride Tablets	Piperonyl Butoxide and Pyrethrins Aerosol Foam
Pirbuterol Acetate Inhalation Aerosol	Poractant Alpha Supension	Porfimer Sodium for Injection
Povacrylate Solution	Povacrylate-Iodine Topical Solution	Povidone-Iodine Gauze
Povidone-Iodine Swabsticks	Povidone-Iodine Topical Aerosol Foam	Povidone-Iodine Vaginal Suppositories
Pramipexole Dihydrochloride Tablets	Prazosin Hydrochloride and Polythiazide Capsules	Prednisolone Sodium Phosphate Oral Solution
Prochlorperazine Maleate Extended-Release Capsules	Progesterone Capsules	Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup
Promethazine and Phenylephrine Hydrochlorides Syrup	Promethazine Hydrochloride and Codeine Phosphate Oral Solution	Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup
Propafenone Hydrochloride Tablets	Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets
Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution	Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets
Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution	Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	
Pyrilamine Maleate Injection	Quinidine Sulfate Injection	
Ramipril Capsules	Ranitidine Capsules	Rauwolfia Serpentina and Endroflumethiazide Tablets
Reserpine and Polythiazide Tablets	Rimantadine Hydrochloride Oral Solution	Risperidone Oral Solution
Risperidone Orally Disintegrating Tablets	Risperidone Tablets ***(Received)***	Rivastigmine Tartrate Capsules
Rivastigmine Tartrate Oral Solution	Rocuronium Bromide Injection	Ropinirole Hydrochloride Tablets
Rose Bengal Ophthalmic Solution	Rosiglitazone Maleate Tablets	Salicylic Acid and Sulfur Cleansing Lotion
Salicylic Acid and Sulfur Lotion	Salicylic Acid and Sulfur Shampoo	Salicylic Acid Cream
Salicylic Acid Ointment	Salmeterol Inhalation Aerosol	Salmeterol Xinafoate Inhalation Powder
Scopolamine Transdermal System	Selegiline Hydrochloride Capsules	Serpacwa Topical Cream
Sertraline Hydrochloride Oral Solution	Sibutramine Hydrochloride Capsules	Sodium Bicarbonate and Sodium Citrate for Oral Solution
Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension	Sodium Chlorophyllin Copper Complex Tablets	Sodium Iodide Injection
Sodium Phenylbutyrate Oral Powder	Sodium Phenylbutyrate Tablets	Sodium Phosphates for Oral Suspension
Sodium Phosphates Tablets	Sodium Salicylate and Sulfur Shampoo	Sterile Talc Aerosol
Streptozocin for Injection	Sucralfate Oral Suspension	Sulconazole Nitrate Cream
Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension	Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sulfacytine Tablets
Sulfanilamide Vaginal Cream	Sulfasalazine Oral Suspension	Sulisobenzone Lotion
Sumatriptan Injection	Sumatriptan Tablets	Tacrolimus Capsules
Tacrolimus Injection	Tacrolimus Ointment	Tamsulosin Hydrochloride Capsules
Technetium Tc 99m Teboroxime Injection	Tenofovir Disoproxil Fumarate Tablets	Terbinafine Hydrochloride Cream
Terbinafine Tablets	Terbinafine Topical Solution	Terconazole Vaginal Cream
Terconazole Vaginal Suppositories	Testosterone Transdermal System	Tetracycline Hydrochloride Periodontal Fiber
Theophylline Extended-Release Tablets	Tioconazole Vaginal Ointment	Tiopronin Tablets
Tolnaftate Topical Aerosol Solution	Topiramate Capsules	Topiramate Tablets
Torsemide Injection	Torsemide Tablets	Trandolapril and Verapamil Hydrochloride Extended-Release Tablets
Trandolapril Tablets	Tranexamic Acid Injection	Tranylcypromine Sulfate
Tranylcypromine Sulfate Tablets	Tretinoin Capsules	Tretinoin Microsphere Gel
Triamcinolone Acetonide Metered-Dose Nasal Suspension	Trifluridine Ophthalmic Solution	Trimetrexate for Injection
Trimipramine Maleate Capsules	Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup	Trolamine Salicylate Cream
Trolamine Salicylate Gel	Trolamine Salicylate Topical Emulsion	Trovafloxacin Injection
Trovafloxacin Mesylate for Injection	Undecylenic Acid Topical Foam Aerosol	Unoprostone Isopropyl Ophthalmic Solution
Urea Cream	Vecuronium Bromide for Injection	Venlafaxine Extended-Release Capsules

Noncomplex Actives (Drug Products) *(Continued)*

Venlafaxine Tablets	Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules
Voriconazole Injection	Voriconazole Oral Suspension	Voriconazole Tablets
Yttrium Y-90 Chloride Solution	Yttrium Y-90 Glass Microspheres	Yttrium Y-90 Microspheres Injection
Zidovudine and Lamivudine Tablets	Zinc Acetate Capsules	Zinc Tridosium Pentetate Injection
Ziprasidone Hydrochloride Capsules	Zoledronic Acid for Injection	

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	Aconitic Acid (Achilleic Acid)
Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal	Aliphatic Polyesters
Allantoin-Sodium Pyrrolidone Carboxylate	Aluminum Ammonium Sulfate	Aluminum Ammonium Sulfate
Aluminum Lactate	Aluminum Oxide	Aluminum Potassium Sulfate
Aluminum Silicate	Aluminum Sodium Sulfate	Aluminum Stearate
Ammonium Bicarbonate	Ammonium Calcium Alginate	Ammonium Phosphate
Batylalcohol Monostearate	Beeswax, Synthetic	Benzododecinium Bromide
Benzyl Chloride	Benzyl Nicotinate	Beta Naphthol
Brominated Vegetable Oil	Butadiene-Styrene Rubber	Butylated Hydromethylphenol
Butylene Glycol	Butylphthalyl Butylglycolate	Calcium Acid Pyrophosphate
Calcium Alginate	Calcium Alginate and Ammonium Alginate	Calcium Bromide
Calcium Chloride Solution	Calcium Glycerophosphate ***(Received)***	Calcium Phosphate Monobasic
Calcium Propionate	Calcium Pyrophosphate	Calcium Sorbate
Calcium Stearoyl Lactylate	Caldiamide Sodium	Calteridol Calcium
Canola Oil	Capric Acid	Caprylic/Capric Diglyceril Succinate
Carbon	Carboxymethyl Starch	Carboxymethylamylopectin Sodium
Carboxymethylcellulose Potassium	Cetostearyl Isononanoate	Chlorodifluoroethane
Cholic Acid	Cinnamaldehyde	Cocamide Diethanolamine
Cocamide Oxide	Coconut Oil	Coconut Oil Hydrogenated ***(Received)***
Cocoyl Caprylocaprate	Crystal Gum	Cutina
Cystine	Dammar Gum	Decanoic Acid
Decyl Oleate	Dehydroacetic Acid	Desoxycholic Acid
Dextrin Palmitate	Dextrins Modified	Diacetyl Tartaric Acid Esters of Mono- and Diglycerides
Dicetyl Phosphate	Dichlorofluoromethane	Diethyl Sebacate
Difluoroethane	Diglycol Stearate	Diisobutyl Adipate
Diisopropyl Adipate	Diisopropylbenzothiazyl-2-Sulfenamide	Dilauryl Thiodipropionate
Dimethyl Dicarbonate	Dimyristoyl Lecithin	Dimyristoyl Phosphatidylglycerol
Dipropylene Glycol	Disodium Edisylate	Disodium Guanylate
Disodium Inosinate	Disodium Monooleamide Sulfasuccinate	D-Mannose
Docusate Sodium/Sodium Benzoate	Erythorbic Acid	Erythrosine
Ethoxylated Mono- and Diglycerides	Ethoxyquin	Ethyl Hexanediol
Ethyl Linoleate	Ethyl Maltol	Ethylene Dichloride
Ethylurea	Ferric Ammonium Citrate	Ferric Citrate
Ferric Oxide, Brown	Ferric Phosphate	Ferric Pyrophosphate
Ferrous Citrate	Ferrous Glycinate	Ferrous Lactate
Fluorochlorohydrocarbons	Formic Acid	Furcelleran
Gamma-Cyclodextrin	Gentistic Acid	Geraniol
Glutamic Acid Hydrochloride	Gluten	Glycerol Ester of Gum Rosin (Ester Gum)
Glyceryl Laurate	Glyceryl Palmitate	Glyceryl Ricinoleate
Glyceryl Tristearate	Glycine Hydrochloride	Glycofurol
Glycol Stearate	Heptafluoropropane	Heptylparaben
Hexadecyl Isostearate	Hexane	Hexanetriol(-1,2,6-)
Hydrocarbon Gel	Hydrogenated Starch Hydrolysate	Hydroxyethylmethylcellulose
Hydroxylated Lecithin	Hydroxypropyl Beta Cyclodextrin	Indigotine
Inositol	Iron Carbonyl	Iron Subcarbonate
Isobutylated-Isoprene Copolymer	Isooctylacrylate	Isopropyl Isostearate
Isopropyl Stearate	Isostearic Acid	Isostearyl Alcohol

Excipients *(Continued)*		
Lactobionic Acid	Lactose Ferrin, Bovine	Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol
Lactylic Esters of Fatty Acids	Lanolin (Wool Fat), Hydrogenated	Lanolin Alcohols, Acetylated
Lanolin Hydrous	L-Ascorbyl Stearate	Lauramine Oxide
Lauric Myristic Diethanolamide	Lauric Acid	Lauric Diethanolamide
Lavender Oil	L-Cysteine Monohydrochloride	Lecithin, Hydroxylated
L-Glutamic Acid	Linoleic Acid	L-Leucine
Macrogol Sorbitan Tristearate	Macrogolglycerol Cocoates	Macrogolglycerol Triisostearate
Magnesium Aluminum Silicate Hydrate	Magnesium Aspartame Dihydrate	Magnesium Aspartate
Magnesium Phosphate Tribasic	Magnesium Phosphate, Diabasic, Trihydrate	Magnesium Tartrate
Malt Syrup	Maltitol Syrup	Maltol Isobutyrate
Manganese Chloride	Manganese Citrate	Manganese Glycerophosphate
Manganese Hypophosphite	Medical Antifoam Emulsion C	Medronate Disodium
Medronic Acid	Methyl Chloride	Methylchloroisothiazolinone
Methylisothiazolinone	Microcrystalline Cellulose, Silicified ***(Received)***	Mineral Spirits
Monoisostearyl Glyceryl Ester	Monopotassium Glutamate Monohydrate	Monosodium Citrate
Mullein Leaf	Myristyl Gamma-Picolinium Chloride	Myristyl Lactate
N,N-Bis(2-Hydroxyethyl) Stearamide	*N*-Acetyl-L- Methionine	Naphtha
N-Methylpyrrolidone ***(Received)***	Non-Pareil Seeds	Nutmeg Oil
Octanoic Acid	Oxystearin	Palm Kernel Oil ***(Received)***
Palm Oil	Pentasodium Triphosphate	Pentetate Calcium Trisodium
Pentetate Pentasodium	Phenprobamate	Phenylmercuric Acetate
Phenylmercuric Nitrate	Pine Oil	Polacrilin
Polydextrose ***(Received)***	Polydextrose Solution	Polyglycerol Esters Of Fatty Acids
Polyglycerol Polyricinoleic Acid	Polyoxyethylene Castor Oil (USP has 35)	Polyoxyl Stearate (USP has 40)
Polypropylene Oleate	Polypropylene Stearyl Ether	Polysorbate 65
Polyvinylacetal	Polyvinylacetal Diethylanoacetate	Polyvinylpolypyrrolidone
Polyvinylpyrrolidone Ethylcellulose	Potassium Acid Tartrate	Potassium Bromate
Potassium Carbonate Solution	Potassium Dichloroisocyanurate	Potassium Gibberellate
Potassium Glycerophospate	Potassium Nitrite	Potassium Phosphate
Potassium Phosphate Tribasic	Potassium Polymetaphosphate	Potassium Pyrophosphate
Potassium Stearate	Potassium Sulfate	Potassium Sulfite
Potassium Tripolyphosphate	Potasssium Iodate	Propyl Propionate
Propylene Glycol Diacetate	Propylene Glycol Mono- and Diesters	Purified Polyoxyl 35 Castor Oil ***(Received)***
Rapeseed Oil, Hydrogenated ***(Received)***	Rapeseed Oil, Superglycerinated ***(Received)***	Rice Bran Wax
Rosin	Silicone	Sodium Acid Pyrophosphate
Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic	Sodium Aluminum Phosphate Basic
Sodium Aspartate	Sodium Bisulfate	Sodium Bisulfite
Sodium Carbonate Hydrate	Sodium Carboxymethyl Betaglucan	Sodium Caseinate
Sodium Chlorate	Sodium Citrate, Dibasic	Sodium Citrate, Monobasic
Sodium Dehydroacetate	Sodium Diacetate	Sodium Erythorbate
Sodium Ferric Pyrophosphate	Sodium Ferrocyanide	Sodium Hypophosphite
Sodium Laureth Sulfate	Sodium Lauroyl Sarcosinate	Sodium Lauryl Sulfoacetate
Sodium Magnesium Aluminosilicate	Sodium Magnesium Silicate	Sodium Malate
Sodium Metaphosphate, Insoluble	Sodium Metasilicate	Sodium Methylate
Sodium Polyphosphates Glassy	Sodium Potassium Tripolyphosphate	Sodium Pyrophosphate
Sodium Pyrrolidone Carboxylate	Sodium Sesquicarbonate	Sodium Sesquinoleate
Sodium Stearoyl Lactylate	Sodium Thiomalate	Sodium Trimetaphosphate
Sodium Trioleate	Sodium Tripolyphosphate	Soy Polysaccharides
Stannous Chloride	Stannous Tartrate	Starch, Pregelatinized Corn
Starch, Pregelatinized Tapioca	Stearalkonium Chloride	Stearyl Citrate
Stearyl Monoglyceridyl Citrate	Succinylated Monoglycerides	Sucrose Acetate Isobutyrate
Sucrose Fatty Acid Esters	Sucrose Stearate	Sugar Fruit Fine
Sulfobutyl Ether Beta Cyclodextran	Tallow	Tallow Glycerides
Tallow Oil	Tetrafluoroethane	Thioglycerol
Thyme Oil	Tribehenin	Tricetearet-4 Phosphate

Excipients *(Continued)*

Trichloroethylene	Trimyristin	Trisidium Citrate
Trolamine Lauryl Sulfate	Vegetable Oil	Wheat Flour
Wheat Germ Oil	Wheat Gluten	Whey

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

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

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

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ▪new text▪, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ▪▪, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement*, and ▪2S (*USP29*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 29*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in the next available *Supplement*, and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

THIRD INTERIM REVISION ANNOUNCEMENT to *USP 29* and to *NF 24*

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

John W. Mauger, *Chair*
USP Board of Trustees

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

Roger L. Williams, M.D., *Chief Standards Officer, Acting*

Official June 1, 2006 **Released May 1, 2006**

All inquiries and comments regarding *USP 29* text and *NF 24* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were not available when the associated monograph was made official, have since become available. The respective official date of each *USP 29* or *NF 24* standard, test, or assay requiring the use of the following USP Reference Standards is indicated in parentheses after the name of the Reference Standard.

USP Berberine Chloride (May 1, 2006)
USP Budesonide RS (September 1, 2006)
USP Fluticasone Propionate RS (November 1, 2006)
USP Fluticasone Propionate Resolution Mixture RS (September 1, 2006)
USP Fluticasone Propionate System Suitability Mixture RS (September 1, 2006)
USP Fluvastatin Related Compound B RS (November 1, 2006)
USP Hydrastine RS (May 1, 2006)
USP Mefloquine Hydrochloride RS (May 1, 2006)
USP Mefloquine Related Compound A RS (May 1, 2006)
USP Norphenylephrine Hydrochloride RS (May 1, 2006)
USP Ondansetron RS (May 1, 2006)
USP Polyisobutylene RS (November 1, 2006)
USP Ropivocaine Hydrochloride RS (November 1, 2006)
USP Ropivacaine Related Compound A RS (September 1, 2006)
USP Ropivacaine Related Compound B RS (September 1, 2006)
USP Somatropin RS (May 1, 2006)
USP Tiagabine Related Compound A RS (May 1, 2006)
USP Racemic Tiagabine Hydrochloride Mixture RS (May 1, 2006)
USP Tiagabine Hydrochloride RS (May 1, 2006)
USP Tinidazole Related Compound B RS (September 1, 2006)

Unavailable First-Time Official USP Reference Standards

The official dates of any *USP 29* or *NF 24* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards. This listing was updated as of March 6, 2006.

USP Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Aprotinin RS
USP Aprotinin System Suitability RS
USP Cetrimonium Bromide RS
USP Citalopram Hydrobromide RS
USP Cladribine RS
USP Cladribine Related Compound A RS
USP Copolymer Polypropylene RS
USP Decoquinate RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Escin RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Gabapentin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Lamivudine Resolution Mixture B RS
USP Alpha Lipoic Acid RS
USP Maritime Pine Extract RS
USP Mecamylamine Related Compound A RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Naratriptan Resolution Mixture RS
USP Near Infrared Calibrator RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Paricalcitol Solution RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Polyoxyl 10 Oleyl Ether RS
USP Potassium Perchlorate RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Powdered St John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Sulisobenzone RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tizanidine Hydrochloride RS
USP Tizanidine Related Compound A RS
USP Tizanidine Related Compound B RS
USP Tizanidine Related Compound C RS
USP Powdered Valerian RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS

MONOGRAPHS (USP)

Amoxicillin Capsules

Add the following:

•**Labeling**—When more than one *Dissolution Test* is given, the labeling states the *Dissolution Test* used only if *Test 1* is not used.•(3)

Change to read:

Dissolution ⟨711⟩—

•TEST 1—•(3)

Medium: water; 900 mL.

Apparatus 1: 100 rpm, for Capsules containing 250 mg.

Apparatus 2: 75 rpm, for Capsules containing 500 mg.

Time: 60 minutes.

Procedure—Determine the amount of $C_{16}H_{19}N_3O_5S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 272 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Amoxicillin RS in the same *Medium.*

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 60 minutes.

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: water; 900 mL.

Apparatus 1: 100 rpm.

Time: 90 minutes.

Procedure—Determine the amount of $C_{16}H_{19}N_3O_5S$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 272 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Amoxicillin RS in the same *Medium.*

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 90 minutes.•(3)

Clopidogrel Tablets

Change to read:

Related compounds—

Phosphate buffer and *Mobile phase*—Prepare as directed in the *Assay* under *Clopidogrel Bisulfate*.

System suitability solution—Dissolve accurately weighed quantities of USP Clopidogrel Bisulfate RS, USP Clopidogrel Related Compound A RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS in methanol. Dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having concentrations of about 1 µg per mL, 1 µg per mL, 2 µg per mL, and 3 µg per mL, respectively.

Standard solution—Dissolve accurately weighed quantities of USP Clopidogrel Related Compound A RS and USP Clopidogrel Related Compound C RS in methanol. Dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 1 µg per mL and 5 µg per mL, respectively.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg of clopidogrel, to a 200-mL volumetric flask, add 5 mL of methanol, dilute with *Mobile phase* to volume, and mix. Allow to stand for 10 minutes, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate after discarding the first 5 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and 4.6-mm × 15-cm column that contains packing L57. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between clopidogrel and each of the two enantiomers of clopidogrel related compound B is not less than 2.5. [NOTE—The relative retention times are about 0.5 for clopidogrel related compound A, 0.8 and 1.2 for the two enantiomers of clopidogrel related compound B, 1.0 for clopidogrel, and 2.0 for clopidogrel related compound C.] Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 15%.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of related compounds in the portion of Tablets taken by the formula:

$$20(C/W)(r_U/r_S)$$

in which C is the concentration, in µg per mL, of the appropriate USP Reference Standard in the *Standard solution; W* is the weight, in mg, of clopidogrel in the portion of Tablets used to prepare the *Test solution* based on the labeled quantity of clopidogrel per Tablet, Tablet weight, and the weight of the portion of Tablets used; and r_U and r_S are the peak responses of the corresponding related compounds obtained from the *Test solution* and the *Standard solution,* respectively: not more than •1.2%•(3) of clopidogrel related compound A is found, not more than •1.5%•(3) of clopidogrel related compound C is found, not more than 0.2% of any other single impurity (excluding clopidogrel related compound B) is found, and not more than •2.5%•(3) of total impurities (excluding clopidogrel related compound B) is found.

Felodipine Extended-Release Tablets

Add the following:

•**Labeling**—When more than one test for *Dissolution* is given, the *Labeling* section states the test for *Dissolution* used only if *Test 1* is not used.•(3)

Change to read:

Dissolution ⟨711⟩—

•TEST 1—•(3)

Medium: pH 6.5 phosphate buffer with 1% sodium lauryl sulfate; 500 mL. (*Medium* is prepared as follows. Transfer 206 mL of 1 M monobasic sodium phosphate monohydrate, 196 mL of 0.5 M dibasic sodium phosphate anhydrous, and 50.0 g of sodium lauryl sulfate to a 5000-mL volumetric flask. Add approximately 4000 mL of water, and mix well. If necessary, adjust with 1 N sodium hydroxide to a pH of 6.5. Dilute with water to volume, and mix well.)

Apparatus 2: 50 rpm.
Times: 2, 6, and 10 hours.
Buffer solution—Prepare as directed in the *Assay.*
Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, *Buffer solution,* and methanol (2.5 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard stock solution—Dissolve an accurately weighed quantity of USP Felodipine RS in alcohol to obtain a solution having a known concentration of 0.25 mg per mL.
Standard solution—Dilute an accurately measured volume of the *Standard stock solution* quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of USP Felodipine RS equivalent to the concentration that would result from about 60% dissolution of a single Tablet in 500 mL of *Medium.*
Test solution—Place each Tablet in a specially made quadrangular basket of stainless steel wire gauze, soldered in one of its upper, narrow sides to the end of a steel rod (see *Figure 1*). Place the tablet cover in the horizontal diagonal of the basket. Put the rod assembly up through the cover of the dissolution vessel, and fix it by means of two teflon nuts, 3.2 cm from the center of the vessel, or by any other appropriate means. Adjust the lower edge of the bottom of the basket to approximately 1 cm above the top of the paddle blade (see *Figure 2*). Orient the large side of the basket tangentially to the flow stream with the Tablet standing on its edge. Pass a 10-mL portion of the solution under test, obtained at each time interval, through a suitable filter.
Chromatographic system—Proceed as directed in the *Assay.*
Procedure—Separately inject equal volumes (100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved in the *Medium* by the formula:

$$CD(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Felodipine RS in the *Standard solution; D* is the dilution factor used in preparing the *Test solution;* and r_U and r_S are the felodipine peak areas obtained from the *Test solution* and the *Standard solution,* respectively.
Tolerances—The percentages of the labeled amount of $C_{18}H_{19}Cl_2NO_4$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	between 10% and 30%
6	between 42% and 68%
10	not less than 75%

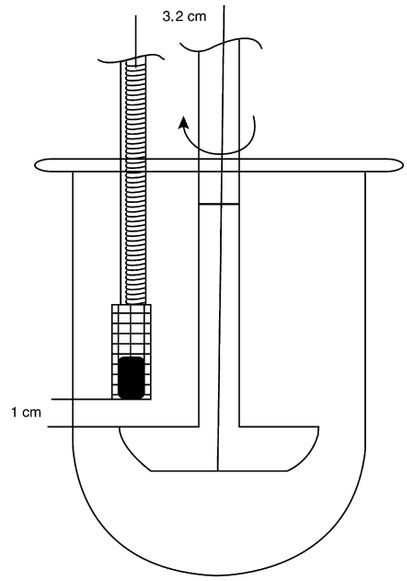


Figure 2. Drug Release Stationary Tablet Basket Configuration Diagram

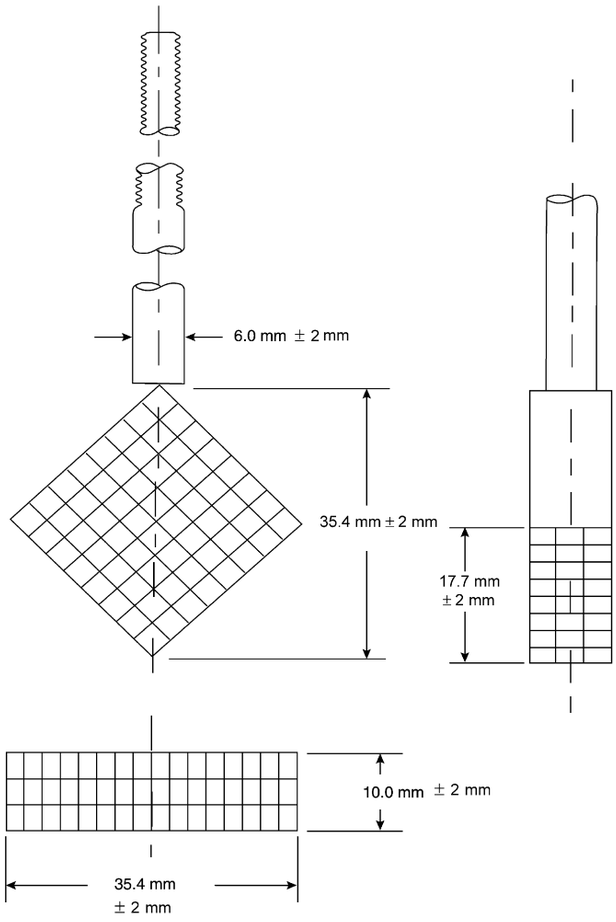
(Official April 1, 2006)

•TEST 2—
Medium: 1% (w/v) polysorbate 80 in water; 500 mL.
Apparatus 1: 100 rpm.
Times: 1, 4, and 8 hours.
Determine the amount of $C_{18}H_{19}Cl_2NO_4$ dissolved by employing the following method.
Buffer solution—Transfer 6.9 g, accurately weighed, of monobasic sodium phosphate into a 1-L volumetric flask containing about 400 mL of water. Add 8.0 mL of 1 M phosphoric acid, dilute with water to volume, and mix.
Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* acetonitrile, and methanol (2 : 2 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Standard stock solution—Transfer 40 mg, accurately weighed, of USP Felodipine RS into a 200-mL volumetric flask, add about 200 mL of methanol. Sonicate for 2 minutes, cool, dilute with methanol to volume, and mix.
Standard working solutions—Transfer the appropriate volume of *Standard stock solution* into a suitable volumetric flask according to the following table.

Tablet Label Claim (mg)	Volume Transferred (mL)	Volumetric Flask (mL)
10	10	100
5	5	100
2.5	2.5	100

Dilute with *Medium* to volume, and mix.
Test solution—Pass a portion of the solution under test through a suitable 0.45-µm filter. Replace the withdrawn amount with *Medium.*
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard working solution,* and record the peak responses as directed for *Procedure:* the capacity factor *(k′)* is not less than 5, the column efficiency *(N)* is not less than 1500 theoretical plates, the tailing factor is not more than 1.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Interim Revision Announcement



NOTES

1. Rod and Basket with a Tablet cover placed in the horizontal diagonal of the basket.
2. Basket and Tablet cover material; stainless steel.
3. Basket gauze wire size: 8 mesh.

Figure 1. Stationary Tablet Basket

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard working solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

in which C_U is the concentration, in mg per mL, of felodipine in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard working solution,* respectively; and C_S is the concentration, in mg per mL, of felodipine in the *Standard working solution.*

Calculate the amount, in percentage, of felodipine ($C_{18}H_{19}Cl_2NO_4$) dissolved, with volume correction, by the formula:

$$\frac{\left[\left\{C_N \times \left[500 - V_U(n-1)\right]\right\} + \left[\sum_{i=1}^{n-1} C_i \times V_U\right]\right] \times 100}{LC}$$

in which C_N is the concentration, in mg per mL, of felodipine in the *Test solution* at each time point; 500 is the volume, in mL, of *Medium;* V_U is the volume, in mL, of sample withdrawn at each time point; n is the time point (at 4 hours, $n + 1$), summation of the concentration of the *Test solution* from the first to the $(n - 1)^{th}$ time point (only applicable for $n = 2$); 100 is the conversion factor to percentage; and LC is the tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of felodipine dissolved at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	between 5% and 30%
4	between 45% and 70%
8	not less than 80%

●3

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Tizanidine Hydrochloride

Change to read:

Assay—

Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 5.3 N potassium hydroxide to a pH of 7.5 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile •(80 : 20).•$_3$ Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve suitable quantities of USP Tizanidine Hydrochloride RS and USP Tizanidine Related Compound C RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 0.00012 mg per mL and 0.046 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.046 mg per mL.

Assay preparation—Transfer about 23 mg of Tizanidine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 35°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for tizanidine related compound C and 1.0 for tizanidine; the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 13.0; and the tailing factor for the tizanidine peak is not more than 1.6. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_9H_8ClN_5S \cdot HCl$ in the portion of Tizanidine Hydrochloride taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Tizanidine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Interim Revision Announcement

GENERAL CHAPTERS

General Tests and Assays

Chemical Tests and Assays

LIMIT TESTS

⟨231⟩ HEAVY METALS

Change to read:

METHOD II

NOTE—This method does not recover mercury.

•**pH 3.5 Acetate Buffer**—Prepare as directed under *Method I.*

Standard Preparation—Prepare as directed under *Method I.*

Test Preparation—Use a quantity, in g, of the substance to be tested as calculated by the formula:

$$2.0 / (1000L)$$

in which L is the *Heavy metals* limit, in percentage. Transfer the weighed quantity of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at 500° to 600°, until the carbon is completely burned off. Cool, add 4 mL of 6 N hydrochloric acid, cover, digest on a steam bath for 15 minutes, uncover, and slowly evaporate on a steam bath to dryness. Moisten the residue with 1 drop of hydrochloric acid, add 10 mL of hot water, and digest for 2 minutes. Add 6 N ammonium hydroxide dropwise until the solution is just alkaline to litmus paper, dilute with water to 25 mL, and adjust with 1 N acetic acid to a pH between 3.0 and 4.0, using short-range pH indicator paper as external indicator. Filter if necessary, rinse the crucible and the filter with 10 mL of water, combine the filtrate and rinsing in a 50-mL color-comparison tube, dilute with water to 40 mL, and mix.

Procedure—To each of the tubes containing the *Standard Preparation* and the *Test Preparation,* add 2 mL of *pH 3.5 Acetate Buffer,* then add 1.2 mL of thioacetamide–glycerin base TS, dilute with water to 50 mL, mix, allow to stand for 2 minutes, and view downward over a white surface*: the color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation*.•[3]

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* In those countries or jurisdictions where thioacetamide cannot be used, add 10 mL of freshly prepared hydrogen sulfide TS to each of the tubes, mix, allow to stand for 5 minutes, and view downward over a white surface.

ERRATA

Following is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP 29–NF 24*. If necessary, this list will be updated with every issue of *PF*. This information will also be available as a cumulative table in future *Supplements* and will appear in its corrected form in a future annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff is available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
530	*Clarithromycin Extended-Release Tablets*	*Dissolution, Test 2*	Lines 18 through 20 under *Procedure:* Change "*n* is the time point (at 2 hours, n = 1), summation of the concentration of the *Test solution* from the first to the (*n* –1)th time point (only applicable for $n \geq 2$)" to: *n* is the number of time points [NOTE—The summation of the amount of clarithromycin removed at previous sampling time points is applicable only where $n > 1$]
2277	*Yohimbine Injection*	*Assay*	Lines 6 through 10 under *Procedure:* Change "(354.45/390.01)(25,000*C*/*V*)(r_u/r_s), in which 354.45 and 390.91 are the molecular weights of yohimbine and yohimbine hydrochloride, respectively; *C* is the concentration, in mg per mL, of USP Yohimbine Hydrochloride RS in the *Standard preparation; V* is the volume, in mL" to: (354.45/390.01)(25,000*C*/*V*)(r_u/r_s), in which 354.45 and 390.91 are the molecular weights of yohimbine and yohimbine hydrochloride, respectively; *C* is the concentration, in mg per mL, of USP Yohimbine Hydrochloride RS in the *Standard preparation; V* is the volume, in µL

IN-PROCESS REVISION

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

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

BRIEFING

> **Name of Item**, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How to Use PF*), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
>
> (DSN: L. Evans) RTS—C55678

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

•new text•

if slated for an *Interim Revision Announcement to USP 29–NF 24* (*IRA*);

▲new text▲*USP30*

if slated for *USP 30–NF 25*; and

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, ■2S (*USP 29*) indicates that the proposed revision is slated for the *Second Supplement to USP 29*, and ▲*USP30* and ▲*NF25* indicate that the revisions are proposed for *USP 30* and *NF 25*, respectively.

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

In-Process Revision

MONOGRAPHS (USP)

BRIEFING

Aluminum Sulfate and Calcium Acetate Powder for Topical Solution. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. It is based on validation data received and on the monograph for *Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution* (see *USP 29* page 107). The proposed monograph was created by request of FDA to amend the OTC monograph for astringent drug products to allow for the marketing of products covered by this proposed new *USP* monograph.

(MD-AA: B. Davani) RTS—C42878

Add the following:

■Aluminum Sulfate and Calcium Acetate Powder for Topical Solution

» Aluminum Sulfate and Calcium Acetate Powder for Topical Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of aluminum sulfate tetradecahydrate [$Al_2(SO_4)_3 \cdot 14H_2O$] and calcium acetate monohydrate ($C_4H_6CaO_4 \cdot H_2O$).

Packaging and storage—Preserve in single-unit containers, and protect from excessive heat.

Identification—

A: Place approximately 0.25 g of Aluminum Sulfate and Calcium Acetate Powder for Topical Solution in a test tube. Add 10 mL of water and 0.25 g of calcium carbonate. Heat on a steam bath for 10 minutes, and filter. Add 3 to 4 drops of ferric chloride TS to the filtrate. A reddish-brown color or precipitate indicates acetate. [NOTE—After the addition of the ferric chloride TS, the solution may be heated for 1 minute to speed the reaction.]

B: Suspend 2 g of sample in 50 mL of water, and filter. The filtrate responds to the tests for *Sulfate* ⟨191⟩ and for *Calcium* ⟨191⟩.

pH ⟨791⟩**:** between 4.0 and 4.8 in a solution (1 in 200).

Assay for aluminum sulfate—

Assay preparation—Transfer 10 g of Aluminum Sulfate and Calcium Acetate Powder for Topical Solution, accurately weighed, to a 1000-mL volumetric flask. Add 100 mL of 1.2 M hydrochloric acid and approximately 250 mL of water. Heat on a steam bath or hot plate until dissolved. Cool, dilute with water to volume, and mix. [NOTE—Retain a portion of this *Assay preparation* for the *Assay for calcium acetate.*]

Procedure—Transfer a 5.0-mL aliquot of the *Assay preparation* to a 250-mL conical flask. Add 40.0 mL of 0.01 M edetate disodium VS and 20 mL of acetic acid–ammonium acetate buffer TS, and mix well. Add 50 mL of alcohol and 2 mL of dithizone TS. [NOTE—Follow the given order of addition.] Titrate with 0.02 M zinc sulfate VS until the color changes from green-violet to clear rose-pink. Perform a blank titration, substituting 5.0 mL of water for the *Assay preparation*. Each mL of 0.01 M edetate disodium is equivalent to 2.972 mg of aluminum sulfate tetradecahydrate [$Al_2(SO_4)_3 \cdot 14H_2O$]. Calculate the percentage of aluminum sulfate tetradecahydrate [$Al_2(SO_4)_3 \cdot 14H_2O$] by the formula:

$$[(1000)(100)C_F M(V_B - V_U)] / 5.0M_T W$$

in which 1000/5.0 is the dilution factor; 100 is the conversion factor to percentage; C_F is the conversion factor (2.972 mg of sample per mL of 0.01 M edetate disodium); M is the actual molarity of the titrant; V_B is the blank titration volume, in mL; V_U is the sample titration volume, in mL; M_T is the theoretical molarity of the titrant (0.02); and W is the weight of the sample, in mg.

Assay for calcium acetate—

Procedure—Transfer a 5.0-mL aliquot of the *Assay preparation* retained from the *Assay for aluminum sulfate* to a 250-mL conical flask. Add 1 to 2 mL of 50% triethanolamine to mask the aluminum. Mix well. Add 100 mL of water, 15 mL of 1 N sodium hydroxide, and approximately 300 mg of hydroxy naphthol blue. [NOTE—Follow the given order of addition.] Titrate the solution with 0.01 M edetate disodium VS. The indicator will change from purple to a clear blue color at the endpoint. Each mL of 0.01 M edetate disodium is equivalent to 1.762 mg of calcium acetate monohydrate ($C_4H_6CaO_4 \cdot H_2O$). Calculate the percentage of calcium acetate monohydrate ($C_4H_6CaO_4 \cdot H_2O$) by the formula:

$$[(1000)(100)V_U C_F M] / 5.0 M_T W$$

in which 1000/5.0 is the dilution factor; 100 is the conversion factor to percentage; V_U is the sample titration volume, in mL; C_F is the conversion factor (1.762 mg of sample per mL of 0.01 M edetate disodium); M is the actual molarity of the titrant; M_T is the theoretical molarity of the titrant (0.01); and W is the weight of the sample, in mg.■1S (*USP30*)

BRIEFING

Amifostine, *USP 29* page 125. It is proposed to correct the equation for calculating the percentage of amifostine thiol in the test for *Related compounds.* In the absence of any adverse comments, it is proposed to implement this revision via the *Fifth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of October 1, 2006.

(MD-CV: S. Ramakrishna) RTS—C44547

Change to read:

Related compounds—

Mobile phase—Dissolve 1.0 mL of nonafluorobutane sulfonic acid in 1200 mL of HPLC grade water, add 400 µL of trifluoroacetic acid, and adjust with triethylamine to a pH of 2.5. Prepare a degassed mixture of this solution and acetonitrile (68 : 32).

Blank solution—Use water.

Standard thiol solution—Transfer about 12.4 mg of USP Amifostine Thiol RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

System suitability solution—Dissolve about 5.0 mg of USP Amifostine RS, accurately weighed, in 1 mL of *Standard thiol solution,* and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 12 hours if maintained at about 5°.]

Test solution—Transfer about 50 mg of Amifostine, accurately weighed, to a 1-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°, and the temperature of the solutions to be injected is maintained at 2° to 8°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and the *Standard thiol solution,* and record the peak responses as directed for *Procedure:* the resolution between the amifostine and amifostine thiol peaks is not less than 2.0; the column efficiency calculated for the amifostine thiol peak is not less than 2300 theoretical plates; the tailing factor is not more than 4.0; the capacity factor, k', is more than 0.5; and the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard thiol solution,* the *Test solution,* and the *Blank solution* into the chromatograph, record the chromatograms, and measure the responses of all the peaks, excluding the peaks corresponding to those obtained from the *Blank solution*. Calculate the percentage of amifostine thiol in the portion of Amifostine taken by the formula:

~~$(134.24/207.17)1000(C/W)(r_U/r_S)$~~

$$\bullet(134.24/207.17)100(C/W)(r_U/r_S)\bullet_S$$

in which 134.24 and 207.17 are the molecular weights of amifostine thiol and amifostine thiol dihydrochloride, respectively; C is the concentration, in mg per mL, of amifostine thiol dihydrochloride in the *Standard thiol solution; W* is the weight, in mg, of Amifostine taken to prepare the *Test solution;* and r_U and r_S are the amifostine thiol peak responses obtained from the *Test solution* and the *Standard thiol solution,* respectively. Calculate the percentage of each of the other impurities in the portion of Amifostine taken by the formula:

$$100(r_i / r_A)$$

in which r_i and r_A are the peak responses for each impurity and amifostine, respectively, obtained from the *Test solution:* not more than 0.1% of any individual impurity, excluding amifostine thiol, is found; and not more than 0.3% of total impurities, including amifostine thiol, is found.

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BRIEFING

Amifostine for Injection, *USP 29* page 126. It is proposed to correct the equation for calculating the percentage of amifostine thiol and also the equation for calculating the percentage of amifostine disulfide in the test for *Related compounds.* In addition, it is proposed to add a *Test solution* subsection under *Related compounds* and also to make minor editorial changes. In the absence of any adverse comments, it is proposed to implement this revision via the *Fifth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of October 1, 2006.

(MD-CV: S. Ramakrishna) RTS—C44548

Change to read:

Related compounds—

Mobile phase, Blank solution, and *System suitability solution* ~~and *Test solution*~~—Prepare as directed in the test for *Related compounds* under *Amifostine.*

Standard thiol solution—Transfer about 40.1 mg of USP Amifostine Thiol RS, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

Standard disulfide solution—Transfer about 18.6 mg of USP Amifostine Disulfide RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

•*Test solution*—Transfer about 50 mg of Amifostine for Injection, accurately weighed, to a 1-mL volumetric flask, dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]•

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a detector capable of recording at both 220 nm and 247 nm, and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°, and the temperature of solutions to be injected is maintained at between 2° and 8°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* the *Standard disulfide solution,* and the *Standard thiol solution,* and record the peak responses as directed for *Procedure:* the column efficiency calculated for the amifostine thiol peak is not less than 2300 theoretical plates; the tailing factor is not more than 4.0; the capacity factor, k', is more than 0.5; and the relative standard deviation for replicate injections is not more than 4.0%. The column efficiency calculated for the amifostine disulfide peak is not less than 2000 theoretical plates; the tailing factor is not more than 4.5; the capacity factor, k', is more than 2.2; and the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard thiol solution,* the *Standard disulfide solution,* the *Test solution,* and the *Blank solution* into the chromatograph, record the chromatograms, and measure the responses of all the peaks except the peaks corresponding to those obtained from the *Blank solution.* Calculate the percentage of amifostine thiol in the portion of Amifostine for Injection taken by the formula:

~~$(134.24/207.17)1000(C/W)(r_U/r_S)$~~

$$\bullet(134.24/207.17)100(C/W)(r_U/r_S)\bullet_{5}$$

in which 134.24 and 207.17 are the molecular weights of amifostine thiol and amifostine thiol dihydrochloride, respectively; C is the concentration, in mg per mL, of amifostine thiol dihydrochloride in the *Standard thiol solution; W* is the weight, in mg, of Amifostine taken to prepare the *Test solution;* and r_U and r_S are the amifostine thiol peak responses recorded at 220 nm, obtained from the *Test solution* and the *Standard thiol solution,* respectively. Calculate the percentage of amifostine disulfide in the portion of Amifostine for Injection taken by the formula:

~~$(266.47/412.31)(10C)(r_U/r_S)$~~

$$\bullet(266.47/412.31)(100C/W)(r_U/r_S)\bullet_{5}$$

in which 266.47 and 412.31 are the molecular weights of amifostine disulfide and amifostine disulfide tetrahydrochloride, respectively; C is the concentration, in mg per mL, of USP Amifostine Disulfide RS in the *Standard disulfide solution;* and r_U and r_S are the peak responses recorded at 247 nm, obtained from the *Test solution* and the *Standard disulfide solution,* respectively: not more than 2.0% of total impurities, including amifostine thiol and amifostine disulfide, is found. Calculate the percentage of each of the other impurities in the portion of Amifostine for Injection taken by the formula:

$$100(r_i/r_A)$$

in which r_i and r_A are the peak responses for each impurity and amifostine, respectively, obtained from the *Test solution:* not more than 0.1% of any individual impurity except amifostine thiol is found.

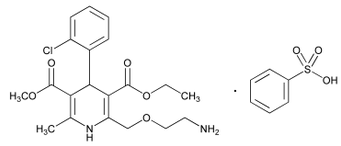
BRIEFING

Amlodipine Besylate. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on the Amlodipine Besilate monograph in the *European Pharmacopoeia* 5.5, is being proposed. The liquid chromatographic procedure in the *Related compounds Test 2* and in the *Assay* is based on analyses performed with the Waters Symmetry or Waters Nova-Pak brand of L1 column. The typical retention time observed for amlodipine is about 7.5 minutes.

(MD-CV: E. Gonikberg) RTS—C44144

Add the following:

■Amlodipine Besylate



$C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ 567.05

3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (±)-, monobenzenesulfonate.

3-Ethyl 5-methyl (±)-2-[(2-aminoethoxy)methyl]-4-(*o*-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulfonate [*111470-99-6*].

» Amlodipine Besylate contains not less than 97.0 percent and not more than 102.0 percent of $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, protected from light. Store at room temperature.

USP Reference standards ⟨11⟩**—***USP Amlodipine Besylate RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩.

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

Optical rotation ⟨781A⟩**:** between -0.10° and +0.10°, measured at 20°.

Test solution: 10 mg per mL, in methanol.

Water, *Method I* ⟨921⟩**:** not more than 0.5%.

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

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

Related compounds—

TEST 1—

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

Test solution—Transfer 140 mg of Amlodipine Besylate to a 2-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

System suitability solution—Transfer about 14 mg of USP Amlodipine Besylate RS to a suitable container, dissolve in 0.2 mL of methanol, and mix.

Standard stock solution—Dissolve an accurately weighed quantity of USP Amlodipine Besylate RS in methanol to obtain a solution containing 7.0 mg per mL.

Standard solution 1—Transfer 3.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Standard solution 2—Transfer 1.0 mL of the *Standard stock solution* to another 100-mL volumetric flask, dilute with methanol to volume, and mix.

Application volume: 10 µL.

Developing solvent system—Use the upper layer of a mixture of methyl isobutyl ketone, water, and glacial acetic acid (50 : 25 : 25).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Dry the plate for 15 minutes at 80°. Examine the plate under UV light at 254 nm and 365 nm. The chromatogram from the *System suitability solution* shows two clearly separated minor spots with R_F values of about 0.18 and 0.22. Compare the intensities of any secondary spots observed in the chromatogram of the *Test solution* with those of the principal spots in the chromatograms of the *Standard solutions*. Any spot obtained from the *Test solution,* except for the principal spot, is not greater in size than the spot

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obtained from *Standard solution 1* (0.3%), and at most two spots are more intense than the spot obtained from *Standard solution 2* (0.1%).

TEST 2—

pH 3.0 Buffer and *Mobile phase*—Prepare as directed in the *Assay.*

System suitability solution—Dissolve about 5 mg of Amlodipine Besylate in 5 mL of hydrogen peroxide, and heat at 70° for 45 minutes.

Standard solution—Dissolve an accurately weighed quantity of USP Amlodipine Besylate RS in *Mobile phase* to obtain a solution having a known concentration of about 0.003 mg per mL.

Test solution—Transfer about 50 mg of Amlodipine Besylate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between amlodipine impurity A and amlodipine is not less than 4.5. [NOTE—For the purpose of identification, the relative retention times are about 0.2 for benzene sulfonate, 0.5 for amlodipine impurity A, and 1.0 for amlodipine. Amlodipine impurity A is 3-ethyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methylpyridine-3,5-dicarboxylate.] Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the standard deviation for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for a period of time that is about 3 times the retention time of amlodipine, and measure the peak responses. Calculate the percentage of each impurity in the portion of Amlodipine Besylate taken by the formula:

$$100(1/F)(C_S/C_T)(r_i/r_S)$$

in which F is the relative response factor, which is equal to 0.5 for amlodipine impurity A and to 1.0 for other impurities; C_S and C_T are the concentrations, in mg per mL, of amlodipine besylate in the *Standard solution* and the *Test solution,* respectively; r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for amlodipine besylate obtained from the *Standard solution:* not more than 0.3% of amlodipine impurity A is found, and not more than 0.3% of total other impurities is found. Disregard any peak less than 0.03%, and disregard any peak due to benzene sulfonate.

Assay—

pH 3.0 Buffer—Dissolve 7.0 mL of triethylamine in 800 mL of water. Adjust with phosphoric acid to a pH of 3.0 ± 0.1, and dilute with water to 1 L.

Mobile phase—Prepare a filtered and degassed mixture of *pH 3.0 Buffer,* methanol, and acetonitrile (50 : 35 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Amlodipine Besylate RS in *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay preparation—Transfer about 50 mg of Amlodipine Besylate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 237-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure

the responses for the major peaks. Calculate the percentage of $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ in the portion of Amlodipine Besylate taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of amlodipine besylate in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Calcitonin Salmon, page 1036 of *PF* 31(4) [July–Aug. 2005]. It is proposed to modify the Definition to allow for a peptide that is produced using recombinant DNA technology.

(BB PP: L. Callahan) RTS—C44540

Add the following:

■Calcitonin Salmon

$C_{145}H_{240}N_{44}O_{48}S_2$ 3432 daltons [*47931-85-1*].

» Calcitonin Salmon is a ~~synthetic polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It lowers the calcium concentration in the plasma of mammals by diminishing the rate of bone resorption.~~ polypeptide that has the same sequence as that of the hormone that regulates calcium metabolism and is secreted by the ultimobranchial gland of salmon. It is produced from either synthetic processes or microbial processes using recombinant DNA (rDNA) technology. The host-cell derived proteins content and the host-cell or vector-derived DNA content of Calcitonin Salmon produced from an rDNA process are determined by validated methods. It contains not less than 90.0 percent and not more than 105.0 percent of calcitonin salmon, calculated on an acetic acid-free and dried basis.

NOTE—One mg of acetic acid-free, anhydrous Calcitonin Salmon is equivalent to 6000 USP Calcitonin Salmon Units.

Packaging and storage—Preserve in tight containers. Store in a refrigerator, protected from light.

Labeling—The labeling states that the material is synthetic.

USP Reference standards ⟨11⟩—*USP Calcitonin Salmon RS. USP Calcitonin Salmon Related Compound A RS* (*N*-acetyl-cys[1]-calcitonin). ~~*USP Endotoxin RS.*~~

Identification—

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

~~**B:** The UV absorption spectrum of a 0.1% solution (based on free peptide) in 0.01 N hydrochloric acid exhibits a minima and a maxima at the same wavelengths as those of a similar solution of USP Calcitonin Salmon RS, concomitantly measured. The absorbance at approximately 275 nm (maxima) is about 0.40 to 0.55, and the ratio of the absorbance at 275 nm (maxima) and 254 nm (minima) is between 1.6 and 2.5.~~

Amino acid profile (see *Amino Acid Analysis* ~~*Method 1,*~~ under *Biotechnology-Derived Articles—Tests* ⟨1047⟩)—[NOTE—The concentration of amino acids in the *Internal*

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standard solution, the *Standard amino acid solution,* and the *Standard solution* and the amount of material used to prepare the *Test solution* can be adjusted depending on the method used for amino acid analysis. The concentrations given are based on analysis using *Method 1.*]

Internal standard solution—Prepare a 1-mM solution of γ-aminobutyric acid.

Standard amino acid solution—Prepare a mixture containing equimolar amounts of ammonia and the L form of lysine, histidine, arginine, aspartic acid, threonine, serine, proline, valine, glutamic acid, glycine, leucine, and tyrosine, together with half the equimolar amount of L-cystine, in 0.1 M hydrochloric acid. The final concentration is about 2.5 mM for each amino acid.

Standard solution—Transfer 5 mL of the *Internal standard solution* and 2 mL of the *Standard amino acid solution* into a 50-mL volumetric flask, dilute with 0.1 M hydrochloric acid to volume, and mix.

Test solution—Place about 1.5 mg of an accurately weighed quantity of Calcitonin Salmon into a heavy-wall ignition tube, add 1.0 mL of 6 N hydrochloric acid, allow to cool, immerse the lower half of the tube in a freezing mixture until the contents are frozen, evacuate to approximately 10 μM, purge with nitrogen (repeat the evacuation and nitrogen purge three times), and seal the tube while it is under a 10-μM vacuum. Heat for 16 hours at 110° to 115° in an air oven. Cool, open the tube, dry in a vacuum desiccator, remove the contents, and allow to cool to room temperature. Dissolve in 0.1 M hydrochloric acid, transfer to a 10-mL volumetric flask, add 1 mL of *Internal standard solution,* dilute with 0.1 M hydrochloric acid to volume, and mix.

Procedure—Standardize the amino acid analyzer, using the *Standard solution.* Inject the *Test solution* into the amino acid analyzer, and determine the relative proportion of amino acids.

Calculation of amino acid profile—Express the content of each amino acid in moles, using an internal standard calibration technique. Calculate the relative proportions of the amino acids by taking as equivalent to 1 the sum of the number of moles of aspartic acid, glutamic acid, proline, glycine, valine, leucine, histidine, arginine, and lysine divided by 20. ~~For threonine and serine, perform the same calculation, and correct the concentrations for degradation by adding 5% and 10%, respectively, to their indicated results.~~ The requirements are met if the values fall within the following limits: aspartic acid, 1.8 to 2.2; glutamic acid, 2.7 to 3.3; proline, 1.7 to 2.3; glycine, 2.7 to 3.3; valine, 0.9 to 1.1; leucine, 4.5 to 5.3; histidine, 0.9 to 1.1; arginine, 0.9 to 1.1; lysine, 1.8 to 2.2; serine, 3.2 to 4.2; threonine, 4.2 to 5.2; tyrosine, 0.7 to 1.1; half cystine, 1.4 to 2.1.

Bioidentity—

RPMI 1640 with L-glutamine—Prepare a mixture of the ingredients, in the quantities shown below, in sufficient water to obtain 1 L of *RPMI 1640 with L-glutamine* solution, and sterilize by filtration.

Calcium Nitrate	100.00 mg
Potassium Chloride	400.00 mg
Magnesium Sulfate, Anhydrous	48.84 mg
Potassium Chloride	400 mg
Sodium Chloride	6000 mg
Sodium Phosphate, Dibasic, Anhydrous	800 mg
Sodium Bicarbonate	2000 mg
Glycine	10 mg
L-Arginine	200 mg
L-Asparagine	50 mg
L-Aspartic Acid	20 mg
L-Cystine Dihydrochloride	65 mg
L-Glutamic Acid	20 mg
L-Glutamine	300 mg
L-Histidine	15 mg
L-Hydroxyproline	20 mg
L-Isoleucine	50 mg
L-Leucine	50 mg
L-Lysine Hydrochloride	40 mg
L-Methionine	15 mg
L-Phenylalanine	15 mg

L-Proline	20 mg
L-Serine	30 mg
L-Threonine	20 mg
L-Tryptophan	5 mg
L-Tyrosine Disodium Salt Dihydrate	29 mg
L-Valine	20 mg
Biotin	0.2 mg
Choline Chloride	3 mg
D-Calcium Pantothenate	0.25 mg
Folic Acid	1 mg
i-Inositol	35 mg
Niacinamide	1 mg
Para-Aminobenzoic Acid	1 mg
Pyridoxine Hydrochloride	1 mg
Riboflavin	0.2 mg
Thiamine Hydrochloride	1 mg
Vitamin B_{12}	0.005 mg

Medium A (growth medium)—Using aseptic technique, prepare the following tissue culture medium.

RPMI 1640 with L-glutamine	500 mL
Fetal bovine serum	50 mL
1 M HEPES	5 mL
Penicillin/streptomycin solution (10,000 IU per mL /10 mg per mL)	5 mL
Human insulin	10 IU
Hydrocortisone	0.5 mg

Medium B (stimulation medium)—Dissolve 5 g of albumin bovine serum (BSA) in 500 mL of 2 mM *RPMI 1640 with L-glutamine.*

2% BSA solution—Dissolve 50 mg of albumin bovine serum in 25 mL of water. [NOTE—Use within 1 day.]

Formic acid/BSA solution—Add 25 mL of 0.1 M formic acid and 5 mL of *2% BSA solution* to a 50-mL volumetric flask, dilute with water to volume, and mix. [NOTE—Use within 2 days.]

Trypsin–EDTA solution (tetrasodium ethylenediamine-tetraacetate)—Prepare a sterile filtered solution containing 0.25% trypsin and 0.53 mM EDTA.

Dulbecco's phosphate buffered saline—Dissolve 8 g of sodium chloride, 1.15 g of dibasic sodium phosphate, 0.2 g of monobasic potassium phosphate, 0.2 g of potassium chloride, 0.1 g of calcium chloride, and 0.1 g of magnesium chloride in 1 L of water.

Standard stock solution—Dissolve an accurately weighed quantity of USP Calcitonin Salmon RS in *Formic acid/BSA solution* to obtain a solution having a known concentration of about 20 µg per mL.

Positive control solution—Quantitatively dilute the *Standard stock solution* with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 1 ng per mL.

Negative control solution: Medium B.

Standard solution A—Quantitatively dilute the *Standard stock solution* with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.1 ng per mL.

Standard solution B—Quantitatively dilute *Standard solution A* with *Medium B* to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.033 ng per mL.

Standard solution C—Quantitatively dilute *Standard solution B* with *Medium B* (1 : 2) to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.011 ng per mL.

Standard solution D—Quantitatively dilute *Standard solution C* with *Medium B* (1 : 2) to obtain a solution of USP Calcitonin Salmon RS having a known concentration of 0.0037 ng per mL.

Test stock solution—Dissolve an accurately weighed quantity of Calcitonin Salmon in *Formic acid/BSA solution* to obtain a solution having a concentration of about 20 µg per mL.

Test solution A—Quantitatively dilute the *Test stock solution* with *Medium B* to obtain a solution of Calcitonin Salmon having a concentration of 0.1 ng per mL.

Test solution B—Quantitatively dilute *Test solution A* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.033 ng per mL.

Test solution C—Quantitatively dilute *Test solution B* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.011 ng per mL.

Test solution D—Quantitatively dilute *Test solution C* with *Medium B* (1 : 2) to obtain a solution of Calcitonin Salmon having a concentration of 0.0037 ng per mL.

Cell culture preparation—Prepare a cell culture of the human mammary tumor cell line T-47D. Cells are propagated using *Medium A* at 37° and 5% carbon dioxide. The medium is changed every 2 days, and cells are passaged every 5 to 9 days, using *Trypsin–EDTA solution* with a 1 : 4 subculture.

Cell suspension—For the test, use a cell culture that is 5 to 9 days old. Remove the cell culture medium from the flask by aspiration, add 10 mL of *Dulbecco's phosphate buffered saline,* and rock the culture flask to rinse the entire monolayer. Remove the liquid by aspiration, add 2 mL of *Trypsin–EDTA solution,* spread over the entire monolayer, allow to stand for 3 to 5 minutes, and add 10 mL of *Medium A.* Homogenize the cell suspension using a pipet, transfer to a 15-mL polypropylene tube, centrifuge at about 220 × *g* for 5 minutes, pour off the supernatant, and resuspend the cell pellet in 10 mL of *Medium A.* Count the cells, and adjust the cell density through dilution, using *Medium A,* to 2.5×10^4 cells per mL.

Procedure—Place 200 µL of the *Cell suspension* into each well of a 96-well culture plate (the *tissue culture plate*), and incubate for 18 to 24 hours at 37° and 5% carbon dioxide. Fill each well of an empty round-bottomed 96-well culture plate (the *prepared plate*) with 150 µL of one of the following solutions: *Positive control solution, Negative control solution, Standard solutions A–D,* and *Test solutions A–D,* so that each solution fills at least five wells on the prepared plate. After incubation, remove the culture medium from the tissue culture plate. Using an 8-channel or 12-channel pipet, rapidly transfer 100 µL of solution from each well of the prepared plate to each well of the tissue culture plate. Incubate for 15 minutes at ambient temperature, remove the solution from each well, stop stimulation by immediately adding an appropriate cell-lysis buffer, and quantitate cAMP produced within the cells, using a validated kit. Perform the test three times, using three different 96-well culture plates. [NOTE—Some kits include a cell-lysis reagent and a sequestering agent for the cell-lysis reagent. The range of the test kit is between 0.05 ng and 10 ng per mL of cAMP. The number of cells used in the assay may vary depending on the validated kit used to quantitate cAMP.] Potency is determined by a 3-dose, 6-point parallel-line assay, using standard statistical methods. The calculation is carried out using both the lower three concentrations and the upper three concentrations. For the assay to be valid, the requirements for regression and parallelism must be met. If the requirements for validity are met to the same extent in both assessments (the lower and the higher assessments), the final result is determined from the concentration range that shows the higher value when the common slope is divided by the mean square error. The potency levels determined from all three performances of the test are homogeneous, and the confidence limits for all three determinations are between 64% and 156% of the calculated potency.

~~**Bacterial endotoxins** ⟨85⟩—It contains not more than 1000 USP Endotoxin Units per mg of calcitonin salmon.~~

Microbial limits ⟨61⟩—The test is performed on a portion of about 0.2 g, accurately weighed. The total aerobic microbial count does not exceed 100 cfu per g. ~~It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.*~~

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pH ⟨791⟩**:** between 4.0 and 6.0 in a 1% solution in carbon dioxide-free water.

Water, *Method Ic* ⟨921⟩**:** not more than 10%.

Heavy metals, *Method II* ⟨231⟩**:** 0.005%.

Limit of trifluoroacetic acid [NOTE—Use deionized, degassed water where water is indicated.]

Solution A: Water.

Solution B: 0.005 N sodium hydroxide.

Solution C: 0.1 N sodium hydroxide.

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

Chloride stock standard solution—Dissolve an accurately weighed quantity of sodium chloride in water to obtain a solution having a concentration of the chloride ion of about 0.1 mg per mL.

Trifluoroacetic acid stock standard solution—Dissolve an accurately weighed quantity of trifluoroacetic acid in water to obtain a solution having a concentration of trifluoroacetic acid of about 0.1 mg per mL.

Resolution solution—Pipet 0.2 mL of *Chloride stock standard solution* and 0.5 mL of *Trifluoroacetic acid stock standard solution* into a 100-mL volumetric flask, dilute with water to volume, and mix to obtain a solution that contains 0.2 µg of chloride and 0.5 µg of trifluoroacetate per mL, respectively.

Standard solutions—Pipet 0.2 mL, 0.5 mL, 1.0 mL, and 2.0 mL of *Trifluoroacetic acid stock standard solution* into ordered 100-mL volumetric flasks. Dilute with water to volume and mix to obtain solutions that contain concentrations of about 0.2 µg, 0.5 µg, 1.0 µg, and 2.0 µg of trifluoroacetate per mL, respectively.

Test solution—Transfer about 10 mg of Calcitonin Salmon, accurately weighed, to a 5-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The ion chromatograph is equipped with a conductivity detector, a 4-mm × 5-cm anion exchange guard column containing packing L31, a 4-mm × 25-cm anion exchange analytical column containing packing L31, a high capacity anion trap column in hydroxide form in the eluant line in front of the injection valve, and a micromembrane anion self-regenerating suppressor. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0–2	90	10	0	isocratic
2–5	90 → 0	10 → 100	0	linear gradient
5–15	0	100 → 65	0 → 35	linear gradient
15–20	0 → 90	65 → 10	35 → 0	linear gradient

Chromatograph the *Resolution solution,* and record the peak responses as directed for the *Procedure:* the resolution, *R,* between the chloride peak and the trifluoroacetic acid peak is not less than 3; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of each of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area of peak responses. Plot the response of the trifluoroacetic acid peak in the *Standard solutions* versus the concentration of trifluoroacetic acid, and draw the straight line best fitting the plotted points. From the graphs so obtained, determine a concentration value, *C,* in µg per mL for trifluoroacetic acid. Calculate the quantity, in ppm, for trifluoroacetic acid in Calcitonin Salmon by the formula:

$$5000(C/W),$$

in which *W* is the weight in mg of Calcitonin Salmon taken to prepare the *Test solution:* not more than 200 ppm of trifluoroacetic acid is found.

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~~**Limit of residual solvents**—~~

~~*Standard stock solution*—Prepare a solution containing about 300 µg of methanol, 40 µg of acetonitrile, 60 µg of methylene chloride, 500 µg of *tert* butyl methyl ether, and 90 µg of dimethylformamide per mL of methyl sulfoxide.~~

~~*Standard solution*—Transfer 5 mL of the *Standard stock solution* to a 25-mL volumetric flask, and dilute with dimethyl sulfoxide to volume. Transfer 1 mL of the *Standard solution* to a 20-mL headspace vial fitted with a septum and a crimp cap, and seal the vial.~~

~~*Test solution 1*—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 20-mL headspace vial fitted with a septum and a crimp cap, add 1 mL of dimethyl sulfoxide, seal the vial, and mix.~~

~~*Test solution 2*—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 20-mL headspace vial fitted with a septum and a crimp cap, add 1 mL of *Standard solution,* seal the vial, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector and a flame ionization detector and contains a 0.32-mm × 60-m fused silica column coated with a 1.0-µm film of stationary phase G38. Nitrogen is used as the carrier gas, flowing at a rate of about 25 mL per minute. The column temperature is maintained at 45° for 2 minutes, then increased at a rate of 10° per minute to 75°, then increased at a rate of 5° per minute to 170° and maintained at 170° for 3 minutes. The split injector temperature is maintained at about 200°, and the detector temperature is maintained at about 170°. The transfer loop and transfer line temperature is 170°, and the pressurize time is 0.5 minute. The *Standard solution* vial and the *Test solutions 1* and *2* vials are maintained at about 90°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.55 for methanol, 0.76 for acetonitrile, 1.0 for methylene chloride, 1.2 for *tert* butyl methyl ether, and 2.3 for dimethylformamide; and the relative standard deviation, determined from peak areas for each peak, for six replicate injections is not more than 10%.~~

~~*Procedure*—Separately inject equal volumes (about 1 mL) of headspace from vials of *Test solution 1* and *Test solution 2* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of methanol, acetonitrile, methylene chloride, *tert* butyl methyl ether, and dimethylformamide in the Calcitonin Salmon taken by the formula:~~

$$100(r_{U1})(C)/(r_{U2})(W_{U1}) \quad (r_{U1})(W_{U2}),$$

~~in which C is the concentration, in mg per mL, of the relevant analyte in the *Standard solution;* W_{U1} and W_{U2} are the weights, in mg, of Calcitonin Salmon taken to prepare *Test solution 1* and *Test solution 2,* respectively; and r_{U1} and r_{U2} are the peak areas of the corresponding analyte obtained from *Test solution 1* and *Test solution 2,* respectively: not more than 3000 µg of methanol, 400 µg of acetonitrile, 600 µg of methylene chloride, 5000 µg of *tert* butyl methyl ether, and 900 µg of dimethylformamide per g of Calcitonin Salmon are found.~~

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

Acetic acid content—

Internal standard stock solution—Mix 1 mL of dioxane with water to obtain 100 mL of solution.

Standard solution—Transfer approximately 100 mg of glacial acetic acid, accurately weighed, and 10 mL of *Internal standard stock solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer about 100 mg of Calcitonin Salmon, accurately weighed, to a 10-mL volumetric flask, add 1 mL of *Internal standard stock solution,* dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 3-m glass column packed with 10% liquid phase G35, 1% phosphoric acid, on support S1A.

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Nitrogen is the carrier gas, flowing at a rate of about 30 mL per minute. The column temperature is maintained at 70° for 4 minutes, then increased at a rate of 8° per minute to 120°, then maintained at 120° for 4 minutes. The injection port and detector temperatures are maintained isothermally at about 200°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention times are about 3 minutes for acetic acid and 1 minute for dioxane; the resolution, *R,* between dioxane and acetic acid is not less than 8; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 4 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of acetic acid in the portion of Calcitonin Salmon taken by the formula:

$$1000(C/W)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of acetic acid in the *Standard solution; W* is the weight, in mg, of Calcitonin Salmon used to prepare the *Test solution;* and R_U and R_S are the peak response ratios of acetic acid to dioxane obtained from the *Test solution* and the *Standard solution,* respectively: not less than 4.0% and not more than 15.0% is found.

Related peptides and other related substances—

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

Solution A, Solution B, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the area percentage of each peak observed in the chromatogram. Disregard any peaks due to the solvent and any peaks whose area is less than 0.1% of the principal peak. No peak other than the principal peak constitutes more than 3.0% of the total area of all peaks. The sum of the areas of all the peaks apart from the principal peak is not greater than 5.0% of the sum of the areas of all the peaks including the principal peak.

Other requirements—Where the label states that Calcitonin Salmon is sterile, it meets the requirements for *Sterility* ⟨71⟩ under *Calcitonin Salmon Injection.*

Assay—

Solution A—Dissolve ~~3.62~~ 3.26 g of tetramethylammonium hydroxide pentahydrate in 900 mL of water, add 100 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5, pass through a filter having a 0.5-µm or finer porosity, and degas.

Solution B—Dissolve 1.45 g of tetramethylammonium hydroxide pentahydrate in 400 mL of water, add 600 mL of acetonitrile, and mix. Adjust with phosphoric acid to a pH of 2.5, pass through a filter having a 0.5-µm or finer porosity, and degas.

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

Standard preparation—Transfer about 10.0 mg of USP Calcitonin Salmon RS, accurately weighed, into a 10-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, and mix.

System suitability solution—Dissolve the contents of a vial of USP Calcitonin Salmon Related Compound A RS in 0.4 mL of *Solution A,* add 0.1 mL of the *Standard preparation,* and mix.

Assay preparation—Transfer about 10.0 mg of Calcitonin Salmon, accurately weighed, into a 10-mL volumetric flask, dissolve in and dilute with *Solution A,* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1.

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The column temperature is maintained at about 65°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–30	72→48	28→52	linear gradient
30–32	48→72	52→28	linear gradient
32–55	72	28	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.15 for calcitonin salmon related compound A and 1.0 for calcitonin salmon; the resolution, *R,* between calcitonin salmon related compound A and calcitonin salmon is not less than 3; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 3%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of calcitonin salmon ($C_{145}H_{240}N_{44}O_{48}S_2$) in the portion of Calcitonin Salmon taken by the formula:

$$P(W_S / W_U)(r_U / r_S)$$

in which P is the percentage of calcitonin salmon in USP Calcitonin Salmon RS; W_S is the weight, in mg, of USP Calcitonin Salmon RS taken to prepare the *Standard preparation;* W_U is the weight, in mg, of Calcitonin Salmon used to prepare the *Assay preparation;* and r_U and r_S are the main peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Calcitonin Salmon Nasal Solution, page 1178 of *PF* 30(4) [July–Aug. 2004]. The monograph is being modified to allow for the use of material derived using recombinant DNA technology.

(BB PP: L. Callahan) RTS—C42086

Add the following:

■Calcitonin Salmon Nasal Solution

» Calcitonin Salmon Nasal Solution is a solution of Calcitonin Salmon in a suitable diluent. It contains suitable preservatives, and is packaged in a form suitable for nasal administration so that the required dosage can be controlled as required. Each mL of Calcitonin Salmon Nasal Solution possesses an activity of not less than 80 percent and not more than 110 percent of that stated on the label.

Packaging and storage—Preserve in containers suitable for spraying the contents into the nasal cavities in a controlled individualized dosage. Store unopened containers in a refrigerator, and opened containers at room temperature.

Labeling—Label it to indicate that it is for intranasal administration only. ~~Label it to state that the origin is synthetic.~~ The labeling also states that it has been prepared either with Calcitonin Salmon of synthetic origin or Calcitonin Salmon of rDNA origin. Label it to state that it is to be stored in a refrigerator and that freezing is to be avoided. Label it to indicate the activity in USP Calcitonin Salmon Units per mL.

USP Reference standards ⟨11⟩—*USP Calcitonin Salmon RS. USP Calcitonin Salmon Related Compound A RS.*

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Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Microbial limits ⟨61⟩**—**The total aerobic microbial count does not exceed 100 cfu per g, and the total combined molds and yeast count does not exceed 50 cfu per g. It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

pH ⟨791⟩**:** between 3.5 and 4.5.

Assay—

Solution A, Solution B, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay* under *Calcitonin Salmon* .

Standard stock preparation and *Standard preparation*—Prepare as directed in the *Assay* under *Calcitonin Salmon Injection.*

System suitability solution—Prepare as directed for *Resolution solution* under *Calcitonin Salmon Injection.*

Diluent—Dissolve 0.75 g of sodium chloride, 0.2 g of sodium acetate, and 0.2 g of glacial acetic acid in 100 mL of water, and mix.

Assay preparation—Transfer 1 mL of Nasal Solution to a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the potency, in USP Calcitonin Salmon Units per mL, in the Nasal Solution taken by the formula:

$$10C(r_U/r_S)$$

in which C is the concentration of the *Standard preparation,* in USP Calcitonin Salmon Units per mL; and r_U and r_S are the main peak areas from the *Assay preparation* and *Standard preparation,* respectively.■1S *(USP30)*

BRIEFING

Chlorhexidine Gluconate Oral Rinse, *USP 29* page 476; **Chlorhexidine Gluconate Solution,** *USP 29* page 477. It is proposed to correct the molecular weight of chlorohexidine acetate given in the *Assay.*

(MD-AA: B. Davani) RTS—C44180

Change to read:

Assay—

Diluent, Solution A, Solution B, Mobile phase, System suitability solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Chlorhexidine Gluconate Solution.*

Assay preparation—Transfer 5.0 mL of Oral Rinse to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Procedure—Proceed as directed in the *Assay* under *Chlorhexidine Gluconate Solution.* Calculate the percentage (w/v) of chlorhexidine gluconate ($C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$) in the portion of Oral Rinse taken by the formula:

~~$(897.77/625.66)(C/500)(r_U/r_S)$~~

■$(897.77/625.55(C/500)(r_U/r_S)$■1S *(USP30)*

in which the terms are as defined therein.

BRIEFING

Chlorhexidine Gluconate Solution, *USP 29* page 477—See briefing under *Chlorhexidine Gluconate Oral Rinse*.

(MD-AA: B. Davani) RTS—C44179

Change to read:

Assay—

Diluent—Prepare a solution of 27.6 g of monobasic sodium phosphate in about 1.5 L of water. Adjust with phosphoric acid to a pH of 3.0, dilute with water to 2000 mL, and mix.

Solution A—Prepare a solution of 27.6 g of monobasic sodium phosphate and 10 mL of triethylamine in about 1.5 L of water. Adjust with phosphoric acid to a pH of 3.0, dilute with water to 2000 mL, and mix. Prepare a mixture of this solution and acetonitrile (70 : 30). [NOTE—Small adjustments in the acetonitrile content may be made to meet acceptable resolution criteria (see *System Suitability* under *Chromatography* ⟨621⟩).] Degas before use and sparge with helium during the analysis.

Solution B—Use acetonitrile.

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

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System suitability solution—Prepare a solution in *Diluent* containing about 50 µg of USP Chlorhexidine Acetate RS per mL and 1 µg of *p*-chloroaniline per mL.

Standard preparation—Prepare a solution of USP Chlorhexidine Acetate RS in water having a known concentration of about 1 mg per mL. Dilute quantitatively an accurately measured volume of this stock solution with *Diluent* to obtain a solution having a known concentration of about 50 µg per mL.

Assay preparation—Transfer 5.0 mL of Solution to a 250-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 250-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-cm column that contains base-deactivated 5-µm packing L1 and is maintained at a constant temperature of about 40°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–9	100	0	isocratic
9–10	100→45	0→55	linear gradient
10–15	45	55	isocratic
15–16	45→100	55→0	linear gradient
16–21	100	0	re-equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between chlorhexidine and *p*-chloroaniline is not less than 3; and the relative standard deviation for replicate injections is not more than 2.0% determined from the chlorhexidine peak, and not more than 5.0% determined from the *p*-chloroaniline peak.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for chlorhexidine. Calculate the percentage (w/v) of chlorhexidine gluconate ($C_{22}H_{30}Cl_2N_{10} \cdot 2C_6H_{12}O_7$) in the portion of Solution taken by the formula:

~~$(897.77/625.66)(0.25C)(r_U/r_S)$~~

■$(897.77/625.55(0.25C)(r_U / r_S)$■1S *(USP30)*

in which 897.77 and ~~625.66~~

■625.55■1S *(USP30)*
are the molecular weights of chlorhexidine gluconate and chlorhexidine acetate, respectively; *C* is the concentration, in µg per mL, of USP Chlorhexidine Acetate RS in the *Standard preparation;* and r_U and r_S are the peak areas for chlorhexidine obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Chlorophyllin Copper Complex Sodium, *USP 29* page 478. On the basis of comments received, the concentrations of two standard solutions in the *Content of total copper* section are being corrected.

(MD-OOD: F. Mao) RTS—C44268

Change to read:

Content of total copper—

Copper stock solution—Transfer 1.000 g of copper to a 1000-mL volumetric flask, dissolve in 20 mL of nitric acid, dilute with 0.2 N nitric acid to volume, and mix. This solution contains 1000 µg of copper per mL. Store in a polyethylene bottle.

Standard solutions—Pipet 5.0 mL of *Copper stock solution* into a 500-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0, 10.0, 15.0, and 20.0 mL, respectively, of this solution to separate 100-mL volumetric flasks, dilute the contents of each flask with water to volume, and mix. These *Standard solutions* contain 0.5, 1.0, ~~2.0, and 3.0~~

■1.5, and 2.0■1S *(USP30)*
µg of copper per mL, respectively.

Test solution—Transfer about 100 mg of previously dried Chlorophyllin Copper Complex Sodium, accurately weighed, to a Kjeldahl flask. Add 2.0 mL of sulfuric acid, 1.0 mL of nitric acid, and 1.0 mL of hydrogen peroxide, and carefully heat under a fume hood until a light green color is obtained. [NOTE—If the solution has any hint of a brown tint, continue to add 0.5-mL portions of nitric acid until a green color is obtained.] Cool, transfer the contents quantitatively to a 1000-mL volumetric flask with several portions of water, dilute the contents of the flask with water to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at the copper emission line of 324.8 nm with an atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a copper hollow-cathode lamp and an air–acetylene flame, using water as the blank. Plot the absorbances of the *Standard solutions* versus the concentration, in µg per mL, of copper, and draw the straight line best fitting the four plotted points. From the graph so obtained, determine the concentration, *C,* in µg per mL, of copper in the *Test solution*. Calculate the percentage of copper in the portion of Chlorophyllin Copper Complex Sodium taken by the formula:

$$500C / W$$

in which *W* is the weight, in mg, on the dried basis, of Chlorophyllin Copper Complex Sodium taken to prepare the *Test solution:* not less than 4.25% is found.

BRIEFING

Cimetidine, *USP 29* page 512. It is proposed to delete the reference to the use of previously dried material in *Identification* test *A* in accordance with changes to the directions for use of the USP Cimetidine Reference Standard. It is also proposed to add a formula to the *Procedure* in the test for *Chromatographic purity* to calculate the percentage of impurities.

(MD-GRE: E. Gonikberg) RTS—C44267

Change to read:

Identification—

A: ~~The IR absorption spectrum of a potassium bromide dispersion of it, previously dried, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Cimetidine RS.~~

■*Infrared Absorption* ⟨197K⟩.■1S *(USP30)*

B: The UV absorption spectrum of a solution (1 in 80,000) in 0.1 N sulfuric acid exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Cimetidine RS, concomitantly measured.

Change to read:

Chromatographic purity—

Mobile phase—Mix 240 mL of methanol, 0.3 mL of phosphoric acid (85%), 940 mg of sodium 1-hexanesulfonate, and sufficient water to make 1 L. Filter before use. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a solution of USP Cimetidine RS in *Mobile phase* having a concentration of 0.80 µg per mL.

Test solution—Transfer 100.0 mg of Cimetidine, accurately weighed, to a 250-mL volumetric flask, dissolve in about 50 mL of *Mobile phase*, and dilute with *Mobile phase* to volume. Mix, sonicate for 15 minutes, and mix again.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution,* and record the peak response as directed for *Procedure:* the capacity factor, k', is not less than 3.0; the number of theoretical plates, n, is not less than 2000; and the relative standard deviation of the response for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. ~~The sum of all the peak responses, excluding the cimetidine response, from the *Test preparation* is not more than 5 times the cimetidine response from the *Standard preparation,* and no single peak response is greater than that of the cimetidine response from the *Standard preparation*.~~

■Calculate the percentage of each impurity in the portion of Cimetidine taken by the formula:

$$100(0.001C_S)/C_U)(r_U/r_S)$$

in which C_S is the concentration, in µg per mL, of cimetidine in the *Standard solution,* the multiplier of 0.001 is for conversion of µg per mL to mg per mL; C_U is the concentration, in mg per mL, of cimetidine in the *Test solution;* r_U is the peak response for each impurity obtained from the *Test solution;* and r_S is the response of the cimetidine peak obtained from the *Standard solution:* not more than 0.2% of any single impurity is found, and not more than 1.0% of total impurities is found.■1S *(USP30)*

BRIEFING

Citalopram Tablets, page 1046 of *PF* 31(4) [July–Aug. 2005]. On the basis of comments received and the acceptance criteria of the approved generic products, it is proposed to modify the acceptance criteria in the *Related compounds* section.

(MD-PP: R. Ravichandran) RTS—C43544

Add the following:

■Citalopram Tablets

» Citalopram Tablets contain an amount of Citalopram Hydrobromide equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of citalopram free base ($C_{20}H_{21}FN_2O$).

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

USP Reference standards ⟨11⟩**—***USP Citalopram Hydrobromide RS. USP Citalopram Related Compound A RS. USP Citalopram Related Compound B RS. USP Citalopram Related Compound C RS. USP Citalopram Related Compound E RS. USP Citalopram Related Compound F RS.*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Extract finely ground Tablet powder containing about 200 mg of citalopram with 30 mL of water, and filter. Add 1 mL of 1 N sodium hydroxide ■to the filtrate,■1S *(USP30)* and extract with 50 mL of cyclohexane by shaking for 10 minutes. Pass the cyclohexane layer through a silicone-treated filter paper into a beaker. Reduce the filtrate down to 3 mL, using gentle heat as necessary. Transfer the hot solution to a small centrifuge tube. Induce crystallization while cooling by scratching the side of the test tube with a

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spatula. Centrifuge the mixture, and decant off the cyclohexane. Dry the residue under vacuum in a desiccator. Mix approximately 2 mg of the residue with approximately 300 mg of potassium bromide, and record the IR spectrum.

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

C: A solution of 2 mg per mL equivalent of citalopram in water meets the requirements of the test for *Bromide* ⟨191⟩.

Dissolution ⟨711⟩—

Medium: pH 1.5 buffer (prepared by transferring 118 mL of 1 N hydrochloric acid and 82 mL of 1 N sodium hydroxide to a 1000-mL volumetric flask, diluting with water to volume, and adjusting with 1 N sodium hydroxide to a pH of 1.5); 800 mL, deaerated.

Apparatus 1: 100 rpm.

Time: 30 minutes.

Procedure—Determine the amount of citalopram hydrobromide dissolved by employing UV absorption at the wavelength of maximum absorbance at about 239 nm on portions of the solution under test passed through a 0.45-µm PVDF filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration (about 12 µg per mL) of USP Citalopram Hydrobromide RS in the same *Medium.* Calculate the amount of citalopram hydrobromide dissolved, in percentage, by the formula:

$$\frac{A_U \times C_S \times 324.39 \times D \times 800 \times 100}{A_S \times 405.30 \times L}$$

in which A_U and A_S are the absorbances obtained from the solution under test and the Standard solution, respectively; C_S is the concentration, in mg per mL, of the Standard solution; D is the dilution factor of the solution under test; 800 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; and L is the tablet label claim, in mg, of citalopram.

Tolerances—Not less than 80% (Q) of the labeled amount of citalopram hydrobromide is dissolved in 30 minutes.

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

PROCEDURE FOR CONTENT UNIFORMITY—

Buffer, Diluent, Internal standard solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Transfer 1 Tablet to a 100-mL volumetric flask, add 10 mL of *Buffer,* and shake by mechanical means until disintegrated. Add 40 mL of methanol, and sonicate for about 5 minutes. Allow to cool to room temperature. Add a sufficient volume of *Internal standard solution,* and dilute, stepwise if necessary, with *Diluent* to volume to obtain a *Test solution* having a concentration of about 0.1 mg per mL of citalopram and 0.025 mg per mL of the internal standard. Pass a portion of this solution through a membrane filter (PVDF) having a 0.45-µm or finer porosity, and use the filtrate.

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

Procedure—Proceed as directed in the *Assay.* Calculate the quantity, in mg, of ($C_{20}H_{21}FN_2O$) in the portion of sample taken by the formula:

$$100(CV)(R_U / R_S)(324.39/405.30)$$

in which C is the concentration, in mg per mL, of USP Citalopram Hydrobromide RS in the *Standard solution; V* is the final volume, in mL, required to obtain the *Test solution; R_U* and R_S are the ratios of the peak responses of citalopram to the Internal standard in the *Test solution* and the *Standard solution,* respectively; and 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively.

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Change to read:

Related compounds—

Phosphate buffer—Dissolve 3.15 g of potassium dihydrogen phosphate and 3.60 g of disodium hydrogen phosphate ($Na_2HPO_4 \cdot 12H_2O$) in 1 L of water.

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer,* methanol, and acetonitrile (55 : 38 : 7). Adjust with phosphoric acid to a pH of 6.5. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard solution—Prepare a solution having a concentration of 0.625 µg per mL of citalopram hydrobromide through stepwise dilution of the *Standard stock solution* with *Mobile phase*.

Sensitivity solution—Prepare a solution having a concentration of 0.05 µg per mL of citalopram hydrobromide through stepwise dilution of the *Standard solution* with *Mobile phase*.

Related compounds stock solutions—Separately dissolve accurately weighed quantities of USP Citalopram Related Compound A RS, USP Citalopram Related Compound B RS, USP Citalopram Related Compound C RS, and USP Citalopram Related Compound E RS in *Mobile phase* to obtain stock solutions having known concentrations of about 0.1 mg per mL of each compound.

Peak identification solution—Prepare a mixture containing about 0.001 mg per mL each of USP Citalopram Related Compound A RS, USP Citalopram Related Compound B RS, USP Citalopram Related Compound C RS, and USP Citalopram Related Compound E RS, using the *Standard stock solution* as the diluent.

Resolution solution—Dilute 0.5 mL of *Citalopram related compound C stock solution* and 25.0 mL of the *Standard stock solution* with *Mobile phase* to 50 mL to obtain a solution containing 0.01 mg per mL of citalopram related compound C and 0.25 mg per mL of citalopram hydrobromide.

Test solution—Transfer 10 Tablets into a 200-mL volumetric flask, add 25 mL of *Phosphate buffer,* and shake by mechanical means until disintegrated. Add about 100 mL of a mixture of methanol and water (50 : 50), mix, and sonicate for about 5 minutes. Allow to cool, dilute with a mixture of methanol and water (50 : 50) to volume, and mix thoroughly. Allow the excipients to settle. Dilute as necessary to obtain a final concentration of 0.5 mg per mL of citalopram. Pass a portion of this solution through a polytetrafluoroethylene (PTFE) membrane filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 45°. The flow rate is about 0.8 mL per minute. Inject the *Standard solution,* and record the peak responses as directed for *Procedure:* the citalopram peak shows no shoulders or excessive tailing; the capacity factor, *k′,* is not less than 3.5; the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation of ~~both the retention time and~~ ■1S (*USP30*) the response for replicate injections is not more than 5%. Inject the *Sensitivity solution* into the chromatograph, and verify that the signal-to-noise ratio is at least 3. Inject the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between citalopram related compound C and citalopram is not less than 3. Inject the *Peak identification solution,* and record the responses as directed for *Procedure:* the four related compound peaks are baseline resolved from each other and the citalopram peak. ■[NOTE—For identification purposes, approximate relative retention times are given in *Table 1*.]■1S (*USP30*)

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

$$100(r_i / r_S)(324.39 / 405.30)(C_S / C_T)(1/F)$$

in which r_i is the individual peak response for each citalopram related compound obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution;* 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; C_S and C_T are the concentrations, in mg per mL, of citalopram hydrobromide in the *Standard solution* and the *Test solution,* respectively; and F is the relative response factor of each impurity relative to citalopram (free base). The limits for the related compounds are listed in *Table 1.*

Change to read:

Assay—

Buffer—Transfer about 0.71 g of anhydrous dibasic sodium phosphate to a 500-mL volumetric flask, and add about 250 mL of water. Shake to dissolve, then dilute with water to volume.

Diluent—Prepare a solution of methanol and *Buffer* (80 : 20).

internal standard solution—Dissolve an accurately weighed amount of USP Citalopram Related Compound F RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.25 mg per mL.

Mobile phase—Prepare a filtered and degassed solution of *Diluent* containing about 770 mg of dodecyltrimethylammonium bromide per L. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1.25 mg of citalopram hydrobromide per mL.

Standard preparation—Pipet 5.0 mL of the *Standard stock preparation* and 5.0 mL of the *internal standard solution* into a 50-mL volumetric flask. Dilute with *Diluent* to volume, and mix.

Table 1

Related Compound	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Citalopram related compound A	0.43	0.77	NMT* ~~0.1~~ ■0.2■1S (*USP30*)
Citalopram related compound B	0.60	0.98	NMT 0.25
Citalopram related compound C	0.83	0.69	NMT 0.25
Citalopram related compound E	1.32	0.91	NMT 0.1
~~Unknown~~ ■Any other individual unidentified impurity■1S (*USP30*)	—	1.0	NMT ~~0.1~~ ■ 0.2■1S (*USP30*) each
Total known and unknown	—	—	NMT ~~0.7~~ ■0.8■1S (*USP30*)

* NMT = not more than.

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Assay preparation—Transfer 10 Tablets to a 200-mL volumetric flask, add 25 mL of *Buffer,* and shake by mechanical means until disintegrated. Add 100 mL of methanol, and sonicate for about 5 minutes. Allow to cool to room temperature, then dilute with *Diluent* to volume. Allow to stand until the residue settles before taking an aliquot for dilution. Transfer an accurately measured volume of the clear supernatant to a 50-mL volumetric flask to obtain a final concentration between 0.090 and 0.10 mg per mL of citalopram, ■based on the label claim.■1S (*USP30*) Add 5.0 mL of *internal standard solution,* dilute with *Diluent* to volume, and mix. Pass a portion through a filter (PTFE) having a 0.45-µm or finer porosity.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 45°. Inject the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.36 for citalopram related compound F and 1.0 for citalopram; the resolution, *R,* between citalopram and citalopram related compound F is not less than 1.5; the column efficiency is not less than 2000 theoretical plates, calculated from the citalopram peak; and the relative standard deviation for replicate injections is not more than 1.5% for the citalopram peak.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the citalopram peaks. Calculate the quantity, in percent of label claim, of citalopram per Tablet taken by the formula:

$$100(C_S / C_U)(324.39/405.30)(R_U / R_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of USP Citalopram Hydrobromide RS in the *Standard preparation* and Citalopram Hydrobromide in the *Assay preparation,* respectively; 324.39 and 405.30 are the molecular weights of citalopram and citalopram hydrobromide, respectively; and R_U and R_S are the ratios of the peak responses of citalopram to the internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP29*)

BRIEFING

Cladribine, page 3563 of the *First Supplement,* and page 1609 of *PF* 31(6) [Nov.–Dec. 2005]. On the basis of comments received, it is proposed to revise the acceptance criterion for *Water.* In the absence of any significant adverse comments, it is proposed to implement this revision via the *Fifth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of October 1, 2006.

(MD-OOD: F. Mao) RTS—C44393

Change to read:

Specific rotation ⟨781S⟩**:** between ~~–17° and –21°~~

▲–17.0° and –21.0°.▲*USP30*

Test solution: 10 mg per mL, in dimethylformamide.

Change to read:

Water, *Method I* ⟨921⟩**:** not more than ~~2.0%~~

•4.0%.•S

Change to read:

Related compounds—

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

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cladribine and cladribine related compound A is not less than 1.5; and the tailing factor is not more than 2.0.

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Cladribine taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of each individual impurity; and r_s is the sum of the responses of all the peaks. Refer to *Table 1* for the impurity limits.

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Table 1

Name	Relative Retention Time	Limit (%)
		~~0.2~~
2,6-Diaminopurine-2′-deoxyriboside	about 0.41	▲0.20▲*USP30*
		~~0.2~~
2′-Deoxyadenosine	about 0.47	▲0.20▲*USP30*
		~~0.2~~
2-Chloroadenine	about 0.60	▲0.20▲*USP30*
		~~0.2~~
2-Methoxy-2′-deoxyadenosine (cladribine related compound A)	about 0.91	▲0.20▲*USP30*
Any ~~other individual~~ ▲individual unspecified▲*USP30* impurity	—	~~0.1~~ ▲0.10▲*USP30*
Total impurities	—	1.0

Change to read:

Limit of residual solvents—

Standard solution—Transfer 15 µL of methanol and 24 µL of alcohol to a 100-mL volumetric flask containing 80 mL of water, dilute with water to volume, and mix. Transfer 3 mL of the solution to a 20-mL headspace vial. The concentrations of methanol and alcohol in the *Standard solution* are 119 µg per mL and 198 µg per mL, respectively.

Test solution—In a 20-mL headspace vial, dissolve 200 mg of Cladribine, accurately weighed, in 5 mL of water.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector and a flame-ionization detector and contains a 0.53-mm × 30-m column coated with a 5-µm film of liquid phase G16. The carrier gas is nitrogen, flowing at a rate of 4 mL per minute. The split ratio is 5 : 1. Vials containing the *Standard solution* and the *Test solution* are equilibrated for 10 minutes at 80° in the headspace sampler. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 80° for 6 minutes, then increased at a rate of 25° per minute to 240°, and held at 240° for 20 minutes. The injection port temperature and the detector temperature are maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between alcohol and methanol is not less than 1.5; and the relative standard deviation for replicate injections is not more than 10.0% for each of the two solvents.

Procedure—Separately inject equal volumes (about 1 mL) of the gaseous headspace of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the concentration, in ppm, of each residual solvent in the portion of Cladribine taken by the formula:

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

in which C is the concentration, in µg per mL, of the respective individual solvent in the *Standard solution; W* is the quantity, in mg, of Cladribine taken to prepare the *Test solution;* and r_U and r_S are the peak responses of the relevant solvent obtained from the *Test solution* and the *Standard solution,* respectively: not more than 5000 ppm of alcohol is found, and not more than ~~450 ppm~~ ▲3000 ppm▲*USP30* of methanol is found.

BRIEFING

Clarithromycin Extended-Release Tablets, *USP 29* page 530. In *Dissolution Test 2* it is proposed to add a compliance statement, as well as a column temperature in the *Chromatographic system,* and a revised formula in the *Procedure* to calculate the amount, in percentage, of clarithromycin dissolved with volume correction. It is also proposed to add a *Dissolution Test 3* and a *Dissolution Test 4* because FDA recently approved new generic versions of this product. The chromatographic procedure in *Dissolution Test 3* was developed using the YMC-Pack ODS-AQ or YMC-Pack ODS-AM brand of L1 packing. The chromatographic procedure in *Dissolution Test 4* was developed using LiChrospher 60 RP-Select brand of L7 packing. In the absence of any significant adverse comment, it is proposed to implement all of these proposed changes via the *Fifth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of October 1, 2006.

(BPC: M. Marques) RTS—C44075

Change to read:

▲**Dissolution** ⟨711⟩▲*USP29*—

TEST 1—

Medium: 0.3 M phosphate buffer, pH 6.0 (prepared by dissolving 816.5 g of monobasic potassium phosphate and 48 g of sodium hydroxide in about 4 L of water, mixing, and diluting with water to 20 L. Adjust with either concentrated phosphoric acid or 1 N sodium hydroxide to a pH of 6.0 ± 0.05); 900 mL.

Apparatus 2: 75 rpm.

Times: 30, 45, 60, and 120 minutes.

Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved using the following method.

Standard solutions—Prepare five solutions of USP Clarithromycin RS dissolved in acetonitrile and diluted with *Medium,* with known concentrations over the range of about 60 to 600 µg per mL.

Test solution—Use portions of the solution under test passed through a 35-µm polyethylene filter.

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 50 µL) of the five *Standard solutions* and the *Test solution* into the chromatograph, and measure the responses for the major peaks. Perform a linear

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regression analysis to generate a standard curve using the peak area of each *Standard solution* versus its concentration. Determine the amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each specified time interval, using the peak area of each *Test solution* and the linear regression statistics for the *Standard solutions.*

Tolerances—The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to the following *Acceptance Table.*

▲TEST 2—

•If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.•5

Medium: 0.05 M phosphate buffer, pH 6.8 containing 0.5% of sodium lauryl sulfate; 900 mL, degassed by sonication and vacuum.

Apparatus 1: 100 rpm.

Times: 2, 12, and 24 hours.

Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved using the following method.

0.067 M Phosphate buffer, pH 2.5—Dissolve 9.2 g of monobasic sodium phosphate monohydrate in about 800 mL of water. Adjust with phosphoric acid to a pH of 2.5. Dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *0.067 M Phosphate buffer, pH 2.5* (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 56 mg of USP Clarithromycin RS, accurately weighed, to a 100-mL volumetric flask. Add 10 mL of methanol, and sonicate to dissolve. Dilute with *Medium* to volume.

Test solution—Centrifuge the solution under test at 2500 rpm for 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute.

•The column temperature is maintained at 50°.•5

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the column efficiency is not less than 2000; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of clarithromycin dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

in which C_U is the concentration, in mg per mL, of clarithromycin in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; and C_S is the concentration, in mg per mL, of clarithromycin in the *Standard solution.*

Calculate the amount, in percentage, of clarithromycin dissolved with volume correction:

$$\frac{\{C_n \times [900 - V_U(n-1)]\} + [\sum_{i=1}^{n-1} C_i \times V_U] \times 100}{LC}$$

•$$\frac{[\{C_n \times [900 - V_U(n-1)]\} + [\sum_{i=1}^{n-1} C_i \times V_U]] \times 100}{LC}$$•5

in which C_n is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; 900 is the volume, in mL, of *Medium;* V_U is the volume, in mL, of sample withdrawn at each time point; n is the number of time points [NOTE—The summation of the amount of clarithromycin removed at previous sampling time points is applicable only where $n > 1$]; 100 is the conversion factor to percentage; and LC is the Tablet label claim.

Acceptance Table

Level	Time (minutes)	Amount dissolved (individual limits)	Amount dissolved (average limits)
L_1	30	not more than 65%	—
	45	between 55% and 85%	—
	60	not less than 75%	—
	120	not less than 85%	—
L_2	30	not more than 75%	not more than 65%
	45	between 45% and 95%	between 55% and 85%
	60	not less than 65%	not less than 75%
	120	not less than 75%	not less than 85%
L_3	30	not more than 2 tablets release more than 75%, and no individual tablet releases more than 85%	not more than 65%
	45	not more than 2 tablets are outside the range of 45% to 95%, and no individual tablet is outside the range of 35% to 105%	between 55% and 85%
	60	not more than 2 tablets release less than 65%, and no individual tablet releases less than 55%	not less than 75%
	120	not more than 2 tablets release less than 75%, and no individual tablet releases less than 65%	not less than 85%

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Tolerances—The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	not more than 20%
12	between 45% and 70%
24	not less than 80%

▲*USP29*

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

Medium: Acetate buffer, pH 4.75 (prepared by dissolving 3.59 g of sodium acetate trihydrate and 11.0 mL of 2 N acetic acid in 1000 mL of water, and adjusting with 2 N acetic acid to a pH of 4.75); 1000 mL.

Apparatus 1: 10 mesh; 50 rpm.

Times: 1, 2, 4, 8, and 12 hours.

Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved by employing the following method.

0.067 M Phosphate buffer—Dissolve 9.12 g of monobasic potassium phosphate in 1000 mL of water, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *0.067 M Phosphate buffer* (65 : 35), mix, and adjust with phosphoric acid to a pH of 4.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve quantitatively an accurately weighed quantity of USP Clarithromycin RS in methanol, shaking and sonicating if necessary to ensure dissolution, to obtain a stock solution having a known concentration of about 625 µg of clarithromycin per mL, taking into account the stated potency, in µg per mg, of USP Clarithromycin RS.

Standard solution—Transfer 10.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 125 µg of clarithromycin per mL.

System suitability solution—Dissolve quantitatively an accurately weighed quantity of USP Clarithromycin Related Compound A RS in methanol to obtain a solution containing about 625 µg of clarithromycin related compound A per mL. Transfer 10 mL of this solution and 10 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Withdraw 10-mL of the solution under test. Transfer 3 mL to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass portions of this dilution through a 0.45-µm filter. Replace 10 mL of *Medium* in each vessel.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for clarithromycin and 1.0 for clarithromycin related compound A; and the resolution, *R,* between clarithromycin and clarithromycin related compound A is not less than 2.0. Chromatograph the *Standard solution,* and record the responses as directed for *Procedure:* the column efficiency, determined from the clarithromycin peak, is not less than 750 theoretical plates; the tailing factor is not less than 0.9 and not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved by the formula:

$$C_U = \frac{r_U \times C_S \times 100}{r_S \times 6C}$$

in which C_U is the concentration, in mg per mL, of clarithromycin in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the

Standard solution, respectively; and C_S is the concentration, in mg per mL, of clarithromycin in the *Standard solution;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Calculate the amount, in percentage, of clarithromycin dissolved with volume correction at time points $n \geq 2$:

$$\frac{[\{C_n \times [1000]\} + [\sum_{i=1}^{n-1} C_i \times V_u]] \times 100}{LC}$$

in which C_n is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; 900 is the volume, in mL, of *Medium;* V_U is the volume, in mL, of sample withdrawn at each time point; n is the time point (at 2 hours, $n = 2$), summation of the concentration of the *Test solution* from the first to the $(n-1)$th time point (only applicable for $n \geq 2$); 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Tolerances—The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	not more than 15%
2	between 10% and 30%
4	between 35% and 55%
8	not less than 80%
12	not less than 90%

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

Medium: phosphate buffer, pH 6.0 (prepared by dissolving 68.0 g of potassium dihydrogen phosphate and 1.8 g of sodium hydroxide in 10 L of water, and adjusting with dilute sodium hydroxide or phosphoric acid to a pH of 6.0 ± 0.1); 900 mL.

Apparatus 2: 50 rpm.

Times: 2, 4, 8, and 12 hours.

Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved by employing the following method.

Buffer solution—Dissolve 6.8 g of potassium dihydrogen phosphate in 1 L of water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 4.5 ± 0.1.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (64 : 36). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 20 mg of USP Clarithromycin RS, accurately weighed, to a 50-mL volumetric flask. Add about 30 mL of *Medium,* and sonicate until dissolved, about 10 minutes. Add 2 mL of methanol, and dilute with *Medium* to volume.

Test solution—Use the solution under test passed through a 0.45-µm suitable filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 203-nm detector and a 4.0-mm × 12.5-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. The column is maintained at 30°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of clarithromycin dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

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in which C_U is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and *Standard solution,* respectively; and C_S is the concentration, in mg per mL, of clarithromycin in the *Standard solution*.

Calculate the amount, in percentage, of clarithromycin dissolved at each time point by the formula:

$$\frac{C_n \times [900 - (n-1) \times V_S] + (C_1 + C_2 + ... + C_{n-1}) \times V_S \times 100}{LC}$$

in which C_n is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; 900 is the volume, in mL, of *Medium; V_S* is the volume, in mL, of the sample taken at each time point; and *LC* is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	not more than 25%
4	between 20% and 40%
8	between 45% and 75%
12	not less than 80%

•S

BRIEFING

Crystallized Trypsin, *USP 29* page 2223. On the basis of comments received, it is proposed to change the definition to allow for the use of porcine-derived material.

(BB PP: L. Callahan) RTS—C44565

Change to read:

» Crystallized Trypsin is a proteolytic enzyme crystallized from an extract of the ~~pancreas gland of the ox, *Bos taurus* Linné (Fam. Bovidae)~~

▪pancreas of healthy bovine or porcine animals, or both.▪1S (*USP30*)

When assayed as directed herein, it contains not less than 2500 USP Trypsin Units in each mg, calculated on the dried basis, and not less than 90.0 percent and not more than 110.0 percent of the labeled potency.

NOTE—Determine the suitability of the substrates and check the adjustment of the spectrophotometer by performing the *Assay* using USP Crystallized Trypsin Reference Standard.

BRIEFING

Dantrolene Sodium for Injection. Because there is no existing *USP* monograph for this dosage form, a new monograph based on validated methods of analysis is being proposed. The proposed liquid chromatographic procedures in the test for *Related compounds* and the *Assay* are based on analyses performed with the Waters Symmetry C18 brand of L1 column. Typical retention time for dantrolene related compound B is about 2.3 minutes and for dantrolene is about 3.3 minutes.

(MD-PP: R. Ravichandran; MSA: R. Tirumalai) RTS—C42656

Add the following:

▪Dantrolene Sodium for Injection

» Dantrolene Sodium for Injection is a sterile, nonpyrogenic, lyophilized formulation containing Dantrolene Sodium, and one or more suitable buffering or sequestering agents. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{14}H_9N_4NaO_5 \cdot 3½H_2O$.

Packaging and storage—Preserve in tight containers. Store at controlled room temperature, and protect from light.

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USP Reference standards ⟨11⟩—*USP Dantrolene RS. USP Dantrolene Related Compound B RS. USP Endotoxin RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—To 0.5 g of Dantrolene Sodium for Injection, add 10 mL of 0.1 N hydrochloric acid and 10 mL of ethyl acetate, and mix. Allow the phases to separate, and transfer the upper ethyl acetate phase to a suitable glass container. Evaporate the solvent, dry the residue at 105° for 10 minutes, and use the residue.

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

Bacterial endotoxins ⟨85⟩—It contains not more than 0.5 USP Endotoxin Unit per mg of dantrolene sodium.

Sterility ⟨71⟩**:** meets the requirements.

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

pH ⟨791⟩—Dissolve the contents of 1 vial in 60 mL of USP Water for Injection. The pH is between 8.8 and 11.0.

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

Related compounds—

Mobile phase and *Diluent*—Proceed as directed in the *Assay.*

Standard solution—Transfer 10 mg of USP Dantrolene Related Compound B RS, accurately weighed, into a 50-mL volumetric flask, and dissolve in 2.5 mL of dimethylformamide. Add 2.5 mL of glacial acetic acid, and dilute with acetone to volume to obtain a solution having a known concentration of about 0.2 mg per mL. Dilute with *Diluent* to obtain a solution having a known concentration of about 0.002 mg per mL of dantrolene related compound B.

Test solution—Use the *Assay preparation.*

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections for dantrolene related compound B is not more than 5.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of dantrolene related compound B in the portion of Dantrolene Sodium for Injection taken by the formula:

$$100(r_U / r_S)(C_S / C_T)$$

in which r_U is the peak response for dantrolene related compound B obtained from the *Test solution;* r_S is the corresponding peak response in the *Standard solution;* C_S is the concentration, in mg per mL, of dantrolene related compound B in the *Standard solution;* and C_T is the concentration, in mg per mL, of dantrolene sodium hydrate in the *Test solution.* Not more than 8% of dantrolene related compound B is found.

Other requirements: meets the requirements under *Injections* ⟨1⟩.

Assay—

Buffer—Dissolve 3.3 mg of ammonium acetate in 1 L of water, and adjust with acetic acid to a pH of 4.5 ± 0.1.

Solution A—Prepare a filtered and degassed mixture of *Buffer,* acetonitrile, and glacial acetic acid (120 : 80 : 7).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and water (70 : 30).

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

Diluent—Prepare a mixture of acetonitrile and water (60 : 40).

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Standard preparation—Transfer 40 mg of USP Dantrolene RS, accurately weighed, into a 50-mL volumetric flask, and dissolve in 2.5 mL of dimethylformamide. Add 2.5 mL of glacial acetic acid, and dilute with acetone to volume to obtain a solution having a known concentration of about 0.8 mg per mL. Dilute this solution with *Diluent* to obtain a solution having a known concentration of about 0.08 mg per mL of dantrolene.

Assay preparation—Using 70 mL of water for each vial, transfer the entire contents of the required number of vials to a suitable flask necessary to obtain a solution having a known concentration of about 0.1 mg of dantrolene sodium hydrate per mL. Sonicate for 2 to 5 minutes to dissolve the sample. Dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 365-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as in *Table 1*:

Table 1

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–8	100	0	isocratic
8–8.1	100→0	0→100	linear gradient
8.1–13	0	100	isocratic
13–13.1	0→100	100→0	linear gradient
13.1–20	100	0	re-equilibration

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections for dantrolene is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for dantrolene. Calculate the percentage of $C_{14}H_9N_4NaO_5 \cdot 3½H_2O$ in the portion of Dantrolene Sodium for Injection taken by the formula:

$$(399.29/314.25)(r_U/r_S)(C_S/C_U)$$

in which 399.29 and 314.25 are the molecular weights of dantrolene sodium hydrate and dantrolene, respectively; r_U and r_S are the peak responses for dantrolene obtained from the *Assay preparation* and *Standard preparation,* respectively; C_S is the concentration, in mg per mL, of dantrolene in the *Standard preparation;* and C_U is the concentration, in mg per mL, of dantrolene sodium hydrate in the *Assay preparation.* ■1S (*USP30*)

BRIEFING

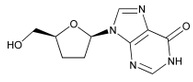
Didanosine, page 1355 of *PF* 31(5) [Sept.–Oct. 2005]. On the basis of comments received, the following revisions are proposed:

1. Clarify the test for *Optical rotation* as a test for *Specific rotation*.
2. Change the acceptance limit for a specified impurity in the test for *Related compounds* based on the regulatory submission.
3. Reformat the formula calculations in the test for *Related compounds* and in the *Assay* based on the recommendations highlighted in a recent stimuli article published on page 626 of *PF* 31(2) [Mar.–Apr. 2005].
4. A note has been added in the test for *Related compounds* and in the *Assay* to report that the relative retention times of components are for information purposes only and not as part of the system suitability requirements. In addition, minor editorial changes have been made in the *Assay.*

(MD-AA: B. Davani) RTS—C43731; C44093

Add the followng:

■Didanosine



$C_{10}H_{12}N_4O_3$ 236.23

Inosine,2′,3′-dideoxy-.

2′,3′-Dideoxyinosine [*69655-05-6*].

» Didanosine contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}N_4O_3$, calculated on the anhydrous basis.

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

USP Reference standards ⟨11⟩**—***USP Didanosine RS. USP Didanosine Related Compound A RS. USP Didanosine Related Compound B RS. USP Didanosine System Suitability Mixture RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Water, *Method I* ⟨921⟩**:** not more than 2.0%.

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

Heavy metals, *Method II* ⟨231⟩**:** not more than 20 ppm.

~~**Optical rotation** ⟨781⟩~~ **Specific rotation** ⟨781S⟩**:** between –28° and –24°, anhydrous.

Test solution: 10 mg per mL, in water.

Related compounds—

0.01 M Ammonium acetate buffer solution—Prepare as directed in the *Assay.*

Diluent—Adjust the pH of *0.01 M Ammonium acetate buffer solution* with sodium hydroxide to 9, and mix. Prepare a degassed mixture of *0.01 M Ammonium acetate buffer solution* and acetonitrile (19 : 1).

Solution A—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate buffer solution* and acetonitrile (19 : 1).

Solution B—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate buffer solution* and acetonitrile (3 : 1).

Standard stock solution A—Dissolve an accurately weighed quantity of USP Didanosine Related Compound A RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.05 mg per mL.

Standard stock solution B—Dissolve an accurately weighed quantity of USP Didanosine RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.025 mg per mL.

Standard stock solution C—Dissolve an accurately weighed quantity of USP Didanosine Related Compound B RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.025 mg per mL.

Standard solution—Transfer 5.0 mL of *Standard stock solution A,* 3.0 mL of *Standard stock solution B,* and 3.0 mL of *Standard stock solution C* into a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

System suitability solution—Dissolve an accurately weighed quantity of USP Didanosine System Suitability Mixture RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.5 mg per mL.

Test solution—Transfer about 50 mg of Didanosine, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

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Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–15	100	0	isocratic
15–20	100→0	0→100	linear gradient
20–30	0	100	isocratic
30–35	0→100	100→0	linear gradient
35–45	100	0	re-equilibration

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* ~~didanosine elutes between 6 and 7.5 minutes; the relative retention times are about 1.0 for didanosine, 0.28 for didanosine related compound A, and 2.11 for didanosine related compound B; and~~ the relative standard deviation for replicate injections determined on the didanosine related compound A peak is not more than 2.0%. [NOTE—For information purposes only, didanosine elutes between 6 and 7.5 minutes; the relative retention times are about 1.0 for didanosine, 0.28 for didanosine related compound A, and 2.11 for didanosine related compound B. 5′-Deoxydideoxyadenosine, a potential impurity not added to the solution, elutes at a relative retention time of 3.1 minutes.] Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are 1.0 for didanosine, 0.39 for inosine, 0.45 for 2′-deoxyinosine, 0.51 for 3′-deoxyinosine, 0.59 for 2′,3′-anhydroinosine, and 0.81 for dideoxydidehydroinosine;~~ the resolution, *R,* between didanosine and dideoxydidehydroinosine is not less than 3.0; and the column efficiency determined on the dideoxydidehydroinosine peak is not less than 6000 theoretical plates. [NOTE—For information purposes only, the relative retention times are about 1.0 for didanosine, 0.39 for inosine, 0.45 for 2′-deoxyinosine, 0.51 for 3′-deoxyinosine, 0.59 for 2′,3′-anhydroinosine, and 0.81 for dideoxydidehydroinosine.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for 30 minutes, and measure all of the peak responses. Calculate the percentage of didanosine related compound A, 5′-deoxydideoxyadenosine, and each other impurity in the portion of Didanosine taken by the formula:

~~$10{,}000(C/W)(r_u/r_s)$~~

$$100(C_S/C_U)(r_U/r_S)$$

in which ~~*C* is the concentration, in mg per mL, of USP Didanosine RS or USP Didanosine Related Compound A RS in the *Standard solution; W* is the weight, in mg, of the sample; r_u is the peak response of the *Test solution; and*~~ C_S is the concentration, in mg per mL, of USP Didanosine RS or USP Didanosine Related Compound A RS in the *Standard solution;* C_U is the concentration, in mg per mL, of the *Test solution;* r_U is the peak response of the *Test solution;* and r_S is the peak response of USP Didanosine RS or USP Didanosine Related Compound A RS in the *Standard solution.* Use the peak response of Didanosine in the *Standard solution* to calculate other individual impurities: not more than 0.5% of didanosine related compound A is found; not more than 0.2% of each specified impurity at the relative retention times of about 0.39, ~~0.45,~~ 0.51, 0.59, 0.81, 2.1, and 3.1 is found; not more than 0.3% of a specified impurity at the relative rentention time of 0.45 is found; not more than 0.1% of each other impurity is found; and not more than 1.0% of total impurities is found.

Assay—

0.01M Ammonium acetate buffer solution—Dissolve 1.54 g of ammonium acetate in a 2000-mL volumetric flask, dilute with water to volume, and mix.

In-Process Revision

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate buffer solution* and acetonitrile (21 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Didanosine RS in water to obtain a solution containing 0.1 mg per mL.

Assay preparation—Transfer an accurately weighed quantity of 50 mg of Didanosine to a 500-mL volumetric flask. Dissolve in and dilute with water to volume. Mix the sample for 1 hour to dissolve completely before use.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the relative retention time of didanosine is between 7 and 11 minutes,~~ the column efficiency is not less than 6000 theoretical plates; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%. [NOTE—For information purposes only, the retention time of didanosine is between 7 and 11 minutes.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate ~~the quantity, in mg, of $C_{10}H_{12}N_4O_3$ in the portion of Didanosine taken by the formula:~~

~~$$500C(r_U/r_S)$$~~

the percentage of $C_{10}H_{12}N_4O_3$ in the portion of Didanosine taken by the formula:

$$500(C/W)(100)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Didanosine RS in the *Standard preparation; W* is the weight, in mg, of Didanosine taken for the *Assay preparation;* 100 is the conversion factor to percentage; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Didanosine Tablets, page 1359 of *PF* 31(5) [Sept.–Oct. 2005]. On the basis of comments received, the following revisions are proposed:

1. In the *Labeling* section, change "Label chewable Tablets" to "Label the Tablets" because the title of the monograph does not contain the word "chewable".
2. Delete the TLC test for *Identification* because there is already an HPLC test for this purpose and TLC is not considered as a complementary test in this case.
3. A note has been added in the test for *Related compounds* and in the *Assay* to report that the relative retention times are for information purposes only and not as part of the system suitability requirements.
4. Correct the formula used in the test for *Related compounds.* Additionally, clarification of the storage condition for the *Standard solution* and some editorial changes have been made.

(MD-AA: B. Davani) RTS—C43733

Add the following:

■Didanosine Tablets

» Didanosine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of didanosine ($C_{10}H_{12}N_4O_3$).

Packaging and storage—Preserve in tight containers, and store between 15° and 30°.

Labeling—Label ~~chewable~~ the Tablets to indicate that they are to be chewed before swallowing or dispersed in liquid before administration.

In-Process Revision

USP Reference standards ⟨11⟩—*USP Didanosine RS. USP Didanosine Related Compound A RS.*

Identification—

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

~~*Adsorbent*—Merck silica gel 60 with fluorescent indicator, or equivalent.~~

~~*Test solution*—Place 1 Tablet in sufficient methanol to make a 1 mg per mL solution. Stir to dissolve, and pass through a 0.45 µm filter.~~

~~*Standard solution*—Transfer 10 mg of USP Didanosine RS into a 10 mL volumetric flask. Dissolve in and dilute with methanol to volume.~~

~~*Developing solvent solution:*—A mixture of 1-butanol, methanol, ethyl acetate, and ammonium hydroxide (11 : 3 : 3 : 3).~~

~~*Procedure*—Spot 10 µL each of the *Test solution* and the *Standard solution* onto the chromatographic plate, approximately 2 cm from the bottom and 2 cm apart. Allow the plate to air dry. Place in a chromatographic chamber, and develop, allowing the developing solution to travel at least 10 cm from the spotting line. Allow the plate to air dry. View under shortwave light (254 nm). Didanosine appears as a blue spot.~~

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

Dissolution ⟨711⟩—[To come.]

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

Loss on drying ⟨731⟩—Dry 4 Tablets at 130° for 16 hours: they lose not more than 6% of their weight.

Related compounds—

0.01 M Ammonium acetate buffer solution—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate buffer solution* and methanol (99 : 1).

Standard stock solution—Transfer 25 mg of USP Didanosine Related Compound A RS to a 200-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Use this solution within 48 hours of preparation.]

Standard solution—Transfer 3 mL of the *Standard stock solution* to a 250-mL volumetric flask. Dilute with water to volume, and mix. [NOTE—Use this solution within 48 hours of preparation of the *Standard stock solution*.]

Test solution—Proceed as directed for the *Assay preparation.*

Diluted test solution—Dilute the *Test solution,* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength detector set at 275 nm, a 4-mm × 12.5-cm column that contains 5-µm packing L7, and a matching guard column. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution* as directed for *Procedure:* ~~the retention time of didanosine related compound A is between 1.5 and 2.5 minutes;~~ the column efficiency is not less than 1000 theoretical plates; and the relative standard deviation for replicate injections is not more than 5.0%. [NOTE—For information purposes only, didanosine related compound A, with the retention time between 1.5 and 2.5 minutes, is hypoxanthine.]

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Diluted test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks, carrying out the chromatography for approximately 30 minutes. Calculate

the percentage of didanosine related compound A in the portion of Tablets taken by the formula:

~~$100(CVDL/N)(r_U/r_S)$~~

$$100(CVD/NL)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Didanosine Related Compound A RS in the *Standard solution;* V is the volume, in mL, of the *Test solution;* D is the dilution factor of the *Diluted test solution;* N is the number of Tablets used to prepare the *Test solution;* L is the label claim of didanosine, in mg per Tablet; and r_U and r_S are the peak responses obtained from the *Diluted test solution* and the *Standard solution,* respectively. Not more than 0.7% of didanosine related compound A is found. Calculate the percentage of any other ~~impurities~~ impurity by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak response of any other individual impurity obtained upon chromatographing the *Diluted test solution;* and r_s is the sum of the responses of all the peaks in the chromatogram of the *Diluted test solution,* including those of didanosine and hypoxanthine: not more than 0.2% of any other individual impurity is found; and not more than 1.2% of total impurities, excluding hypoxanthine, is found.

Assay—

0.01 M Ammonium acetate buffer solution—Dissolve 1.54 g of ammonium acetate in a 2000-mL volumetric flask, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate buffer solution* and methanol (95 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Didanosine RS in water to obtain a solution containing 0.1 mg per mL. [NOTE—Use this solution within 24 hours of preparation.]

Assay preparation—Transfer not fewer than 5 crushed Tablets to a 500-mL volumetric flask. Dissolve in 250 mL of water, dilute with water to volume, and shake for about 10 minutes.

Diluted assay preparation—Dilute the *Assay preparation,* quantitatively, and stepwise if necessary, with water to obtain a solution containing about 0.1 mg of didanosine per mL. [NOTE—Use this solution within 72 hours of preparation; because of the buffering agents in the Tablets, the *Assay preparation* is stable longer than the *Standard preparation.*]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength detector set at 275 nm, a 4-mm × 12.5-cm column that contains 5-µm packing L7, and a matching guard column. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the retention time of didanosine is greater than 3.0 minutes;~~ the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%. [NOTE—For information purposes only, the retention time of didanosine is greater than 3.0 minutes.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Diluted assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of didanosine ($C_{10}H_{12}N_4O_3$) taken by the formula:

$$[CVD(r_U/r_S)]/N$$

in which C is the concentration, in mg per mL, of USP Didanosine RS in the *Standard preparation;* V is the volume, in mL, of the *Assay preparation;* D is the dilution factor of the *Diluted assay preparation;* r_U and r_S are the peak responses of the *Diluted assay preparation* and the *Standard preparation,* respectively; and N is the number of Tablets used to prepare the *Assay preparation.* ■1S (*USP30*)

In-Process Revision

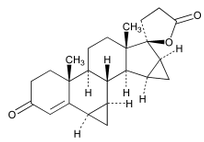
BRIEFING

Drospirenone, page 754 of *PF* 31(3) [May–June 2005]. It is proposed to revise this monograph to correct the chemical structure and chemical formula and to provide additional information in the test for *Specific rotation*. It is also proposed to revise the test for *Chromatographic purity* to correct the injection volume and the formula and to delete the relative response factors because they are not used in the formula. In addition, a minor editorial correction has been made in the *Assay*.

(MD-PS: D. Bempong) RTS—C43347; C43739; C43756

Add the following:

■Drospirenone



~~$C_{24}H_{30}O_3 \cdot 5H_2O$~~

$C_{24}H_{30}O_3$ 366.49

(6*R*,7*R*,8*R*,9*S*,10*R*,13*S*,14*S*,15*S*,16*S*,17*S*)-1,3′,4′,6,6a,7,8,9,10,11,12,13,14,15,15a,16-Hexadecahydro-10,13-dimethylspiro-[17*H*-dicyclopropa[6,7 : 15,16]-cyclopenta[*a*]phenanthrene-17,2′(5′*H*)-furan]-3,5′(2*H*)-dione.

17-Hydroxy-6β,7β: 15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone [*67392-87-4*].

» Drospirenone contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{30}O_3$, calculated on the anhydrous, solvent-free basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

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

Identification—

A: *Infrared Absorption* ⟨197M⟩.

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

Melting range, *Class 1* ⟨741⟩: between 198° and 203°. [NOTE—Dry over silica gel for not less than 24 hours prior to testing.]

Specific rotation ⟨781S⟩**:** between –186° and –196° on the anhydrous and solvent-free basis (10 mg per mL in methanol).

Water, *Method I* ⟨921⟩**:** not more than 0.2%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

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

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

Solvent—Use dimethylformamide.

Limit of 1,2-dimethoxyethane and diisopropyl ether—

Standard solution—Prepare a solution of 1,2-dimethoxyethane and diisopropyl ether in dimethylformamide to obtain a solution having known concentrations of about 0.1 mg per mL and 0.05 mg per mL, respectively.

Test solution—Dissolve an accurately weighed portion of Drospirenone in dimethylformamide to obtain a solution having a known concentration of about 50 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a headspace injector, a flame-ionization detector, and a 0.25-mm × 30-m capillary column coated with a 1.4-µm film of liquid phase G43. The column temperature is programmed according to the following steps: it is held at 40° for 10 minutes, then increased at a rate of 5° per minute to 70°; it is then increased at a rate of 30° per minute to 220°. The injection port temperature is maintained at 160°, and the detector

In-Process Revision

temperature is maintained at 250°. The carrier gas is helium, flowing at a rate of about 32 ± 8 cm per second. [NOTE—For pressure-controlled systems, a column pressure of approximately 130 kPa will be necessary.] Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.6 for diisopropyl ether and 1.0 for 1,2-dimethoxyethane; and the relative standard deviation for the *Standard solution* is not more than 4.0%.

Procedure—Transfer 2.0 mL each of the *Test solution* and the *Standard solution* to separate headspace vials, and seal. The vials are maintained at 80° for 60 minutes prior to headspace injection. Record the chromatograms, and measure the peak areas for the 1,2-dimethoxyethane and diisopropyl ether peaks. Separately calculate the percentage of 1,2-dimethoxyethane and diisopropyl ether in the portion of Drospirenone taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of 1,2-dimethoxyethane or diisopropyl ether in the *Standard solution;* C_U is the concentration, in mg per mL, of Drospirenone in the *Test solution;* and r_U and r_S are the 1,2-dimethoxyethane or diisopropyl ether peak areas in the chromatograms obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.2% of 1,2-dimethoxyethane and 0.1% of diisopropyl ether are found.

Chromatographic purity—

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

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

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

Procedure—Separately inject equal volumes (about ~~10 L~~ 10 µL) of the *Standard solution,* the *Test solution,* and the ~~*Diluting solution*~~ *Diluent* into the chromatograph, and record the chromatograms. Calculate the percentage of each impurity in the portion of Drospirenone taken by the formula:

~~$100F(r_i/r_s)$~~

$$100(r_i/r_s)$$

in which ~~*F* is the relative response factor equal to 1.3 for 15β,16β methylene 3-oxo-4,6-pregnadiene-21,17-carbolactone with a relative retention time of 0.78, 0.5 for 15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone with a relative retention time of 0.73, and 1.0 for all other impurities;~~ r_i is the peak area for each impurity; and r_s is the sum of the responses of all the peaks. Disregard peaks that are less than 0.05% of the drospirenone peak. Not more than 0.1% of any individual impurity is found; and not more than 0.4% of total impurities is found.

Assay—

Solution A—Use water.

Solution B—Use acetonitrile.

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

Diluent—Prepare a degassed mixture of water and acetonitrile (1 : 1).

Standard preparation—Dissolve accurately weighed quantities of USP Drospirenone RS in *Diluent* to obtain a solution having known concentrations of about 2 mg per mL.

Assay preparation—Transfer about 20 mg of Drospirenone, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 245-nm detector and a 4.0-mm × 25-cm column containing 5-µm packing L1 that is maintained at a constant temperature of about 30°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–28.5	64	36	isocratic
28.5–45	64→10	36→90	linear gradient
45–45.5	10→0	90→100	linear gradient
45.5–52	0	100	isocratic
52–53	0→64	100→36	linear gradient
53–80	64	36	re-equilibration

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 7000 theoretical plates; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.0%. No peaks with a signal-to-noise ratio greater than 10 should be present in the chromatogram of the ~~*Diluting solution*~~ *Diluent* between 5 and 45 minutes.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the response for the drospirenone peak. Calculate the quantity, in mg, of $C_{24}H_{30}O_3$ in the portion of Drospirenone taken by the formula:

$$10C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Drospirenone RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

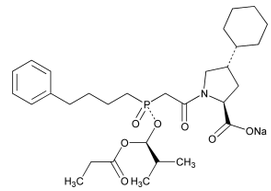
BRIEFING

Fosinopril Sodium, page 110 of *PF* 32(1) [Jan.–Feb. 2006]. On the basis of comments received, it is proposed to add two additional impurities to the table in the test for *Related compounds*. In accordance with the originator's NDA submission, the limits for those impurities are 0.3% for *Impurity 1* and 0.2% for *Impurity 2*.

(MD-CV: S. Ramakrishna) RTS—C44484

Add the following:

■Fosinopril Sodium



$C_{30}H_{45}NNaO_7P$ 585.64

L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, [1[*S*(R*)*],2α,4β]-.

(4*S*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt [*88889-14-9*].

» Fosinopril Sodium contains not less than 97.5 percent and not more than 102.0 percent of $C_{30}H_{45}NNaO_7P$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

In-Process Revision

USP Reference standards ⟨11⟩—*USP Fosinopril Sodium RS. USP Fosinopril Related Compound A RS. USP Fosinopril Related Compound B RS. USP Fosinopril Related Compound C RS. USP Fosinopril Related Compound D RS. USP Fosinopril Related Compound E RS. USP Fosinopril Related Compound F RS.*

Identification, *Infrared Absorption* ⟨197M⟩.

Water, ~~*Method II*~~ *Method I* ⟨921⟩**:** not more than 0.2%.

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

Related compounds—

TEST 1—

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

Test solution—Use the *Assay preparation*.

Procedure—Proceed as directed in the *Assay,* and measure the areas for each component in the chromatogram obtained, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentage of each individual related compound by the formula:

$$100(r_i / r_s)$$

in which r_i is the response of any individual peak, other than the fosinopril sodium peak; and r_s is the sum of the responses of all the peaks. [NOTE—If present, two more diastereomers may not be resolved from fosinopril related compound B by this method. These peaks, appearing at a relative retention time of 0.7, should be integrated together to determine conformance with the limit in *Table 1*.]

Table 1

Relative Retention Time	Fosinopril Related Compound	Test	Limit (%)
2.0	A[1]	1	0.3
0.7	B[2]	1	1.0
1.2	C[3]	2	0.3
1.3	D[4]	2	0.3
0.8	E[5]	3	0.3
0.9	F[6]	3	0.3
0.12	Impurity 1[7]	1	0.3
0.24	Impurity 2[8]	1	0.2

[1] (4*S*)-4-Cyclohexyl-1-[(4-phenylbutyl)phosphinyl]acetyl-L-proline
[2] (4*R*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-D-proline propionate (ester)
[3] Mixture of (4*S*)-4-Cyclohexyl-1-[*(S)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt and (4*S*)-4-Cyclohexyl-1-[[*(R)*-[*(R)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
[4] (4*R*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
[5] (4*S*)-4-~~Cyclohexyl~~ Phenyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt
[6] (4*S*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-ethoxy](4-phenylbutyl)-phosphinyl]acetyl-L-proline propionate (ester)
[7] (2*S*,4*S*)-4-Cyclohexyl-1-pivaloylpyrrolidine-2-carboxylic acid
[8] 2-(*(RS)*-(*(SR)*-2-Methyl-1-(propionyloxy)propoxy)(4-phenylbutyl)-phosphinyl)acetic acid

TEST 2—

Mobile phase—Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (4000 : 15 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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

Resolution solution—Transfer about 1 mg each of USP Fosinopril Sodium RS, USP Fosinopril Related Compound C RS, and USP Fosinopril Related Compound D RS to a 100-mL volumetric flask. Dissolve in and dilute with the *Standard solution* to volume, and mix.

Test solution—Use the *Assay preparation.*

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains packing L12. The column temperature is maintained at 45°. The flow rate is about 0.9 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fosinopril sodium and fosinopril related compound C is not less than 1.5.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to two times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compound C and fosinopril related compound D only by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of fosinopril related compound C or fosinopril related compound D; and r_s is the sum of the responses of all the peaks.

TEST 3—

0.2% Phosphoric acid solution—Prepare a 1 in 500 solution of phosphoric acid.

Mobile phase—Prepare a degassed mixture of acetonitrile and *0.2% Phosphoric acid solution* (560 : 440). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Transfer about 1 mg each of USP Fosinopril Sodium RS, USP Fosinopril Related Compound E RS, and USP Fosinopril Related Compound F RS to a 100-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer about 10 mg of Fosinopril Sodium, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 25-cm column that contains packing L11. The column temperature is maintained at 45°. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fosinopril related compound F and fosinopril sodium is not less than 1.5, and the resolution between fosinopril related compound E and fosinopril related compound F is not less than 1.5.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compound E and fosinopril related compound F only, ~~by~~ using the formula below:

$$100(r_i / r_s)$$

in which r_i is the peak response of fosinopril related compound E or fosinopril related compound F; and r_s is the sum of the responses of all the peaks. In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.1% of any other individual impurity is found (calculated as directd for the *Procedure* in TEST 1); and not more than 1.5% of total impurities is found.

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

Assay—

Mobile phase—Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (2000 : 10 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 10 mg of USP Fosinopril Sodium RS, and about 1 mg each of USP Fosinopril Related Compound A RS and USP Fosinopril Related Compound B RS to a 100-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Fosinopril Sodium RS in *Mobile phase* to obtain a solution having a known concentration of about 0.10 mg per mL.

Assay preparation—Transfer about 25 mg of Fosinopril Sodium, accurately weighed, to a 250-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 3.9-mm × 15-cm column that contains packing L3. The column temperature is maintained at 33°. The flow rate is about 1.2 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fosinopril related compound B and fosinopril sodium is not less than 2.0; and the relative standard deviation of the fosinopril sodium peak response for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in mg, of $C_{30}H_{45}NNaO_7P$ in the portion of Fosinopril Sodium taken by the formula:

$$250C_S(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Fosinopril Sodium RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard prepapration,* respectively. ■1S (*USP30*)

In-Process Revision

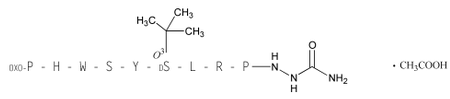
BRIEFING

Goserelin Acetate, page 1637 of *PF* 31(6) [Nov.–Dec. 2005]. On the basis of comments received, it is proposed to add definite requirements on chemical shift differences in the test for *Amino acid content.*

(BB PP: L. Callahan) RTS—C44471

Add the following:

▲Goserelin Acetate



$C_{59}H_{84}N_{18}O_{14} \cdot xC_2H_4O_2$

Luteinizing hormone-releasing factor (pig), 6-[*O*-(1,1-dimethylethyl)-D-serine]-10-deglycinamide-, 2-(aminocarbonyl)hydrazide, acetate (salt) [*145781-92-6*].

1-(5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-*O-tert*-butyl-D-seryl-L-leucyl-L-arginyl-L-prolyl)semicarbazide (Goserelin) 1269.41 [*65807-02-5*].

» Goserelin Acetate is a synthetic nonapeptide analog of the hypothalmic decapeptide, gonadorelin. It is obtained by chemical synthesis and is available as an acetate salt. It contains not less than 94.5 percent and not more than 103.0 percent of goserelin ($C_{59}H_{84}N_{18}O_{14}$), calculated on the anhydrous and acetic acid-free basis.

Packaging and storage—Preserve in a tight, light-resistant container, and store in a refrigerator.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Goserelin Acetate RS. USP Goserelin Related Compound A RS. USP Goserelin Validation Mixture RS.*

~~**Identification—**~~

~~**A:** *Nuclear Magnetic Resonance* ⟨761⟩—~~

~~*Standard solution*—Prepare a 10% w/v solution of USP Goserelin Acetate RS in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.~~

~~*Test solution*—Prepare a 10% w/v solution of Goserelin Acetate in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.~~

~~*Procedure*—Obtain a ^{13}C, proton decoupled NMR spectrum of both the *Standard solution* and the *Test solution*. The spectra from both solutions should be qualitatively similar, and all the resonances from the spectrum of the *Standard solution* should be present in the spectrum of the *Test solution* and have the same chemical shift values; any other resonances in the spectrum of the *Test solution* should be identified.~~

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

Specific rotation ⟨781S⟩**:** between –52° and –56°.

Test solution: 2 mg per mL, in water, calculated on the anhydrous and acetic acid-free basis.

Bacterial endotoxins ⟨85⟩—It contains not more than 16 USP Endotoxin Units of goserelin per mg, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

Water, *Method I* ⟨921⟩**:** not more than 10.0%.

Limit of acetic acid—

Mobile phase—Transfer 49.04 g of sulfuric acid to a 1000-mL volumetric flask, dilute with water to volume, and mix. Accurately transfer 20 mL of this solution to a 2000-mL volumetric flask, dilute with water to volume, mix, filter, and degas.

Test solution—Dissolve about 20 mg of Goserelin Acetate, accurately weighed, in 2 to 3 mL of *Mobile phase*. Connect a 1-mL cartridge containing L44 packing to a 1-mL cartridge containing L2 packing, which is then attached to a suitable vacuum apparatus. With the vacuum applied, wash the cartridge combination with 2 mL of methanol followed by 15 mL of *Mobile phase,* and discard the washings. Quantitatively apply the solution containing Goserelin Acetate to the cartridge combination, and wash through the cartridge system with several small volumes of *Mobile phase*. Collect the solution and washings in a 10-mL volumetric flask, and dilute with *Mobile phase* to volume.

Standard solution—Transfer 2.0 mL of glacial acetic acid to a 500-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a standard stock solution. Transfer 5.0 mL of the standard stock solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—[NOTE—Condition the column for about 24 hours until a stable baseline is obtained.] The liquid chromatograph is equipped with a 206-nm detector and a 7.8-mm × 30-cm column that contains packing L17. The column temperature is maintained at 65°, and the flow rate is about 0.8 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time is about 11 minutes for acetic acid; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 3.1%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of acetic acid in the portion of Goserelin Acetate taken by the formula:

$$(1.049/5)(r_U / r_S)(1/W)$$

in which 1.049 is the weight, in g per mL, of glacial acetic acid; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; and W is the sample weight of Goserelin Acetate, in g, taken to prepare the *Test solution* and corrected (for purposes of the calculation) to eliminate the water content, which is determined immediately prior to the test. The content of acetic acid is between 4.5% and 15.0%.

In-Process Revision

Related compounds—

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

Standard solution and *Diluted standard solution*—Use the *Standard preparation* and the *Diluted standard preparation,* respectively, prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Diluted test solution—Transfer 1 mL of the *Test solution* into a 100-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Separately inject equal volumes (about 10 µL) of the *Test solution, Diluted test solution, Resolution solution,* and *System suitability solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of goserelin-related impurities in the portion of Goserelin Acetate taken by the formula:

$$r_i / r_S$$

in which r_i is the peak area response for any individual impurity in the *Test solution;* and r_S is the peak area response of the main goserelin peak in the *Diluted test solution:* not more than 1.0% of decarbamoylgoserelin is found, not more than 0.5% of any other impurity is found, and not more than 2.5% of total impurities is found.

Change to read:

Amino acid content, *Nuclear Magnetic Resonance* ⟨761⟩—[NOTE—Concentrations of goserelin in both the *Standard solution* and the *Test solution* must be the same (within 5% of each other) but can be adjusted based on the quality of the ^{13}C spectrum obtained. The spectra must be acquired under the same conditions for both the *Standard solution* and the *Test solution*. The spectra obtained are of sufficient quality to allow quantification of the integrals of the resonances specified below to be obtained. Integrals and spectra of both the *Standard solution* and the *Test solution* can be repeated and averaged.]

Standard solution—Dissolve USP Goserelin Acetate RS in deuterium oxide to obtain a solution having a known concentration of about 10% w/v, and adjust with deuterated acetic acid-d4 to a pH of 4.

Test solution—Prepare a 10% w/v solution of Goserelin Acetate in deuterium oxide, and adjust with deuterated acetic acid-d4 to a pH of 4.

Procedure—Obtain a ^{13}C, proton-decoupled NMR spectrum of both the *Standard solution* and the *Test solution*. The spectra from both solutions are qualitatively similar, and all the resonances from the spectrum of the *Standard solution* are present in the spectrum of the *Test solution* and have the same chemical shift values ■(±0.1 ppm for goserelin, ±0.5 ppm for acetate);■1S *(USP30)* identify any other resonances in the spectrum of the *Test solution.* The relative amino acid ratio between the *Standard solution* and the *Test solution* can be calculated as follows. Integrate the resonances at the approximate ppm corresponding to each amino acid in the following table.

Amino Acids	Resonances (ppm)
Azo-glycine	162.2
Histidine	118.4
Tyrosine	116.7
tert-Butyl serine	62.5
Serine	62.2
Tryptophan	55.7
Arginine	41.8
Pyroglutamic acid	26.3
Proline	26.0
Leucine	23.5

In-Process Revision

Calculate the ratio of each of the amino acids from the integrals of the *Standard solution* and the *Test solution* by the formula:

$$r_U / r_S$$

in which r_U and r_S are the integrals of the resonances of a designated amino acid obtained from the *Test solution* and the *Standard solution,* respectively. The resulting ratios fall within the following limits: histidine, tyrosine, *tert*-butyl serine, serine, tryptophan, arginine, pyroglutamic acid, proline, and leucine 0.9 to 1.1; azo-glycine 0.8 to 1.2.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (1600 : 400 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve the contents of a vial of USP Goserelin Validation Mixture RS with 1 mL of water.

Standard preparation—Dissolve an accurately weighed quantity of USP Goserelin Acetate RS in water to obtain a solution having a known concentration of about 1 mg per mL.

Diluted standard preparation—Transfer 1 mL of the *Standard preparation* to a 10–mL volumetric flask, dilute with water to volume, and mix.

Resolution solution—Dissolve the contents of a vial of USP Goserelin Related Compound A RS in water to obtain a concentration of 0.1 mg per mL, and mix with an equal volume of *Diluted standard preparation.*

Assay preparation—Transfer about 25 mg of Goserelin Acetate, accurately weighed, to a 25-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L1. The column temperature is maintained between 50° and 55°, and the flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the retention time for goserelin is between 40 and 50 minutes, the relative retention times are about 0.67 for 4-D-ser-goserelin, 0.89 for decarbamoylgoserelin, 0.92 for 5-D-tyr-goserelin, 0.94 for 2-D-his-goserelin, and 1.0 for goserelin; and the resolution, *R,* between 4-D-ser-goserelin and goserelin is not less than 7.0. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* two peaks, corresponding to decarbamoylgoserelin and 2-D-his-goserelin and eluting prior to the principal peak, are visible; three peaks eluting after the principal peak are visible; the column efficiency for the principal peak is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of goserelin ($C_{59}H_{84}N_{18}O_{14}$) in the portion of Goserelin Acetate taken (where sample weight has been corrected for water and acetic acid content, both determined immediately prior to the assay) by the formula:

$$25C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Goserelin Acetate RS in the *Standard preparation;* and r_U and r_S are the goserelin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

In-Process Revision

BRIEFING

Ibuprofen, *USP 29* page 1100; **Ibuprofen Oral Suspension,** *USP 29* page 1101; **Ibuprofen Tablets,** *USP 29* page 1102 and page 1374 of *PF* 31(5) [Sept.–Oct. 2005]. It is proposed to introduce a new USP Reference Standard, USP Ibuprofen Related Compound C RS, to replace the reagent, 4-isobutylacetophenone, used in the limit test and in the *Assay.*

(MD-CCA: C. Anthony) RTS—C44306

Change to read:

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

■*USP Ibuprofen Related Compound C RS.*■1S (*USP30*)

Change to read:

Limit of ~~4-isobutylacetophenone~~

■**ibuprofen related compound C**—■1S (*USP30*)
Using the chromatograms of the *Assay preparation* and the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution,*■1S (*USP30*)
obtained as directed in the *Assay,* calculate the percentage of ~~4-isobutylacetophenone~~

■ibuprofen related compound C■1S (*USP30*)
($C_{12}H_{16}O$) in the portion of Ibuprofen taken by the formula:

$$10{,}000(C/W)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of ~~4-isobutylacetophenone~~

■USP Ibuprofen Related Compound C RS■1S (*USP30*)
in the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution;*■1S (*USP30*)
W is the weight, in mg, of Ibuprofen taken to prepare the *Assay preparation;* and R_U and R_S are the peak response ratios of ~~4-isobutylacetophenone~~

■ibuprofen related compound C■1S (*USP30*)
to valerophenone obtained from the *Assay preparation* and the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution,*■1S (*USP30*)
respectively: not more than 0.1% is found.

Change to read:

Assay—

Mobile phase—Dissolve 4.0 g of chloroacetic acid in 400 mL of water, and adjust with ammonium hydroxide to a pH of 3.0. Add 600 mL of acetonitrile, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of valerophenone in *Mobile phase* having a concentration of about 0.35 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Ibuprofen RS in *Internal standard solution* to obtain a solution having a known concentration of about 12 mg per mL.

~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution*—■1S (*USP30*)
Quantitatively dissolve an accurately weighed quantity of ~~4-isobutylacetophenone~~

■USP Ibuprofen Related Compound C RS■1S (*USP30*)
in acetonitrile to obtain a solution having a known concentration of about 0.6 mg per mL. Add 2.0 mL of this stock solution to 100.0 mL of *Internal standard solution,* and mix to obtain a solution having a known concentration of about 0.012 mg of ~~4-isobutylacetophenone~~

■ibuprofen related compound C■1S (*USP30*)
per mL.

Assay preparation—Transfer about 1200 mg of Ibuprofen, accurately weighed, to a 100-mL volumetric flask, dilute with *Internal standard solution* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.4 for the internal standard and 1.0 for ibuprofen; the resolution, R, between ibuprofen and the internal standard is not less than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution,*■1S (*USP30*)
and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for valerophenone and 1.2 for ~~4-isobutylacetophenone~~

■ibuprofen related compound C;■1S (*USP30*)
the resolution, R, between valerophenone and ~~4-isobutylacetophenone~~

■ibuprofen related compound C■1S (*USP30*)
is not less than 2.5; the tailing factors for the individual peaks are not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation,* the *Assay preparation,* and the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution*■1S (*USP30*)
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{13}H_{18}O_2$ in the portion of Ibuprofen taken by the formula:

$$100C(R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Ibuprofen RS in the *Standard preparation;* and R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ibuprofen Oral Suspension, *USP 29* page 1101—See briefing under *Ibuprofen*.

(MD-CCA: C. Anthony) RTS—C44326

In-Process Revision

Change to read:

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

■*USP Ibuprofen Related Compound C RS.* ■1S *(USP30)*

Change to read:

Limit of ~~4 isobutylacetophenone~~

■ibuprofen related compound C—■1S *(USP30)*

Mobile phase and *Diluent*—Proceed as directed in the *Assay.*

Standard solution—Quantitatively dissolve an accurately weighed quantity of ~~4 isobutylacetophenone~~

■USP Ibuprofen Related Compound C RS■1S *(USP30)* in acetonitrile to obtain a stock solution having a known concentration of about 0.5 mg per mL. Transfer 3.0 mL of this stock solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Transfer 2.0 mL of this solution to a second 50-mL volumetric flask, add 18 mL of *Diluent,* dilute with acetonitrile to volume, mix, and pass through a filter having a porosity of 0.22-µm. This *Standard solution* contains about 0.0012 mg of ~~4 isobutylacetophenone~~

■ibuprofen related compound C■1S *(USP30)* per mL.

Test solution—Transfer 20.0 mL of the portion of the stock solution retained from the *Assay preparation* in the *Assay* into a 50-mL volumetric flask, dilute with acetonitrile to volume, mix, and pass through a filter having a porosity of 0.22-µm.

System suitability solution—Transfer 1.5 mL of the stock solution of ~~4 isobutylacetophenone~~ ■USP Ibuprofen Related Compound C RS■1S *(USP30)* prepared as directed for *Standard solution* and 9 mL of the stock solution of USP Ibuprofen RS prepared as directed for *Standard preparation* in the *Assay* to a 25-mL volumetric flask, dilute with acetonitrile to volume, mix, and pass through a filter having a porosity of 0.22-µm. This solution contains about 0.03 mg of ~~4-isobutylacetophenone~~ ■ibuprofen related compound C■1S *(USP30)* and about 0.4 mg of ibuprofen per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 2 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.3 for ~~4 isobutylacetophenone~~ ■ibuprofen related compound C■1S *(USP30)* and 1.0 for ibuprofen; the resolution, *R,* between ibuprofen and ~~4-isobutylacetophenone~~ ■ibuprofen related compound C■1S *(USP30)* is not less than 1.5; and the tailing factor is not more than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 35 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of ~~4-isobutylacetophenone~~ ■ibuprofen related compound C■1S *(USP30)* in the Oral Suspension, based on the labeled content of ibuprofen, taken by the formula:

$$(12{,}500C/DL)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of ~~4 isobutylacetophenone~~ ■USP Ibuprofen Related Compound C RS■1S *(USP30)* in the *Standard solution; D* is the quantity, in mL, of Oral Suspension taken to prepare the stock solution for the *Assay preparation; L* is the labeled quantity, in mg, of ibuprofen in each mL of Oral Suspension; and r_U and r_S are the ~~4-isobutylacetophenone~~ ■ibuprofen related compound C■1S *(USP30)* peak areas obtained from the *Test solution* and the *Standard solution,* respectively. Not more than 0.25% is found.

Change to read:

Assay—

Mobile phase—Dilute 0.7 mL of phosphoric acid with water to obtain 1000 mL of 0.01 M phosphoric acid. Prepare a mixture of this solution and acetonitrile (63 : 37). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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

Internal standard solution—Prepare a solution of benzophenone in acetonitrile containing about 3.2 mg per mL.

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Ibuprofen RS in *Diluent* to obtain a stock solution having a known concentration of about 1.2 mg per mL. Transfer 20.0 mL of this stock solution and 5.0 mL of *Internal standard solution* to a 50-mL volumetric flask, dilute with acetonitrile to volume, mix, and filter. This solution contains about 0.48 mg of ibuprofen per mL.

Density—Using a tared 50-mL volumetric flask, weigh 50 mL of Oral Suspension that has been previously well shaken to ensure homogeneity, allow to stand until the entrapped air has risen, and finally invert carefully just prior to transferring it to the volumetric flask. From the observed weight of 50 mL of the Oral Suspension, calculate the density, in g per mL, of the Oral Suspension.

Assay preparation—Transfer an accurately weighed portion of Oral Suspension, equivalent to about 60 mg of ibuprofen, to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix (stock solution). Transfer 20.0 mL of this stock solution and 5.0 mL of *Internal standard solution* to a second 50-mL volumetric flask, dilute with acetonitrile to volume, mix, and filter. [NOTE—Retain a portion of the stock solution for use in the test for ~~*Limit of 4-isobutylacetophenone*~~

■*Limit of ibuprofen related compound C.*]■1S *(USP30)*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for benzophenone and 1.0 for ibuprofen; the resolution, *R,* between benzophenone and ibuprofen is not less than 1.5; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{13}H_{18}O_2$ in each mL of the Oral Suspension taken by the formula:

$$125C(D/W_U)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Ibuprofen RS in the *Standard preparation; D* is the density, in g per mL, of Oral Suspension; W_U is the weight, in g, of the portion of Oral Suspension taken to prepare the *Assay preparation;* and R_U and R_S are the ratios of the ibuprofen peak areas to the benzophenone peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ibuprofen Tablets, *USP 29* page 1102, and page 1374 of *PF* 31(5) [Sept.—Oct. 2005]. See briefing under *Ibuprofen*.

(MD-CCA: C. Anthony) RTS—C44330

Change to read:

USP Reference standards ⟨11⟩—*USP Ibuprofen RS,*

■*USP Ibuprofen Related Compound C RS.*■1S (*USP30*)

Change to read:

Limit of ~~4-isobutylacetophenone~~

■**ibuprofen related compound C**—■1S (*USP30*)
Using the chromatograms of the *Assay preparation* and the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution*■1S (*USP30*)
obtained as directed in the *Assay,* calculate the percentage of ~~4-isobutylacetophenone~~

■ibuprofen related compound C■1S (*USP30*)
($C_{12}H_{16}O$) in the Tablets taken by the formula:

$$10{,}000C(A/WI)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of ~~4-isobutylacetophenone~~

■USP Ibuprofen Related Compound C RS■1S (*USP30*)
in the ~~4-Isobutylacetophenone standard solution~~

■*Ibuprofen related compound C standard solution;*■1S (*USP30*)
A is the average weight, in mg, of a Tablet; W is the weight of Tablet powder taken to prepare the *Assay preparation; I* is the quantity, in mg, of ibuprofen per Tablet as obtained in the *Assay;* and R_U and R_S are the ratios of the ~~4-isobutylacetophenone~~

■ibuprofen related compound C■1S (*USP30*)
peak response to the valerophenone peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively: not more than 0.1% per Tablet is found.

Change to read:

Assay—

Mobile phase, Internal standard solution, and *Standard preparation*—Prepare as directed in the *Assay* under *Ibuprofen*.

~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution*—■1S (*USP30*)
Quantitatively dissolve an accurately weighed quantity of ~~4-isobutylacetophenone~~

■USP Ibuprofen Related Compound C RS■1S (*USP30*)
in acetonitrile to obtain a solution having a known concentration of about 0.6 mg per mL. Add 2.0 mL of this stock solution to ~~100 mL of *Internal standard solution,*~~ ■a 100-mL volumetric flask, dilute with *Internal standard solution* to volume,■2S (*USP29*)
and mix to obtain a solution having a known concentration of about 0.012 mg ~~of 4-isobutylacetophenone~~

■■2S (*USP29*)
per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1200 mg of ibuprofen, to a suitable container, add 100.0 mL of *Internal standard solution,* and shake for 10 minutes. [NOTE—Where the Tablets are coated, place an accurately counted number of Tablets, equivalent to not less than 1200 mg of ibuprofen, in a container, add an accurately measured volume of *Internal standard solution*, sufficient to obtain an *Assay preparation* containing about 12 mg of ibuprofen per mL, and about 15 glass beads, and shake until the Tablets are completely disintegrated.] Centrifuge a portion of the suspension so obtained and use the clear supernatant as the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for ibuprofen and 1.0 for valerophenone; the resolution, *R,* between ibuprofen and valerophenone is not less than 2.5; the tailing factors for the individual peaks are not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution,*■1S (*USP30*)
and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for valerophenone and 1.2 for ~~4-isobutylacetophenone~~

■ibuprofen related compound C;■1S (*USP30*)
the resolution, *R,* between valerophenone and ~~4-isobutylacetophenone~~

■ibuprofen related compound C■1S (*USP30*)
is not less than 2.5; the tailing factors for the individual peaks are not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation,* the *Assay preparation,* and the ~~*4-Isobutylacetophenone standard solution*~~

■*Ibuprofen related compound C standard solution*■1S (*USP30*)
into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ibuprofen ($C_{13}H_{18}O_2$) in each Tablet taken by the formula:

$$100C(A/W)(R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Ibuprofen RS in the *Standard preparation; A* is the average weight, in mg, of a Tablet; W is the weight, in mg, of Tablet powder taken to prepare the *Assay preparation;* and R_U and R_S are the ratios of the ibuprofen peak response to the valerophenone peak response obtained from the *Assay preparation* and the *Standard preparation,* respectively; or where intact Tablets were taken, calculate the quantity, in mg, of $C_{13}H_{18}O_2$ in each Tablet taken by the formula:

$$(CV/N)(R_U/R_S)$$

in which V is the volume, in mL, of *Internal standard solution* used to prepare the *Assay preparation; N* is the number of Tablets taken; and the other terms are as defined above.

In-Process Revision

BRIEFING

Irbesartan, *USP 29* page 1177 and page 115 of *PF* 32(1) [Jan.–Feb. 2006]. It is proposed to include the preparation of the *Test solution* in the *Related compounds* section. This procedure is missing in the current official monograph for this drug substance.

(MD-CV: S. Ramakrishna) RTS—C44284

Change to read:

Limit of azide—

Mobile phase—Prepare a filtered and degassed 0.1 N sodium hydroxide solution (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 25 mg of sodium azide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 250 µL of this solution into a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 0.312 µg of sodium azide per mL.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductimetric detector and a 4.0-mm × 25-cm column that contains packing ~~L46~~

■L31.■1S *(USP30)*
The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the azide peak is not less than 10.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas for azide. Calculate the amount of azide, in ppm, in the portion of Irbesartan taken by the formula:

$$1000(C_S / C_T)(42.02/65.01)(r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of sodium azide in the *Standard solution;* C_T is the concentration, in mg per mL, of Irbesartan in the *Test solution;* 42.02 is the molecular weight of azide; 65.01 is the molecular weight of sodium azide; r_U is the peak area for azide obtained from the *Test solution;* and r_S is the peak area for azide obtained from the *Standard solution:* not more than 10 ppm of azide is found.

Change to read:

Related compounds—

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

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

■*Test solution*—Dissolve an accurately weighed quantity of Irbesartan in methanol to obtain a solution having a known concentration of about 0.05 mg per mL.■1S *(USP30)*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph the *Standard solution* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area for the irbesartan related compound A peak. Calculate the percentage of irbesartan related compound A in the portion of Irbesartan taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Irbesartan Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Irbesartan in the *Test solution;* r_U is the peak response for irbesartan related compound A obtained from the *Test solution;* and r_S is the peak response for irbesartan related compound A obtained from the *Standard solution:* not more than 0.2% of irbesartan related compound A is found; not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.

BRIEFING

Irbesartan Tablets, page 1080 of *PF* 31(4) [July–Aug. 2005]. It is proposed to change the test methods for the *Identification* section and the *Assay.* It is also proposed to delete the *Chromatographic purity* test and add a test for *Related compounds.* The proposed test methods are based on validated test procedures, rather than the existing literature test methods in the current monograph. A spectrometric *Identification* method using IR spectrometry is included in this revision. The liquid chromatography procedure in the test for *Related compounds* and the *Assay* is based on an analysis performed with the YMC ODS-A brand of L1 packing. The typical retention time of the irbesartan peak is about 13.4 minutes, and that of irbesartan related compound A is about 11.9 minutes.

(MD-CV: S. Ramakrishna) RTS—C44305

Add the following:

■Irbesartan Tablets

» Irbesartan Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of irbesartan ($C_{25}H_{28}N_6O$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—***USP Irbesartan RS. USP Irbesartan Related Compound A RS.*

In-Process Revision

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen: Transfer 1 Tablet into a suitable vial. Add 10 mL of methanol, and sonicate for 10 minutes. Pass the solution through a glass microfiber membrane filter having a 0.45-µm or finer porosity, and evaporate to dryness, using a stream of nitrogen. Mix approximately 1 mg of the residue with approximately 250 mg of potassium bromide, and mix well to obtain a homogenous mixture. The IR absorption spectrum of a potassium bromide dispersion of the residue so obtained exhibits maxima only at the same wavelengths as that of a potassium bromide dispersion of a similar preparation using USP Irbesartan RS.

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

Dissolution ⟨711⟩—

Medium: ~~0.01 N hydrochloric acid~~ 0.1 N hydrochloric acid; ~~900 mL~~ 1000 mL.

Apparatus 2: 50 rpm.

Time: ~~45 minutes~~ 20 minutes.

Procedure—Determine the amount of ($C_{25}H_{28}N_6O$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about ~~254 nm on filtered portions of the solution under test,~~ 244 nm on portions of the solution under test, passed through a 0.45-µm filter of acrylic copolymer on a nylon support,* and suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Irbesartan RS in the same *Medium*. Calculate the amount of ($C_{25}H_{28}N_6O$) dissolved, in percentage, by the formula:

$$\frac{A_U \times C_S \times 1000 \times 100}{A_S \times L}$$

in which A_U and A_S are the absorbances obtained from the solution under test and the Standard solution, respectively; C_S is the concentration, in mg per mL, of the Standard solution; 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the label claim, in mg, of irbesartan.

Tolerances—Not less than ~~75%~~ 80% *(Q)* of the labeled amount of ($C_{25}H_{28}N_6O$) is dissolved in ~~45 minutes~~ 20 minutes.

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

~~**Chromatographic purity**~~

~~*Diluent, Mobile phase, Standard preparation,* and *Chromatographic system*—Proceed as directed in the *Assay.* under *Irbesartan.*~~

~~*Test solution*—Use the *Assay preparation.*~~

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

~~$100(r_i/r_s)$~~

~~in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 1.0% of any individual impurity is found, and not more than 2.0% of total impurities is found.~~

Related compounds—

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

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

Test solution—Use the *Assay preparation.*

In-Process Revision

* A suitable filter is Acrodisc, manufactured by Gelman Sciences and distributed by Pall Corp. (www.pall.com).

Procedure—Inject a volume of about 15 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 0.3% of irbesartan related compound A is found; not more than 0.2% of any individual impurity is found; and not more than 0.6% of total impurities is found.

Assay—

~~*Diluent, Triethylamine solution, and Mobile phase*—Proceed as directed in the *Assay* under *Irbesartan.*~~

~~*Diluent*—Prepare a solution of phosphoric acid (1 in 100).~~

~~*Triethylamine solution*—Add 1.0 mL of triethylamine to 1000 mL of water, mix, and adjust with phosphoric acid to a pH of 3.5.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of *Triethylamine solution* and acetonitrile (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Irbesartan RS in *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL.~~

~~*Assay preparation*—Weigh and finely powder not fewer than 30 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 10 mg of irbesartan, to a 100-mL volumetric flask. Add about 80 mL of *Diluent,* and stir on a magnetic stir plate for 15 minutes. Dilute with *Diluent* to volume, and mix. Centrifuge a portion of this solution for 10 minutes, and use the clear supernatant.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay* under *Irbesartan.* The liquid chromatograph is equipped with a fluorometric detector that has an excitation wavelength of 250 nm and an emission wavelength of 371 nm, and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.~~

Buffer solution—Dilute about 5.5 mL of phosphoric acid in approximately 950 mL of water, and add triethylamine, slowly and dropwise, to adjust to a pH of 3.0. Further dilute this solution with water to a final volume of 1 L.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (60 : 40). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve accurately weighed quantities of USP Irbesartan RS and USP Irbesartan Related Compound A RS in methanol to obtain a solution having a known concentration of about 0.1 mg per mL of each of the USP Reference Standards.

Standard preparation—Dissolve an accurately weighed quantity of USP Irbesartan RS in methanol to obtain a solution having a known concentration of about 0.15 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 5 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 15 mg of irbesartan, to a 100-mL volumetric flask. Add methanol up to about three-fourths of the volume of the flask. Sonicate for 15 minutes, with stirring at 5-minute intervals. Dilute with methanol to volume, and pass a portion of this solution through a glass microfiber membrane filter having a 0.45-µm or finer porosity.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1.

The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between irbesartan and irbesartan related compound A is not less than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for five replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about ~~20~~ 15 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of irbesartan ($C_{25}H_{28}N_6O$) in the portion of Tablets taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Irbesartan RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

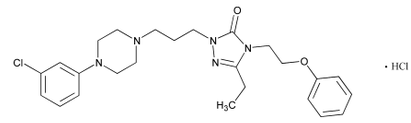
Nefazodone Hydrochloride, page 1094 of *PF* 31(4) [July–Aug. 2005]. It is proposed to correct the relative retention times for nefazodone related compound A and nefazodone related compound B in the *Chromatographic system* in the *Related compounds* test, which were inadvertently switched. It is also proposed to indicate in the same test that the relative retention times provided are intended for information purposes only. In the absence of any significant adverse comment, it is proposed to implement this revision via the *Fifth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of October 1, 2006.

(MD-PP: R. Ravichandran) RTS—C44415

In-Process Revision

Add the following:

■Nefazodone Hydrochloride



$C_{25}H_{32}ClN_5O_2 \cdot HCl$ 506.47

3*H*-1,2,4-Triazol-3-one, 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-5-ethyl-2,4-dihydro-4-(2-phenoxyethyl)-, monohydrochloride.

1-[3-[4-(*m*-Chlorophenyl)-1-piperazinyl]propyl]-3-ethyl-4-(2-phenoxyethyl)-Δ^2-1,2,4-triazolin-5-one monohydrochloride [*82752-99-6*].

» Nefazodone Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{25}H_{32}ClN_5O_2 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers. Store at a temperature between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Nefazodone Hydrochloride RS. USP Nefazodone Related Compound A RS. USP Nefazodone Related Compound B RS.*

Completeness of solution ⟨641⟩—A solution of 25 mg per mL in methanol meets the requirements.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: A solution of 10 mg per mL meets the requirements of the test for *Chloride* ⟨191⟩.

Loss on drying ⟨731⟩—Dry it in vacuum at 105° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

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

Add the following:

•Related compounds—

Diluent—Prepare a solution of water and acetonitrile (50 : 50).

Solution A—Dissolve 0.77 g of ammonium acetate in about 950 mL of water. Adjust with triethylamine to a pH of 7.10 ± 0.05. Dilute with water to 1 L. Filter and degas.

Solution B—Use filtered and degassed acetonitrile.

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

Standard stock solution—Dissolve an accurately weighed amount of USP Nefazodone Hydrochloride RS in *Diluent* to obtain a solution containing 0.1 mg per mL of nefazodone hydrochloride.

Nefazodone related compound A stock solution and *Nefazodone related compound B stock solution*—Transfer about 20 mg each of USP Nefazodone Related Compound A RS and USP Nefazodone Related Compound B RS, accurately weighed, into separate 200-mL volumetric flasks. Dissolve in and dilute with *Diluent* to volume.

Resolution solution—Pipet 5.0 mL of *Nefazodone related compound A stock solution* and 5.0 mL of *Nefazodone related compound B stock solution* into a 100-mL volumetric flask. Dilute with *Standard stock solution* to volume, and mix. This solution contains about 90 µg per mL of nefazodone hydrochloride, and about 5 µg per mL each of nefazodone related compounds A and B.

Standard solution—Pipet 2.0 mL each of the *Standard stock solution, Nefazodone related compound A stock solution,* and *Nefazodone related compound B stock solution* into a 200-mL volumetric flask. Dilute with *Diluent* to volume, and mix well to obtain a final concentration of 1 µg per mL each of nefazodone hydrochloride, nefazodone related compound A, and nefazodone related compound B.

Test solution—Transfer about 100 mg of Nefazodone Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 250-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.7 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	50	50	equilibration
0–10	50→45	50→55	linear gradient
10–16	45→35	55→65	linear gradient
16–25	35	65	isocratic
25–26	35→50	65→50	linear gradient
26–35	50	50	re-equilibration

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.94 for nefazodone related compound A, 1.0 for nefazodone hydrochloride, and 1.2 for nefazodone related compound B.~~ the resolution, *R,* between nefazodone related compound A and nefazodone hydrochloride is not less than 1.5, and it is not less than 4.0 between nefazodone hydrochloride and nefazodone related compound B. Chromatograph the *Standard solution,* and measure the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0% for nefazodone related compound A and nefazodone related compound B. [NOTE—For identification purposes, the approximate relative retention times are about 1.2 for nefazodone related compound A, 1.0 for nefazodone hydrochloride, and 0.94 for nefazodone related compound B.]

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each nefazodone related compound in the portion of Nefazodone Hydrochloride taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of the relevant USP Reference Standard in the *Standard solution;* C_T is the concentration of Nefazodone Hydrochloride, in mg per mL, in the *Test solution;* and r_U and r_S are the peak areas of the corresponding nefazodone related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.2% of nefazodone related compound A is found; not more than 0.2% of nefazodone related compound B is found; not more than 0.1% of any unknown impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Use the peak area for nefazodone hydrochloride in the *Standard solution* as r_S to calculate any unknown impurity.]•S

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

Assay—Dissolve about 800 mg of Nefazodone Hydrochloride, accurately weighed, in 50 mL of glacial acetic acid, and add 15 mL of 3% (v/v) mercuric acetate in glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid VS is equivalent to 50.65 mg of $C_{25}H_{32}ClN_5O_2 \cdot HCl$.■2S *(USP29)*

In-Process Revision

BRIEFING

Nefazodone Hydrochloride Tablets, page 1096 of *PF* 31(4) [July–Aug. 2005].

1. On the basis of comments received, it is proposed to revise the test for *Related compounds* to delete 1,3-Bis[4-(3-chlorophenyl)piperazine-1-yl]propane from the list of specified impurities. It is also proposed to increase the limit of any individual unknown impurity from 0.1% to 0.2%.
2. The relative retention times (RRT) for nefazodone related compound A and nefazodone related compound B previously published in the test for *Related compounds* were inadvertently reversed. It is proposed to correct the erroneous RRT values.
3. System suitability requirements in the *Assay* and in the test for *Related compounds* have been appropriately separated to improve clarity. Also, the plate count requirement in the *Assay* has been deleted as a system suitability requirement.
4. It is also proposed to add a *Note* under *Chromatographic system* in the test for *Related compounds* to indicate that the RRT values are intended for informational purposes only.
5. Also, the *Packaging and storage* statement has been revised in accordance with the *General Notices.*

Other editorial changes have also been made.

(MD-PP: R. Ravichandran) RTS—C44417

Add the following:

■Nefazodone Hydrochloride Tablets

» Nefazodone Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of nefazodone hydrochloride ($C_{25}H_{32}ClN_5O_2 \cdot HCl$).

Packaging and storage—Preserve in tight containers. ~~Store between 15° and 30°.~~ Store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Nefazodone Hydrochloride RS. USP Nefazodone Related Compound A RS. USP Nefazodone Related Compound B RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Standard stock solution—Transfer about 70 mg of USP Nefazodone Hydrochloride RS, accurately weighed, to a 50-mL volumetric flask. Add 2.5 mL of methanol, dilute with *Medium* to volume, and mix.

Standard solution—Dilute the *Standard stock solution* with *Medium* in such a way that the final concentration is similar to the one expected in the *Test solution.*

Test solution—Use portions of the solution under test passed through a 0.45-µm PVDF filter, discarding the first 5 mL.

Procedure—Determine the percentage of the labeled amount of nefazodone hydrochloride dissolved by employing UV absorption, using a suitable spectrophotometer, at the wavelength of maximum absorbance at about 246 nm, on the *Test solution* in comparison with the *Standard solution,* using *Medium* as the blank. Calculate the percentage of nefazodone hydrochloride ($C_{25}H_{32}ClN_5O_2 \cdot HCl$) dissolved by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the USP Nefazodone Hydrochloride RS in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{25}H_{32}ClN_5O_2 \cdot HCl$ is dissolved in 30 minutes.

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

Related compounds—

~~*Diluted acetic acid*~~ *Dilute acetic acid, Buffer solution,* and *Mobile phase* ~~*Nefazodone related compound A stock solution, Nefazodone related compound B stock solution, System suitability preparation,* and *Chromatographic system*~~—Proceed as directed in the *Assay.*

Nefazodone related compound A stock solution—Prepare a solution of USP Nefazodone Related Compound A RS in *Mobile phase* having a known concentration of about 80 µg per mL.

Nefazodone related compound B stock solution—Prepare a solution of USP Nefazodone Related Compound B RS in *Mobile phase* having a known concentration of about 80 µg per mL.

System suitability solution—Transfer about 10 mg of USP Nefazodone Hydrochloride RS into a 10-mL volumetric flask. Add 2.0 mL of *Nefazodone related compound A stock solution* and 2.0 mL of *Nefazodone related compound B stock solution,* and mix to dissolve the nefazodone hydrochloride. Dilute with *Mobile phase* to volume, and mix.

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

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

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*. Identify the peaks using the relative retention times given in *Table 1:* the resolution, *R,* between nefazodone related compound A and nefazodone hydrochloride is not less than 2.0; and the resolution, *R,* between nefazodone related compound B and nefazodone hydrochloride is not less than 1.5. [NOTE—Approximate relative retention times are provided in *Table 1* for informational purposes only.]

Procedure—Inject ~~a volume (about 10 µL) of the~~ equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatogram,

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and measure the peak responses. Calculate the percentage of individual nefazodone related compounds in the portion of Tablets taken by the formula:

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

in which r_U is the individual peak response for each nefazodone related compound obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution,* respectively; C_S and C_T are the concentrations, in mg per mL, of nefazodone hydrochloride in the *Standard solution* and the *Test solution,* respectively; and F is the relative response factor obtained from *Table 1.* The related compound requirements are listed in *Table 1.*

Assay—

~~*Diluted acetic acid*~~ —*Dilute acetic acid*—Prepare a mixture of acetic acid and water (1 : 1).

Buffer solution—Dissolve 0.77 g of ammonium acetate in 1 L of water. Add 1.0 mL of triethylamine, and mix well. Adjust with ~~*Diluted acetic acid*~~ *Dilute acetic acid* to a pH of 7.10 ± 0.05, and mix.

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

~~*Nefazodone related compound A stock solution*—Prepare a solution of USP Nefazodone Related Compound A RS in *Mobile phase* having a known concentration of about 80 µg per mL.~~

~~*Nefazodone related compound B stock solution*—Prepare a solution of USP Nefazodone Related Compound B RS in *Mobile phase* having a known concentration of about 80 µg per mL.~~

~~*System suitability preparation*—Transfer about 10 mg of USP Nefazodone Hydrochloride RS into a 10-mL volumetric flask. Add 2.0 mL of *Nefazodone related compound A stock solution* and 2.0 mL of *Nefazodone related compound B stock solution,* and mix to dissolve the nefazodone hydrochloride. Dilute with *Mobile phase* to volume, and mix.~~

Standard preparation—Prepare a solution of USP Nefazodone Hydrochloride RS in *Mobile phase* having a known concentration of about 0.1 mg per mL.

Assay stock preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mg of nefazodone hydrochloride, based on the label claim, to a 250-mL volumetric flask, add about 125 mL of *Mobile phase*, and sonicate for about 10 minutes with occasional shaking. Dilute with *Mobile phase* to volume, and mix to obtain a solution having a concentration of about 1 mg per mL of nefazodone hydrochloride. Pass a portion of this solution through a filter

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Table 1

Related Compound	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Nefazodone related compound A	~~0.9~~ 1.4	~~1.0~~ 1.2	0.2
Nefazodone related compound B	~~1.4~~ 0.9	~~1.2~~ 1.0	0.2
~~1,3-Bis[4-(3-chlorophenyl)piperazine-1-yl]propane~~	~~2.2~~	~~1.6~~	~~0.2~~
~~Unknown~~ Any individual unknown impurity	—	1.0	~~0.1~~ 0.2 each
Total known and unknown	—	—	0.5

having a 0.45-µm or finer porosity, and use the filtrate, which has a concentration of about 1 mg per mL of nefazodone hydrochloride.

Assay preparation—Transfer 5.0 mL of *Assay stock preparation* into a 50-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix to obtain a solution having a concentration of 0.1 mg per mL of nefazodone hydrochloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 250-nm detector and a 4.6-mm × 25-cm column containing 5-µm L1 packing. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. ~~Inject the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for nefazodone related compound A, 1.0 for nefazodone hydrochloride, and 1.4 for nefazodone related compound B; the resolution, *R,* between nefazodone related compound A and nefazodone hydrochloride is not less than 1.5, and the resolution, *R,* between nefazodone related compound B and nefazodone hydrochloride is not less than 2.0.~~ Inject the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the column efficiency is not less than 2000 theoretical plates;~~ the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in percent of label claim, of nefazodone hydrochloride ($C_{25}H_{32}ClN_5O_2 \cdot HCl$) in the portion of Tablets taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of nefazodone hydrochloride in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

BRIEFING

Nevirapine Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Nova-Pack C18 (Waters) brand of L1 column. Typical retention times are about 4 minutes for nevirapine and about 6 minutes for nevirapine related compound A.

(MD-AA: B. Davani; BPC: M. Marques) RTS—C42828; C43839

Add the following:

■Nevirapine Tablets

» Nevirapine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$).

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

USP Reference standards ⟨11⟩**—***USP Nevirapine Anhydrous RS. USP Nevirapine Related Compound A RS.*

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Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Transfer a portion of powdered Tablets equivalent to 25 mg of nevirapine to a 50-mL volumetric flask. Dissolve in 10 mL of methylene chloride. Swirl the solution for about 30 to 60 seconds, and pass through a medium sintered-glass, fritted vacuum funnel. Using a glass syringe, pass the filtrate through a 0.45-µm Teflon filter. Dry the extract at 105° for a minimum of 1 hour.

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

Dissolution ⟨711⟩—

Medium: 0.1 M phosphate buffer, pH 2.0, prepared by transferring 3.9 mL of concentrated phosphoric acid and 5.73 g of monobasic sodium phosphate monohydrate to a 1-L volumetric flask, dissolving in and diluting with water to volume, and if necessary, adjusting with phosphoric acid to a pH of 2.0 ± 0.02; 900 mL.

Apparatus 2: 50 rpm. Use stainless steel paddles only. Do not use paddles coated with polytetrafluoroethylene.

Time: 60 minutes.

Determine the amount of $C_{15}H_{14}N_4O$ dissolved by employing the following method.

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

Stock standard solution 1—Transfer 27 mg, accurately weighed, of USP Nevirapine Anhydrous RS into a 500-mL volumetric flask. Add 50 mL of alcohol, followed by 250 mL of *Medium*. Sonicate for about 20 minutes to dissolve, allow to cool to room temperature, and dilute with *Medium* to volume.

Stock standard solution 2—Transfer 7 mg, accurately weighed, of USP Nevirapine Related Compound A RS into a 250-mL volumetric flask. Add about 2 mL of *Diluent,* sonicate until completely dissolved, and dilute with *Medium* to volume.

Standard solution—Transfer 25.0 mL of the *Stock standard solution 1* into a 100-mL volumetric flask, dilute with *Medium* to volume, and mix well.

Resolution solution—Transfer 25.0 mL of *Stock standard solution 1* into a 50-mL volumetric flask, and dilute with *Medium* to volume. Transfer 25.0 mL of this solution into a 50-mL volumetric flask, dilute with *Stock standard solution 2* to volume, and mix well.

Test solution—Pass 20 mL of the solution under test through a nylon or glass fiber 0.45-µm filter, and dilute with *Medium* to obtain a solution having a final concentration of about 0.0135 mg of nevirapine per mL.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of $C_{15}H_{14}N_4O$ dissolved by the formula:

$$\frac{r_U \times W_S \times D_S \times 900 \times 100}{r_S \times D_U \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; W_S is the amount, in mg, of USP Nevirapine Anhydrous RS taken; D_S is the dilution factor for the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; D_U is the dilution factor for the *Test solution;* and *LC* is the Tablet label claim in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{15}H_{14}N_4O$ is dissolved in 60 minutes.

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

Chromatographic purity—

Mobile phase, Diluent, Resolution solution, Stock standard solution 1, and *Stock standard solution 2*—Proceed as directed in the *Assay.*

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Standard solution—Quantitatively dilute *Stock standard solution 1* with *Diluent* to obtain a solution having a known concentration of about 0.125 µg of nevirapine per mL.

Test solution—Use the *Assay preparation,* as obtained in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay* except that the relative standard deviation for replicate injections of the *Standard solution* is not more than 5.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least 13 minutes, and measure the peak responses. Calculate the percentage of each impurity/degradation product in the portion of Tablets taken by the formula:

$$8000(C/W)(A/L)(r_i/r_S)(100)$$

in which C is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the *Standard solution; W* is the weight, in mg, of powdered Tablets taken to prepare the *Test solution; A* is the average weight of each Tablet, in mg; L is the labeled amount, in mg, of nevirapine in each Tablet; r_i is the peak response obtained for each impurity/degradation product in the *Test solution;* and r_S is the peak response for nevirapine in the *Standard solution*. Disregard all peaks due to the solvent or excipients and impurity peaks less than 0.1%. Not more than 0.1% of any individual unknown impurity/degradation product is found; and not more than 0.2% of total unknown impurities/degradation products is found.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (77 : 23). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of dehydrated alcohol and water (1 : 1).

Stock standard solution 1—Transfer about 25 mg of USP Nevirapine Anhydrous RS, accurately weighed, into a 250-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume.

Stock standard solution 2—Transfer about 5 mg of USP Nevirapine Related Compound A RS, accurately weighed, into a 50-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume.

Standard preparation—Transfer 25.0 mL of *Stock standard solution 1* into a 100-mL volumetric flask, and dilute with *Diluent* to volume. The final concentration is about 0.025 mg of nevirapine per mL.

Resolution solution—Transfer 25.0 mL of *Stock standard solution 1* and 25.0 mL of *Stock standard solution 2* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix well.

Assay preparation—Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to 200 mg of nevirapine into a 200-mL volumetric flask, and add about 150 mL of *Diluent*. Sonicate the solution for about 20 minutes, and then shake for about 20 minutes. Cool to room temperature, dilute with *Diluent* to volume, and mix. Centrifuge a portion of the resulting solution at about 1500 rpm for about 5 minutes. Transfer 5.0 mL of the supernatant into a 200-mL volumetric flask, and dilute with *Diluent* to volume. Filter, and discard the first 2 mL of filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 3.9-mm × 15-cm column containing L1 packing. The column is maintained at ambient temperature. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution* (about 20 µL), and record the peak responses as directed for *Procedure:* the resolution, *R,* between nevirapine and nevirapine related compound A is not less than 3.0. Chromatograph the *Standard preparation,* and record the

peak responses as directed for *Procedure:* the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the nevirapine peak. Calculate the quantity, in mg, of nevirapine ($C_{15}H_{14}N_4O$) in the portion of Tablets taken by the formula:

$$8000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Oxybutynin Chloride, *USP 29* page 1602. On the basis of comments received, it is proposed to use a relative response factor of 1.0 for unknown impurities in the test for *Related compounds,* which is the generally accepted approach within the industry.

(MD-GRE: E. Gonikberg) RTS—C44481

In-Process Revision

Change to read:

Related compounds—

Phosphate buffer and *Mobile phase*—Prepare as directed in the *Assay.*

System suitability stock solution—Dissolve accurately weighed quantities of USP Oxybutynin Related Compound B RS and USP Oxybutynin Related Compound C RS in *Mobile phase* to obtain a solution having known concentrations of about 100 µg of each USP Reference Standard per mL.

Standard stock solution—Dissolve an accurately weighed quantity of USP Oxybutynin Chloride RS in *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL.

System suitability solution—Transfer 10.0 mL of the *System suitability stock solution* to a 100-mL volumetric flask, add 10.0 mL of the *Standard stock solution,* and dilute with *Mobile phase* to volume.

Standard solution—Transfer 15.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume. Transfer 5.0 mL of the solution obtained to a separate 100-mL volumetric flask, and dilute with *Mobile phase* to volume. This solution contains about 7.5 µg of USP Oxybutynin Chloride RS per mL.

Test solution—Transfer about 50 mg of Oxybutynin Chloride, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between oxybutynin related compound B and oxybutynin related compound C is not less than 1.1; and the relative standard deviation for replicate injections, determined from the oxybutynin peak, is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for a total time of not less than twice the retention time of the oxybutynin peak, and measure all the peak responses (see *Table 1* for known impurities). Calculate the percentage of each impurity in the portion of Oxybutynin Chloride taken by the formula:

$$(C/W)(1/F)(r_U / r_S)$$

in which C is the concentration, in µg per mL, of USP Oxybutynin Chloride RS in the *Standard solution; W* is the weight, in mg, of Oxybutynin Chloride taken to prepare the *Test solution; F* is the relative response factor for each impurity (see *Table 1* for the values); and r_U and r_S are the peak responses for each impurity obtained from the *Test solution* and for the oxybutynin peak in the *Standard solution,* respectively. [NOTE—For unknown impurities, use the relative response factor of ~~the closest known impurity.~~ ■1.0.]■1S (*USP30*)

Table 1

Compound Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Oxybutynin related compound A[1]	0.08	1.4	0.5
Diphenyl analog of oxybutynin chloride[2]	0.37	2.7	0.1
Oxybutynin related compound B[3]	0.65	1.3	1.0
Oxybutynin related compound C[4]	0.79	1.0	1.0
Cyclohexenyl analog of oxybutynin chloride[5]	1.8	0.4	1.0
Ethylpropyl analog of oxybutynin chloride[6]	1.9	1.0	0.1

[1] phenylcyclohexylglycolic acid (cyclohexylmandelic acid, or CHMA)
[2] 4-(diethylamino)but-2-ynyl 2-hydroxy-2,2-diphenylacetate
[3] methyl ester of phenylcyclohexylglycolic acid (methyl ester of cyclohexylmandelic acid, or CHMME)
[4] methylethyl analog of oxybutynin chloride (4-(ethylmethylamino) but-2-ynyl (±)-2-cyclohexyl-2-hydroxy-2-phenylacetate)
[5] 4-(diethylamino)but-2-ynyl (±)-2-(cyclohex-3-enyl)-2-cyclohexyl-2-hydroxyacetate
[6] 4-(ethylpropylamino)but-2-ynyl (±)-2-cyclohexyl-2-hydroxy-2-phenylacetate

In addition to not exceeding the limits for each impurity in *Table 1,* not more than 0.1% of any other single impurity is found; and not more than 1.0% of total impurities is found.

BRIEFING

Paroxetine Hydrochloride, *USP 29* page 1644 and page 1112 of *PF* 31(4) [July–Aug. 2005]. Comments were received regarding the difficulty of meeting the system suitability requirements in the *Assay,* particularly the tailing factor and the requirement for the resolution in the *Chromatographic system* section. On the basis of supporting data received, it is proposed to change the tailing factor requirement from "not more than 1.6" to "not more than 2.0", and to allow the flexibility in the *Mobile phase* composition to meet the system suitability requirements. The original method for the *Assay* was validated with the Zorbax TMS brand column; the proposed revised procedure for the *Assay* will also allow the use of the Adsorbosphere XL brand L13 column.

(MD-PP: R. Ravichandran) RTS—C44056

Change to read:

USP Reference standards ⟨11⟩—*USP Paroxetine Hydrochloride RS.* ~~★*USP Paroxetine Hydrochloride for System Suitability RS.*▲*USP29*~~

■*USP Paroxetine System Suitability Mixture A RS.*■2S *(USP29)* *USP Paroxetine Related Compound B RS. USP Paroxetine Related Compound C RS.* ~~*USP Paroxetine Related Compound E RS.*~~

■*USP Paroxetine Related Compound E Mixture RS.*■2S *(USP29)* *USP Paroxetine Related Compound F RS. USP Paroxetine Related Compound G RS.*

Change to read:

Limit of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine—

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

Solution B: acetonitrile, filtered and degassed.

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

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

Standard solution—Dissolve an accurately weighed quantity of ~~USP Paroxetine Hydrochloride Related Compound E RS,~~ ■USP Paroxetine Related Compound E Mixture RS,■2S *(USP29)* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 42 ng per mL of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine.

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

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

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

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

Procedure—Separately inject equal volumes (about 75 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken by the formula:

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

in which C is the concentration, in mg per mL, of ~~USP Paroxetine Hydrochloride Related Compound E RS~~ ■USP Paroxetine Related Compound E Mixture RS■2S *(USP29)* in the *Standard solution; I* is the fraction, by weight, of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in ~~USP Paroxetine Hydrochloride Related Compound E RS;~~ ■USP Paroxetine Hydrochloride Related Compound E Mixture RS;■2S *(USP29)* W is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* and r_i and r_S are the peak areas for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.0001% of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine is found.▲*USP29*

Change to read:

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

TEST 1—

Solution A—Prepare a filtered and degassed mixture of water, tetrahydrofuran, and trifluoroacetic acid (180 : 20 : 1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, tetrahydrofuran, and trifluoroacetic acid (180 : 20 : 1).

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

Diluent: a mixture of water and tetrahydrofuran (9 : 1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1 µg per mL.

System suitability solution—▲Dissolve, by sonication if necessary, a suitable quantity of ~~USP Paroxetine Hydrochloride for System Suitability RS~~ ■USP Paroxetine System Suitability Mixture A RS■2S *(USP29)* in *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.▲*USP29*

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

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	80	20	equilibration
0–30	80	20	isocratic
30–50	80→20	20→80	linear gradient
50–60	20	80	isocratic
60–70	20→80	80→20	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about ▲0.66 for paroxetine related compound A, 0.73 for paroxetine related compound B, and 1.0 for paroxetine;▲*USP29* the resolution, *R,* between paroxetine related compound A and paroxetine related compound B is not less than 2.0; the tailing factor of the paroxetine related compound A peak is between 0.8 and 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for paroxetine related compound A.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution,* the *Test solution,* and the *Diluent* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* r_U is the peak area of each impurity in the *Test solution,* excluding the peaks obtained from the chromatogram of the *Diluent;* and r_S is the peak area of paroxetine obtained from the *Standard solution:* not more than 0.3% of any peak at a retention time of paroxetine related compound B is found; not more than 0.1% of any other individual impurity is found; and not more than 1.0% of total impurities is found.

TEST 2—

Phosphate buffer—Dissolve 3.4 g of monobasic potassium phosphate and 3.4 g of tetrabutylammonium hydrogen sulfate in 1.0 L of water.

Solution A—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (98 : 2).

Solution B—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (6 : 4).

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

Diluent: a mixture of *Phosphate buffer* and acetonitrile (9 : 1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 4 µg per mL, 10 µg per mL, 10 µg per mL, and 4 µg per mL, respectively.

Identification solution—Dissolve an accurately weighed quantity of Paroxetine Hydrochloride, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in *Diluent* to obtain a solution having known concentrations of about 2 mg per mL, 10 µg per mL, 10 µg per mL, and 4 µg per mL, respectively.

Test solution—Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–5	100	0	isocratic
5–70	100→40	0→60	linear gradient
70–90	40→0	60→100	linear gradient
90–95	0	100	isocratic
95–95.1	0→100	100→0	linear gradient
95.1–110	100	0	re-equilibration

Chromatograph the *Identification solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.91 for paroxetine related compound B, about 0.96 for paroxetine related compound F, 1.0 for paroxetine, and about 1.34 for paroxetine related compound G. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10.0% for the paroxetine related compound B, paroxetine related compound F, paroxetine hydrochloride, and paroxetine related compound G peaks.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound B, paroxetine related compound F, and paroxetine related compound G in the portion of Paroxetine Hydrochloride taken by the formula:

$$5000(C/W)(r_i/r_S)$$

in which C is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* and r_i and r_S are the peak areas for the corresponding impurity in the *Test solution* and the *Standard solution,* respectively: not more than 0.5% of paroxetine related compound B is found; not more than 0.2% of paroxetine related compound F is found; and not more than 0.2% of paroxetine related compound G is found. Calculate the percentage of any unknown impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$5000(C/W)(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* r_i is the peak area for any unknown impurity in the *Test solution;* and r_S is the peak area of paroxetine in the *Standard solution:* not more than 0.1% of any single unknown impurity is found, and not more than 1.0% of total impurities is found.

Change to read:

Assay—

Acetate buffer—Prepare a 0.05 M solution of ammonium acetate in water, adjust with glacial acetic acid to a pH of 4.5, mix, and filter.

Mobile phase—Prepare a filtered and degassed mixture of *Acetate buffer,* acetonitrile, and triethylamine ~~(60 : 40 : 1).~~

■(70 : 30 : 1). [NOTE—The *Acetate buffer*–acetonitrile–triethylamine ratio can be varied between 70 : 40 : 1 and 75 : 25 : 1 to meet the system suitability requirements.]■1S (*USP30*)

Adjust with glacial acetic acid to a pH of 5.5. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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System suitability solution—Dissolve suitable quantities of USP Paroxetine Related Compound B RS and USP Paroxetine Hydrochloride RS in water to obtain a solution having known concentrations of about 0.5 mg of each USP Reference Standard per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Paroxetine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 295-nm detector and a 4.6-mm × 25-cm column that contains packing L13. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.9 for paroxetine related compound B and 1.0 for paroxetine;~~

■ ■1S (*USP30*)
the resolution, *R,* between paroxetine related compound B and paroxetine is not less than 2.0; ~~the column efficiency determined from the paroxetine peak is not less than 3000 theoretical plates; the tailing factor for the paroxetine peak is not more than 1.6;~~

■the tailing factor for the paroxetine peak is not more than 2.0;■1S (*USP30*)
and the relative standard deviation for replicate injections is not more than 2.0%.

■[NOTE—For information purposes, the approximate relative retention times are about 0.9 for paroxetine related compound B and 1.0 for paroxetine.]■1S (*USP30*)

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{19}H_{20}FNO_3 \cdot HCl$ in the portion of Paroxetine Hydrochloride taken by the formula:

$$100C(r_U/r_S)$$

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

BRIEFING

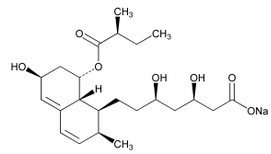
Pravastatin Sodium, page 1394 of *PF* 31(5) [Sept.–Oct. 2005].

1. It is proposed to change the acceptance criteria in the Definition from "not less than 98.0 percent and not more than 102.0 percent" to "not less than 97.5 percent and not more than 102.0 percent". These limits are representative of marketed products.
2. Comments were received that different manufacturers have different storage conditions for this material, supported by stability data. It is proposed to use a flexible monograph approach to indicate that manufacturers could store the material as per their labeling instruction. Possible storage conditions would also be listed.
3. Because Pravastatin Sodium is highly hygroscopic, it is proposed to use USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS in the test for *Chromatographic purity* and in the *Assay.*
4. On the basis of comments received, the name for pravastatin sodium related compound A is corrected, and the complete chemical name is added to the monograph. In addition, minor corrections to the Pravastatin Sodium chemical name and to the composition of *Solution A* under the *Assay* are proposed.

(MD-GRE: E. Gonikberg) RTS—C44138; C44072

Add the following:

■Pravastatin Sodium



$C_{23}H_{35}NaO_7$ 446.51

~~1-Napththalenecheptanoic acid,~~ 1-Naphthaleneheptanoic acid, 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-, monosodium salt, [1*S*-[1α(β*S**,δ*S**),2α,6α,8β(*R**),8aα]]-.

Sodium (+)-(β*R*,δ*R*,1*S*, 2*S*,6*S*,8*S*,8a*R*)-1,2,6,7,8,8a-hexahydro-β,δ,6,8-tetrahydroxy-2-methyl-1-naphthaleneheptanoate, 8-[(2*S*)-2-methylbutyrate] [*81131-70-6*].

» Pravastatin Sodium contains not less than ~~98.0~~ 97.5 percent and not more than 102.0 percent of $C_{23}H_{35}NaO_7$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve in tight containers. ~~Store under nitrogen in a cold place.~~ Store as per labeling instructions. Possible storage conditions could include the following, in the presence of stability data supporting the condition: Store under nitrogen in a cold place. Store at room temperature.

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USP Reference standards ⟨11⟩—*USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS. USP Pravastatin Sodium RS. USP Pravastatin Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of the pyroantimonate precipitation test for *Sodium* ⟨191⟩.

Specific rotation ⟨781⟩**:** between +150° and +160° (at 20°), calculated on the anhydrous and solvent-free basis.

Test solution: 5 mg per mL in water.

pH ⟨791⟩**:** between 7.2 and 9.0, in a solution (1 in 20).

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

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

Limit of alcohol *(if present)—*

Test solution—Transfer about 0.2 g of Pravastatin Sodium, accurately weighed, to a 20-mL volumetric flask, dilute with water to volume, and mix. Pipet 5 mL of this solution into a vial fitted with a septum and a crimp cap, add 1 mL of water, seal the vial, and mix. Heat the sealed vial at 80° for 60 minutes.

Standard solution—Pipet 2 mL of dehydrated alcohol into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix. Pipet 1 mL of this solution into a vial fitted with a septum and a crimp cap, and calculate the amount of alcohol, W_A, added, in g, the specific gravity of dehydrated alcohol being 0.79 g per mL. Add 5 mL of the *Test solution* to the same vial, seal the vial, and mix. Heat the sealed vial at 80° for 60 minutes.

Blank solution—Pipet 6 mL of water into a vial fitted with a septum and a crimp cap, and seal the vial. Heat the sealed vial at 80° for 60 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m fused silica capillary column coated with a 3-µm film of stationary phase G43. The carrier gas is helium, with a split ratio of 1 : 5, and flowing with a linear velocity of about 35 cm per second. The chromatograph is programmed as follows. The column temperature is maintained at 40° for 20 minutes, then the temperature is increased at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The transfer line temperature is maintained at 85°, the injection port temperature is maintained at 140°, and the detector is maintained at 250°. Chromatograph the *Blank solution,* and record the peak responses as directed for *Procedure:* no interfering peaks are observed.

Procedure—Separately inject equal volumes (about 1 mL) of headspace gas of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the percentage (w/w) of alcohol in the portion of Pravastatin Sodium taken by the formula:

$$100(W_A / W)(V/5)[r_U / (r_S - r_U)]$$

in which W_A is as defined above; W is the weight, in g, of Pravastatin Sodium taken to prepare the *Test solution; V* is the volume, in mL, of the *Test solution;* 5 is the volume, in mL, of the *Test solution* taken; and r_U and r_S are the peak area responses of alcohol obtained from the *Test solution* and the *Standard solution,* respectively: not more than 3.0% is found.

Chromatographic purity—[NOTE—The *Standard solution* and the *Test solution* are maintained at 15° until injected into the chromatograph.]

Diluent—Prepare a mixture of methanol and water (1 : 1).

Buffer pH 7.0—Prepare a 0.08 M phosphoric acid solution, adjust with triethylamine to a pH of 7.0, and mix.

Solution A—Prepare a filtered and degassed mixture of water, *Buffer pH 7.0,* and acetonitrile (52 : 30 : 18).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, *Buffer pH 7.0,* and water (60 : 30 : 10).

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

Standard solution—Dissolve an accurately weighed quantity of ~~USP Pravastatin Sodium RS~~ USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about ~~1 µg per mL~~ 1.25 µg of pravastatin 1,1,3,3-tetramethylbutylamine per mL.

System suitability solution—Dissolve accurately weighed quantities of ~~USP Pravastatin Sodium RS~~ USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS and USP Pravastatin Related Compound A RS in *Diluent* to obtain a solution containing about ~~0.5 mg of USP Pravastatin Sodium RS~~ 0.6 mg of USP Pravastatin 1,1,3,3-tetramethylbutylamine RS and 0.001 mg of USP Pravastatin Related Compound A RS per mL. [NOTE—USP Pravastatin Related Compound A RS is a sodium salt of ~~6α-hydroxyisocompactin acid~~ 3α-hydroxyisocompactin acid.]

Test solution—Transfer about 50 mg of Pravastatin Sodium, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩—The liquid chromatograph is equipped with a 238-nm detector and a 4.6-mm × 7.5-cm column that contains 3.5-µm packing L1. Alternatively, a 4.0-mm × 10-cm column that contains 3-µm packing L1 can be used. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–3.0	100	0	isocratic
3.0–26.5	100→0	0→100	linear gradient
26.5–26.6	0→100	100→0	linear gradient
26.6–30.0	100	0	re-equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for pravastatin and 1.1 for pravastatin related compound A; and the resolution, *R,* between pravastatin and pravastatin related compound A is not less than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, identify the impurities listed in *Table 1,* and measure the peak responses. Calculate the percentage of each impurity in the portion of Pravastatin Sodium taken by the formula:

~~$100C(V/W)(r_i/r_s)$~~

$$100 \times (446.51/553.78)C(V/W)(r_i/r_S)$$

in which 446.51 and 553.78 are the molecular weights of pravastatin sodium and pravastatin 1,1,3,3-tetramethylbutylamine, respectively; ~~*C* is the concentration, in mg per mL, of USP Pravastatin Sodium RS in the *Standard solution;*~~ *C* is the concentration, in mg per mL, of pravastatin 1,1,3,3-tetramethylbutylamine in the *Standard solution; V* is the volume, in mL, of the *Test solution; W* is the weight, in mg, of Pravastatin Sodium taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the pravastatin peak response obtained from the *Standard solution*. In addition to not exceeding the

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limits for each impurity specified in *Table 1,* not more than 0.1% of any other individual impurity is found, and not more than 0.6% of total impurities is found.

Table 1

Name	Relative Retention Time	Limit (%)
3″-Hydroxypravastatin	0.33	0.2
6′-Epipravastatin	0.92	0.3
~~6α-Hydroxyisocompactin~~ 3α-Hydroxyisocompactin[1]	1.1	0.2
Pentanoyl impurity[2]	1.2	0.2
Pravastatin lactone	1.8	0.2
Compactin	3.1	0.2

[1] Sodium (3*R,*5*R*)-3,5-dihydroxy-7-[(1*S,*2*S,*3*S,*8*S,*8a*R*)-3-hydroxy-2-methyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl]heptanoate(pravastatin related compound A).

[2] (3*R*,5*R*)-3,5-dihydroxy-7-[(1*S*,2*S*,6*S*,8*S*,8a*R*)-6-hydroxy-2-methyl-8-[[(2*S*)-2-methylpentanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoic acid.

Assay—

Solution A—Prepare a ~~0.05 M~~ 0.08M phosphoric acid solution, adjust with a 25% sodium hydroxide solution to a pH of 5.0, mix, filter, and degas.

Solution B—Use acetonitrile.

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

Standard preparation—Dissolve an accurately weighed quantity of ~~USP Pravastatin Sodium RS~~ USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about ~~0.2 mg per mL~~ 0.25 mg of pravastatin 1,1,3,3-tetramethylbutylamine per mL.

System suitability preparation—Dissolve accurately weighed quantities of ~~USP Pravastatin Sodium RS~~ USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS and USP Pravastatin Related Compound A RS in methanol to obtain a solution containing about ~~0.2 mg of USP Pravastatin Sodium RS~~ 0.25 mg of USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS and 0.001 mg of USP Pravastatin Related Compound A RS per mL.

Assay preparation—Transfer about 20 mg of Pravastatin Sodium, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩—The liquid chromatograph is equipped with a 238-nm detector and a 4.0-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–7.0	80→72	20→28	linear gradient
7.0–10.0	72→50	28→50	linear gradient
10.0–17.0	50	50	isocratic
17.0–17.1	50→80	50→20	linear gradient
17.1–20.0	80	20	re-equilibration

Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for pravastatin and 1.2 for pravastatin related compound A; the resolution, *R,* between pravastatin and pravastatin related compound A is not less than 1.2; and the relative standard deviation for replicate injections for the pravastatin peak is not more than 2.0%.

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Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the pravastatin peaks. Calculate the quantity, in mg, of $C_{23}H_{35}NaO_7$ in the portion of Pravastatin Sodium taken by the formula:

~~$VC(r_u/r_s)$~~

$$(446.51/553.78)VC(r_U/r_S)$$

in which 446.51 and 553.78 are the molecular weights of pravastatin sodium and pravastatin 1,1,3,3-tetramethylbutylamine, respectively; V is the volume, in mL, of the *Assay preparation;* ~~C is the concentration, in mg per mL, of USP Pravastatin Sodium RS in the *Standard preparation;*~~ C is the concentration, in mg per mL, of pravastatin 1,1,3,3-tetramethylbutylamine in the *Standard preparation;* and r_U and r_S are the responses of the pravastatin peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.■ IS *(USP30)*

BRIEFING

Pravastatin Sodium Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph, based on validated methods of analysis, is being proposed. Because Pravastatin Sodium is highly hygroscopic, USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS is used as a Reference Standard for quantitative applications. The liquid chromatographic procedure in the test for *Related compounds* and in the *Assay* is based on analyses performed with the Spherisorb or Nova-Pak brand of endcapped L1 column. The typical retention time for the pravastatin peak is about 3 to 5 minutes.

(MD-GRE: E. Gonikberg; BPC: M. Marques) RTS—C43516

Add the following:

■Pravastatin Sodium Tablets

» Pravastatin Sodium contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of pravastatin sodium ($C_{23}H_{35}NaO_7$).

Packaging and storage—Preserve in tight containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Pravastatin Related Compound B RS. USP Pravastatin Sodium RS. USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS.*

Identification—

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

B: *Ultraviolet Absorption* ⟨197U⟩—Finely powder a number of Tablets, and extract a portion equivalent to about 10 mg of pravastatin sodium with water. The UV absorption spectrum of a solution of pravastatin sodium in water containing about 10 µg per mL exhibits maxima at the same wavelength as that of a similar solution of USP Pravastatin Sodium RS, concomitantly measured between 220 and 340 nm.

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_{23}H_{35}NaO_7$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 238 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Pravastatin 1,1,3,3-

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Tetramethylbutylamine RS in the same *Medium.* [NOTE—To express the concentration of the Standard solution as pravastatin sodium, use the conversion factor of (446.51/553.78), in which 446.51 and 553.78 are the molecular weights of pravastatin sodium and pravastatin 1,1,3,3-tetramethylbutylamine, respectively.]

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{23}H_{35}NaO_7$ is dissolved in 30 minutes.

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

Related compounds—

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

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.* [NOTE—Use this solution within 24 hours of preparation.]

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatograms for up to 4 times the retention time of the pravastatin peak, identify the impurities listed in *Table 1,* and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of the individual impurity, and r_s is the sum of the responses of all the peaks obtained from the *Test solution.* In addition to not exceeding the limits of each impurity in *Table 1*, not more than 0.2% of any unspecified individual impurity is found, and not more than 3% of total impurities is found. Disregard the peak due to pravastatin related compound B that elutes at the relative retention time of about 0.7 and the peak due to 3″-hydroxypravastatin at the relative retention time of about 0.3 as these impurities are controlled in the drug substance monograph. Disregard any impurity that is less than 0.05%.

Table 1

Name	Relative Retention Time	Limit (%)
Oxidation impurity[1]	0.5	1
Pravastatin sodium	1.0	n/a
Specified unknown impurity 1	1.6	0.2
Specified unknown impurity 2	1.8	0.2
Pravastatin lactone	2.1	2
Specified unknown impurity 3	2.8	0.2
Specified unknown impurity 4	3.2	0.2
Specified unknown impurity 5	3.8	0.2

[1] Sodium (3*R*,5*R*)-3,5-dihydroxy-7-((1*S*,2*S*)-6-hydroxy-2-methyl-1,2-dihydronaphthalen-1-yl)heptanoate.

Assay—[NOTE—The *Standard preparation*, *Assay stock preparation,* and *Assay preparation* can be stored for up to 7 days at room temperature.]

Mobile phase—Prepare a filtered and degassed mixture of methanol, water, glacial acetic acid, and triethylamine (500 : 500 : 1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent 1—Transfer 16.4 g of anhydrous sodium acetate into a 2000-mL volumetric flask. Add 1600 mL of water, adjust with glacial acetic acid to a pH of 5.6, dilute with water to volume, and mix.

Diluent 2—Prepare a mixture of *Diluent 1* and methanol (80 : 20).

Standard preparation—Transfer an accurately weighed quantity of USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS to a suitable volumetric flask, and dissolve in *Diluent 1* using sonication to obtain a solution having a known concentration of about 0.6 mg of pravastatin 1,1,3,3-tetramethylbutylamine per mL. Dilute 5.0 mL of this solution with *Diluent 2* to 25.0 mL, and mix.

Assay stock preparation—Transfer not fewer than 5 Tablets to a suitable volumetric flask with at least a ($NL \times 2$)-mL capacity, N being the number of Tablets transferred, and L

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being the label claim per Tablet, filled to at least 80% capacity with *Diluent 1.* [NOTE—It is necessary to fill the flask to 80% capacity to maintain the correct pH throughout the preparation.] Shake for at least 1 hour, and then sonicate for at least 15 minutes with periodic shaking of the flask by hand, until the Tablets have completely disintegrated. Allow to cool, and then dilute with *Diluent 1* to volume. Centrifuge a portion of the solution for 15 minutes at 2000 rpm, or filter.

Assay preparation—Dilute approximately 5 mL of the *Assay stock preparation* with *Diluent 2* to obtain a solution having an expected concentration of about 0.1 mg per mL, based on the label claim.

Resolution solution—Transfer about 2 mg of USP Pravastatin Related Compound B RS to a 10-mL volumetric flask. Dissolve in and dilute with methanol to volume. Transfer 0.1 mL of this solution and 1.0 mL of the *Standard preparation* to a small tube, and mix. [NOTE—Pravastatin related compound B is the 6′-epipravastatin sodium.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 238-nm detector and a 4.6-mm × 5-cm column than contains endcapped packing L1. Alternatively, a 3.9- × 7.5-cm column containing endcapped packing L1 can be used. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for pravastatin related compound B and 1.0 for pravastatin; the resolution, *R,* between the pravastatin related compound B and the pravastatin peaks is not less than 3.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak response for pravastatin. Calculate the percentage of pravastatin sodium ($C_{23}H_{35}NaO_7$) in the portion of Tablets taken by the formula:

$$100 \times (446.51/553.78)(CVD/NL)(r_U/r_S)$$

in which 100 is the conversion factor to percentage; 446.51 and 553.78 are the molecular weights of pravastatin sodium and pravastatin 1,1,3,3-tetramethylbutylamine, respectively; *C* is the concentration, in mg per mL, of pravastatin 1,1,3,3-tetramethylbutylamine in the *Standard preparation; V* is the volume, in mL, of the *Assay stock preparation; D* is the dilution factor of the *Assay preparation; N* is the number of Tablets taken to prepare the *Assay stock preparation; L* is the label claim, in mg of pravastatin sodium per Tablet; and r_U and r_S are the pravastatin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

BRIEFING

Prednicarbate Cream, page 1655 of *PF* 31(6) [Nov.–Dec. 2005]; **Prednicarbate Ointment,** page 1657 of *PF* 31(6)[Nov.–Dec. 2005]. In the test for *Related compounds* and in the *Assay,* it is proposed (1) to rename the related compound 1,2-dihydroprednicarbate as USP Prednicarbate Related Compound A and (2) to rename the related compounds prednisolone-17-ethylcarbonate and prednisolone-21-propionate as USP Prednicarbate Related Compound B RS and USP Prednicarbate Related Compound C RS, respectively. It is also proposed to simplify the procedure for preparing *Solution 1* in the *Assay.*

(MD-PS: D. Bempong) RTS—C44285

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Add the following:

■Prednicarbate Cream

» Prednicarbate Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of prednicarbate ($C_{27}H_{36}O_8$). It may contain a suitable preservative.

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

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

Identification—The retention time of the prednicarbate peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Consistency—At room temperature, a string of Cream having a length of 2 cm retains its shape on a glass plate for at least 10 minutes. It can be spread easily and has no visible lumps.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The total aerobic bacterial count does not exceed 100 cfu per g.

Minimum fill ⟨755⟩**:** meets the requirements.

pH ⟨791⟩**:** between 3.5 and 5.0, in a solution prepared in the following manner. Add 15 mL of boiling water to 3.5 g of Cream in a 50-mL centrifuge tube, and shake vigorously until an emulsion is formed. Loosen the cap, and place in a steam bath for 5 minutes. Centrifuge the hot solution. After cooling to room temperature, collect the lower aqueous solution in a glass tube, and determine the pH.

Related compounds—

Solution A, Solution B, Mobile phase, Solution 1, Solution 2, and *Resolution solution*—Prepare as directed in the *Assay.*

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

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

System sensitivity solution—Dilute 1.0 mL of the *Standard solution* with dehydrated alcohol to 50.0 mL. Dilute 1.0 mL of the solution thus obtained with *Solution A* to 20.0 mL.

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

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *System sensitivity solution:* the signal-to-noise ratio is not less than 3. ~~Chromatograph the *Test solution,* and record the responses of all the peaks other than the prednicarbate peak, as directed for *Procedure:* the relative retention times are about 0.57 for prednisolone 17-ethylcarbonate, 0.64 for prednisolone 21-propionate, 1.0 for prednicarbate, and 1.04 for 1,2-dihydroprednicarbate.~~ Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.57 for prednicarbate related compound B, 0.64 for prednicarbate related compound C, 1.0 for prednicarbate, and 1.04 for prednicarbate related compound A.

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Procedure—Inject a volume (about 60 µL) of *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound and unknown impurity in the portion of Cream taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each individual impurity obtained from the *Test solution,* and r_s is the sum of the peak responses obtained from the *Test solution:* not more than 2.0% of ~~prednisolone 17-ethylcarbonate and prednisolone 21-propionate~~ prednicarbate related compound B and prednicarbate related compound C is found; not more than 0.1% of any individual related compound is found; and not more than 5.0% of total related compounds is found.

Assay—

Solution A—Prepare a 0.01 M solution of monobasic potassium phosphate in water.

Solution B—Prepare a mixture of acetonitrile and dehydrated alcohol (2 : 1).

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

Standard stock preparation—Dissolve an accurately weighed quantity of USP Prednicarbate RS in dehydrated alcohol, and dilute quantitatively, and stepwise if necessary, with dehydrated alcohol to obtain a solution having a known concentration of 0.3 mg per mL.

Standard preparation—Transfer 10.0 mL of *Standard stock preparation* to a 100-mL volumetric flask, add 15 mL of tetrahydrofuran and 30 mL of *Solution B,* and dilute with *Solution A* to volume.

Assay preparation—Transfer an accurately weighed quantity of Cream, equivalent to about 3.0 mg of prednicarbate, to a 100-mL volumetric flask. Add 15 mL of tetrahydrofuran, shake vigorously, and allow to stand in an ultrasonic bath until the sample has dissolved. Add 20 mL of dehydrated alcohol, and shake vigorously. Add 20 mL of acetonitrile, and shake vigorously. Immediately dilute with *Solution A* to volume, and shake vigorously. Allow to stand in an ice bath for at least 15 minutes. Shake the samples vigorously, and pass through a folded paper filter. Pass the filtrate through a membrane filter of 0.45-µm porosity.

Solution 1—~~Transfer about 15 mg each of prednisolone 17-ethylcarbonate and prednisolone 21-propionate, accurately weighed, to a 50-mL volumetric flask, and dissolve in and dilute with dehydrated alcohol to volume.~~ Prepare a solution containing 0.3 mg per mL each of USP Prednicarbate Related Compound B RS and USP Prednicarbate Related Compound C RS in dehydrated alcohol.

Solution 2—Transfer about 15 mg of ~~1,2-dihydroprednicarbate,~~ USP Prednicarbate Related Compound A RS, accurately weighed, to a 50-mL volumetric flask; add 1.0 mL of *Solution 1,* and dilute with dehydrated alcohol to volume.

Resolution solution—Transfer 10.0 mL of the *Standard preparation* to a volumetric flask; add 1.0 mL of *Solution 2,* 1 mL of tetrahydrofuran, and 2 mL of acetonitrile; and dilute with *Solution A* to 20.0 mL.

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Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 243-nm detector and a 4.0-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	67	33	equilibration
5–45	67→40	33→60	linear gradient
45–50	40	60	isocratic
50–55	40→20	60→80	linear gradient
55–70	20	80	isocratic
70–75	20→67	80→33	linear gradient
75–85	67	33	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between prednicarbate and ~~1,2-dihydroprednicarbate~~ prednicarbate related compound A is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the prednicarbate peak is between 0.7 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 60 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of prednicarbate ($C_{27}H_{36}O_8$) in each g of Cream taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Prednicarbate RS in the *Standard preparation; W* is the weight, in g, of Cream taken; and r_U and r_S are the prednicarbate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

BRIEFING

Prednicarbate Ointment, page 1657 of *PF* 31(6) [Nov.–Dec. 2005]—See briefing under *Prednicarbate Cream.*

(MD-PS: D. Bempong) RTS—C44286

Add the following:

■Prednicarbate Ointment

» Prednicarbate Ointment contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of prednicarbate ($C_{27}H_{36}O_8$), in a suitable ointment base.

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

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

Identification—It meets the requirements of the *Identification* test under *Prednicarbate Cream*.

Consistency—At room temperature, a string of Ointment having a length of 2 cm retains its shape on a glass plate for at least 10 minutes. It can be spread easily and has no visible lumps.

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Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The total aerobic bacterial count does not exceed 100 cfu per g.

Minimum fill ⟨755⟩**:** meets the requirements.

Related compounds—

Solution A, Solution B, Mobile phase, Solution 1, Solution 2, and *Resolution solution*—Prepare as directed for the *Assay* under *Prednicarbate Cream.*

Standard stock solution—Prepare as directed for the *Standard stock preparation* under *Prednicarbate Cream.*

System sensitivity solution—Prepare as directed in the test for *Related compounds* under *Prednicarbate Cream.*

Test solution—Prepare as directed for the *Assay preparation* under *Prednicarbate Cream.*

Chromatographic system—Prepare as directed for the *Assay* under *Prednicarbate Cream.* Chromatograph the ~~*Resolution solution,*~~ *System sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 3. Chromatograph the ~~*Test solution,* and record the responses of all the peaks other than the prednicarbate peak, as directed for *Procedure:* the relative retention times are about 0.57 for prednisolone 17-ethylcarbonate, 0.64 for prednisolone 21-propionate, 1.0 for prednicarbate, and 1.04 for 1,2 dihydroprednicarbate.~~ *Resolution solution,* and record the responses as directed for *Procedure:* the relative retention times are about 0.57 for prednicarbate related compound B, 0.64 for prednicarbate related compound C, 1.0 for prednicarbate, and 1.04 for prednicarbate related compound A.

Procedure—Inject a volume (about 60 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound and unknown impurity in the portion of Ointment taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity obtained from the *Test solution,* and r_s is the sum of all the peak responses obtained from the *Test solution:* not more than 2.0% of ~~prednisolone 17-ethylcarbonate and prednisolone 21-propionate~~ prednicarbate related compound B and prednicarbate related compound C is found; not more than 0.1% of any individual related compound is found; and not more than 5.0% of total related compounds is found.

Assay—

Solution A, Solution B, Mobile phase, Standard stock preparation, Standard preparation, Assay preparation, Solution 1, Solution 2, and *Resolution solution*—Prepare as directed in the *Assay* under *Prednicarbate Cream*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 243-nm detector and a 4.0-mm × 25-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	67	33	equilibration
5–45	67→40	33→60	linear gradient
45–50	40	60	isocratic
50–55	40→20	60→80	linear gradient
55–70	20	80	isocratic
70–75	20→67	80→33	linear gradient
75–85	67	33	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between prednicarbate and ~~1,2 dihydroprednicarbate~~ prednicarbate related compound A is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the prednicarbate peak is between 0.7 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 60 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of prednicarbate ($C_{27}H_{36}O_8$) in each g of Ointment taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Prednicarbate RS in the *Standard preparation; W* is the weight, in g, of Ointment taken; and r_U and r_S are the prednicarbate peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

BRIEFING

Saquinavir Capsules, *USP 29* page 1946. It is proposed to specify the final volume of the *Citrate buffer* in the *Dissolution* test.

(BPC: M. Marques) RTS—C43922

Change to read:

Dissolution ⟨711⟩—

Citrate buffer— ~~Prepare a degassed solution containing 5.82 mg of anhydrous dibasic sodium phosphate and 16.7 mg of citric acid monohydrate in water. Adjust to a pH of 3.0.~~

■Transfer 5.82 g of anhydrous dibasic sodium phosphate and 16.7 g of citric acid monohydrate to a 1-L volumetric flask. Dissolve in and dilute with water to volume. ■1S (*USP30*)

Medium: Citrate buffer; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_{38}H_{50}N_6O_5$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 240 nm on filtered portions of the solution under test, suitably diluted with *Medium,* in comparision with a Standard solution having a known concentration of USP Saquinavir Mesylate RS in the same *Medium*.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{38}H_{50}N_6O_5$ is dissolved in 45 minutes.

BRIEFING

Sodium Fluoride and Phosphoric Acid Topical Solution, *USP 29* page 1982. It is proposed to delete this monograph because it is identical with the monograph for *Sodium Fluoride and Acidulated Phosphate Topical Solution*.

(MD-GRE: E. Gonikberg) RTS—C44451

Delete the following:

■~~Sodium Fluoride and Phosphoric Acid Topical Solution~~

~~» Sodium Fluoride and Phosphoric Acid Topical Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluoride ion.~~

~~**Packaging and storage**— Preserve in tight, plastic containers.~~

~~**Labeling**— Label Topical Solution in terms of the content of sodium fluoride (NaF) and in terms of the content of fluoride ion.~~

~~**USP Reference standards** ⟨11⟩— *USP Sodium Fluoride RS.*~~

~~**pH** ⟨791⟩— Using 40 mL of Topical Solution, proceed as directed in the test for *pH* under *Sodium Fluoride and Phosphoric Acid Gel:* the pH is between 3.0 and 4.5.~~

~~**Residual solvents** ⟨467⟩**:** — meets the requirements.~~

~~(Official January 1, 2007)~~

~~**Other requirements**— It responds to the *Identification* tests under *Sodium Fluoride and Phosphoric Acid Gel.*~~

~~**Assay**— [NOTE—Store all solutions, except *Buffer solution,* in plastic containers.]~~

~~*Buffer solution* and *Standard preparations*— Prepare as directed in the *Assay* under *Sodium Fluoride Oral Solution.*~~

~~*Assay preparation*— Transfer an accurately measured volume of Topical Solution, equivalent to about 20 mg of fluoride ion, to a 1000-mL volumetric flask, add water to dissolve, dilute with water to volume, and mix.~~

~~*Procedure*— Proceed as directed for *Procedure* in the *Assay* under *Sodium Fluoride Oral Solution*. Calculate the quantity, in mg, of fluoride ion in each mL of the Topical Solution taken by the formula:~~

~~C/V~~

~~in which C is the determined concentration of fluoride ion, in µg per mL, in the *Assay preparation;* and V is the volume, in mL, of Topical Solution taken.~~ ■1S (*USP30*)

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BRIEFING

Sodium Salicylate Tablets, *USP 29* page 1991 and page 1116 of *PF* 31(4) [July–Aug. 2005]. It is proposed to correct the wavelength of maximum absorption in the test for *Dissolution.*

(BPC: M. Marques) RTS—C43348

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Sodium Salicylate RS.* ■2S (*USP29*)

Change to read:

Dissolution ⟨711⟩—
Medium: water; 900 mL.
Apparatus 1: 100 rpm.
Time: 45 minutes.
Procedure—Determine the amount of $C_7H_5NaO_3$ dissolved from UV absorbances at the wavelength of maximum absorbance at about ~~266 nm.~~

■230 nm,■1S (*USP30*)
using filtered portions of the solution under test, diluted with water, if necessary, in comparison with a Standard solution having a known concentration of USP Sodium Salicylate RS in the same *Medium*.
Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_7H_5NaO_3$ is dissolved in 45 minutes.

BRIEFING

Vinorelbine Injection, *USP 29* page 2257 and page 3586 of the *First Supplement.* On the basis of comments received, it is proposed to make the following changes:
1. Change the assay percentage limits, shown in the Definition, from "not less than 92.5 percent and not more than 105.0 percent" to "not less than 90.0 percent and not more than 110.0 percent."
2. In the *Assay* section, for clarification, change the formula to ensure that the quantity calculated is vinorelbine, not vinorelbine tartrate.
3. In the *Assay* section, change the concentration of the *Standard preparation* from vinorelbine to vinorelbine tartrate.

In the absence of significant adverse comment, it is proposed to implement this revision via the *Fifth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of October 1, 2006.

(MD-OOD: F. Mao) RTS—C44125; C44257

Change to read:

» Vinorelbine Injection is a sterile solution of Vinorelbine Tartrate in Water for Injection. It contains not less than ~~92.5~~

•90.0•5
percent and not more than ~~105.0~~

•110.0•5
percent of the labeled amount of vinorelbine ($C_{45}H_{54}N_4O_8$).
Caution—Handle Vinorelbine Injection with great care, because it is a potent cytotoxic agent.

Change to read:

■**Assay—**
Phosphate buffer, Mobile phase, and *System suitability solution*—Proceed as directed in the test for *Related compounds* under *Vinorelbine Tartrate*.
Standard preparation—Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in water to obtain a solution having a known concentration of about ~~0.10 mg of vinorelbine (base)~~

•0.14 mg•5
per mL.
Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 10 mg of vinorelbine, to a 100-mL volumetric flask, dilute with water to volume, and mix.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a diode-array detector and a 3.9-mm × 15-cm column that contains packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for the photodegradation product, 1.0 for vinorelbine, and about 1.2 for vinorelbine related compound A; and the relative retention, α, between vinorelbine tartrate and vinorelbine related compound A is not less than 1.1.
Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the vinorelbine peaks, using a diode array detector. Calculate the quantity, in mg, of vinorelbine ($C_{45}H_{54}N_4O_8$) in each mL of the Injection taken by the formula:

~~$C(L/D)(r_u/r_s)$,~~

•$(778.93/1079.11)C(L/D)(r_u/r_s)$

in which 778.93 and 1079.11 are the molecular weights of vinorelbine and vinorelbine tartrate, respectively;•5
C is the concentration, in mg per mL, of USP Vinorelbine Tartrate RS in the *Standard preparation; L* is the labeled quantity, in mg, of vinorelbine in each mL of Injection taken; D is the concentration, in mg per mL, of vinorelbine in the *Assay preparation;* and r_U and r_S are the peak responses at 267 nm obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

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DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Methylsulfonylmethane; Methylsulfonylmethane Tablets. Because there are no existing *USP* monographs for these dietary supplements, new monographs, based on validated methods of analysis, are being proposed. The gas chromatographic procedures in the test for *Chromatographic purity and limit of dimethyl sulfoxide* and in the *Assay* are based on analyses performed with the Zebron ZB-1 brand of G2 column. The typical retention time for the methylsulfonylmethane peak is about 4.4 minutes.

(DSN: L. Evans; MSA: R. Tirumalai) RTS—C44099

Add the following:

■Methylsulfonylmethane

$C_2H_6O_2S$ 94.13

Dimethyl sulfone

Sulfonylbismethane [*67-71-0*].

» Methylsulfonylmethane contains not less than 98.0 percent and not more than 102.0 percent of $C_2H_6O_2S$, calculated on the anhydrous basis. The chromatographic purity is not less than 99.8%.

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩**—***USP Methylsulfonylmethane RS. USP Dimethyl Sulfoxide RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Melting range ⟨741⟩: between 108.5° and 110.5°.

Microbial enumeration ⟨2021⟩**—**It meets the requirements of the tests for absence of *Escherichia coli* in 10 g. The total aerobic microbial count does not exceed 1000 cfu per g or mL, and the total combined molds and yeasts count does not exceed 100 cfu per g or mL.

Water, *Method I* ⟨921⟩**:** not more than 0.1%.

Heavy metals, *Method I* ⟨231⟩**:** 3 µg per g.

Chromatographic purity and limit of dimethyl sulfoxide—

Standard stock solution—Dissolve an accurately weighed quantity of USP Dimethyl Sulfoxide RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 1.0 mg of USP Dimethyl Sulfoxide RS per mL.

Sensitivity check solution—Dilute the *Standard stock solution* with methanol to obtain a solution having a concentration of 0.001 mg per mL.

System suitability solution—In a 50-mL volumetric flask, dissolve 20 mg of USP Methylsulfonylmethane RS in 5 mL of the *Standard stock solution,* dilute with methanol to volume, and mix to obtain a solution having a known concentration of about 0.1 mg of USP Dimethyl Sulfoxide RS per mL and 0.4 mg of USP Methylsulfonylmethane RS per mL.

Test solution—Transfer about 100 mg of methylsulfonylmethane, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Sonicate at 50° for 1 minute, allow to cool to room temperature, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m capillary column coated with 5-µm phase G2. The column temperature is maintained at 120°. Helium is used as the carrier gas, flowing at a rate of 30 mL per minute. The split ratio is 20 : 1. The injection port temperature is maintained at 250°, and the detector temperature is maintained at 250°. Chromatograph the *Sensitivity check solution:* the dimethyl sulfoxide peak

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height to the noise height ratio is not less than 10, noise height being determined by a suitable procedure. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between dimethyl sulfoxide and methylsulfonylmethane is not less than 2.0.

Procedure—Inject a volume (about 1 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Methylsulfonylmethane taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the response of each individual impurity in the chromatogram of the *Test solution;* and r_s is the sum of the responses of all of the peaks other than the solvent peak: not more than 0.1% of dimethyl sulfoxide is found; not more than 0.05% of any other individual impurity is found; and the sum of all impurities, including dimethyl sulfoxide, is not more than 0.2%.

Assay—

Diluent—Transfer about 950 mL of methanol to a 1-L volumetric flask. Add 0.60 mL of di(ethylene glycol) methyl ether, and dilute with methanol to volume.

Standard preparation—Dissolve an accurately weighed quantity of USP Methylsulfonylmethane RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.4 mg per mL. Sonicate at 50° for 1 minute, allow to cool to room temperature, and mix.

Assay preparation—Transfer about 40 mg of Methylsulfonylmethane, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix. Sonicate at 50° for 1 minute, allow to cool to room temperature, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m capillary column coated with 5-µm phase G2. The column temperature is maintained at 120°. Helium is used as the carrier gas, flowing at a rate of 30 mL per minute. The split ratio is 20 : 1. The injection port temperature is maintained at 250°, and the detector is maintained at 250°. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_2H_6O_2S$ in the portion of Methylsulfonylmethane taken by the formula:

$$100C(R_U / R_S)$$

in which C is the concentration, in mg per mL, of USP Methylsulfonylmethane RS in the *Standard preparation;* and R_U and R_S are the peak response ratios of methylsulfonylmethane to di(ethylene glycol) methyl ether obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

BRIEFING

Methylsulfonylmethane Tablets—See briefing under *Methylsulfonylmethane.*

(DSN: L. Evans; DS-BA: D. Cairatti) RTS—C44099

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Add the following:

■Methylsulfonylmethane Tablets

» Methylsulfonylmethane Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of methylsulfonylmethane ($C_2H_6O_2S$).

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

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

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Disintegration and dissolution ⟨2040⟩**:** meet the requirements for *Disintegration* only; 30 minutes.

Weight variation ⟨2091⟩**:** meet the requirements.

Assay—

Diluent, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Methylsulfonylmethane*.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Dissolve an accurately weighed portion of the finely powdered material, equivalent to about 1 Tablet, in *Diluent,* mix, and sonicate for 15 minutes at 50°. Allow to cool to room temperature, dilute with *Diluent* to volume, and mix. Quantitatively dilute with *Diluent* to obtain a final concentration of 0.4 mg of methylsulfonylmethane per mL. Transfer about 1 mL of the suspension to a 1.5-mL microcentrifuge tube, and centrifuge for 20 seconds. Use the supernatant.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of methylsulfonylmethane ($C_2H_6O_2S$) in the portion of Tablets taken by the formula:

$$DC(R_U / R_S)$$

in which D is the dilution factor; C is the concentration, in mg per mL, of USP Methylsulfonylmethane RS in the *Standard preparation;* and R_U and R_S are the peak response ratios of methylsulfonylmethane to di(ethylene glycol) methyl ether obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

MONOGRAPHS (NF)

BRIEFING

Polyisobutylene, *NF 24* page 3399. On the basis of comments received, it is proposed to revise the specification limit in the test for *Loss on drying* from 0.1% to 0.3%. This limit is representative of marketed products and consistent with the official limit for *Volatiles* in the Polyisobutylene monograph in the *Food Chemicals Codex, Fifth Edition,* page 344.

(EM2: H. Wang) RTS—C44344

Change to read:

Loss on drying ⟨731⟩—Dry a 5-g sample for 2 hours at 105°: it loses not more than ~~0.1%~~

■0.3%■1S (*NF25*)
of its weight.

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**11**〉 **USP Reference Standards,** *USP 29* page 2458, page 3591 of the *First Supplement,* page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], page 1154 of *PF* 31(4) [July–Aug. 2005], page 1433 of *PF* 31(5) [Sept.–Oct. 2005], page 1680 of *PF* 31(6) [Nov.–Dec. 2005], page 181 of *PF* 32(1) [Jan.–Feb. 2006], and page 407 of *PF* 32(2) [Mar.–Apr. 2006].

(HDQ) RTS—C44072; C44099; C44144; C44285; C43516

Add the following:

■**USP Amlodipine Besylate RS.**■1S (*USP30*)

Add the following:

■**USP Methylsulfonylmethane RS—[**dimethyl sulfone**]** ($C_2H_6O_2S$) ✧ 94.13.■1S (*USP30*)

Change to read:

▲~~**USP Paroxetine Hydrochloride for System Suitability RS**~~

■**USP Paroxetine System Suitability Mixture A RS**■2S (*USP29*) —Mixture of approximately 1% paroxetine related compound A **[**piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-methoxyphenyl)-, hydrochloride (3 *S-trans*); and 1% of paroxetine related compound B [piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-phenyl)-, hydrochloride (3 *S-trans*)]**]** in a matrix of paroxetine hydrochloride.▲*USP29*

Change to read:

USP Phenylethyl Alcohol RS

■($C_8H_{10}O$ ✧ 122.17).■2S (*USP29*)
~~Do not dry. After opening ampul, store in a tightly closed container.~~

■■1S (*USP30*)

Add the following:

■**USP Pravastatin Related Compound A RS** ~~**[**6α-hydroxyisocompactin sodium**]**~~ **[**3-α-hydroxyisocompactin**]** or **[**sodium (3*R,*5*R*)-3,5-dihydroxy-7-[(1*S,*2*S,*~~6*S,*~~ 3*S,*8*S,*8a*R*)-3-hydroxy-2-methyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,3,7,8,8a-hexahydronaphthalen-1-yl]heptanoate**]** ($C_{23}H_{35}NaO_7$ ✧ 446.51).■1S (*USP30*)

Add the following:

■**USP Pravastatin Related Compound B RS [**6′-epi-pravastatin**]** or **[**sodium (3*R,*5*R*)-3,5-dihydroxy-7-[(1*S,*2*S,*6*R,*8*S,* 8a*R*)-6-hydroxy-2-methyl-8-[[(2*S*)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]heptanoate**]** ($C_{23}H_{35}NaO_7$ ✧ 446.51).■1S (*USP30*)

Add the following:

■**USP Pravastatin 1,1,3,3-Tetramethylbutylamine RS.**■1S (*USP30*)

Add the following:

■**USP Prednicarbate Related Compound B RS [**prednisolone-17-ethylcarbonate**]**—[To come.]■1S (*USP30*)

Add the following:

■**USP Prednicarbate Related Compound C RS [**prednisolone-21-propionate**]**—[To come.]■1S (*USP30*)

Physical Tests and Determinations

BRIEFING

⟨**611**⟩ **Alcohol Determination,** *USP 29* page 2637 and page 823 of *PF* 31(3) [May–June 2005]. On the basis of comments received, it is proposed that the injection volume for *Method IIb* can be increased up to 0.5 µL. The new *Method IIb* was validated using a DB-624 brand of G43 column, manufactured by J&W Scientific. Manufacturers interested in incorporating *Method IIb* in compendial monographs are encouraged to submit appropriate requests for revision with supporting documentation.

(GC: H. Pappa) RTS—C43216

Change to read:

METHOD II—GAS ~~LIQUID~~

■■2S (*USP29*)

CHROMATOGRAPHIC METHOD

~~Method II is to be used where~~

■Use *Method IIa* when *Method II* is■2S (*USP29*) specified in the individual monograph. For a discussion of the principles upon which it is based, see *Gas Chromatography* under *Chromatography* ⟨621⟩.

USP Reference Standards—*USP Alcohol Determination—Acetonitrile RS. USP Alcohol Determination—Alcohol RS.*

▪Method IIa■2S (*USP29*)

Apparatus—Under typical conditions, use a gas chromatograph equipped with a flame-ionization detector and a 4-mm × 1.8-m glass column packed with 100- to 120-mesh chromatographic column packing support S3, using nitrogen or helium as the carrier. Prior to use, condition the column overnight at 235° with a slow flow of carrier gas. The column temperature is maintained at 120°, and the injection port and detector temperatures are maintained at 210°. Adjust the carrier flow and temperature so that acetonitrile, the internal standard, elutes in 5 to 10 minutes.

Solutions—

Test Stock Preparation—Dilute the specimen under examination stepwise with water to obtain a solution containing approximately 2% (v/v) of alcohol.

Test Preparation—Pipet 5 mL each of the *Test Stock Preparation* and the USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution] into a 50-mL volumetric flask, dilute with water to volume, and mix.

Standard Preparation—Pipet 5 mL each of the USP Alcohol Determination—Alcohol RS and the USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution] into a 50-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Inject about 5 µL each of the *Test Preparation* and the *Standard Preparation,* in duplicate, into the gas chromatograph, record the chromatograms, and determine the peak response ratios. Calculate the percentage of alcohol (v/v) in the specimen under test according to the formula:

$$CD(R_U / R_S)$$

in which C is the labeled concentration of USP Alcohol Determination—Alcohol RS; D is the dilution factor (the ratio of the volume of the *Test Stock Preparation* to the volume of the specimen taken); and R_U and R_S are the peak response ratios obtained from the *Test Preparation* and the *Standard Preparation,* respectively.

System Suitability Test—In a suitable chromatogram, the resolution factor, R, is not less than 2; the tailing factor of the alcohol peak is not greater than 2.0; and six replicate injections of the *Standard Preparation* show a relative standard deviation of not more than 2.0% in the ratio of the peak of alcohol to the peak of the internal standard.

▪Method IIb

Apparatus—The gas chromatograph is equipped with a split injection port with a split ratio of 5 : 1, a flame-ionization detector, and a 0.53-mm × 30-m capillary column coated with a 3.0-µm film of phase G43. Helium is used as the carrier gas at a linear velocity of 34.0 cm per second. The chromatograph is programmed to maintain the column temperature at 50° for 5 minutes, then to increase the temperature at a rate of 10° per minute to 200°, and hold at this temperature for 4 minutes. The injection port temperature is maintained at 210° and the detector temperature at 280°.

Solutions—

Test Stock Preparation—Dilute the specimen under examination stepwise with water to obtain a solution containing approximately 2% (v/v) of alcohol.

Test Preparation—Pipet 5 mL each of the *Test Stock Preparation* and the USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution] into a 25-mL volumetric flask, dilute with water to volume, and mix.

Standard Preparation—Pipet 5 mL each of the USP Alcohol Determination—Alcohol RS and the USP Alcohol Determination—Acetonitrile RS [NOTE—Alternatively, a 2% aqueous solution of acetonitrile of suitable quality may be used as the internal standard solution] into a 25-mL volumetric flask, dilute with water to volume, and mix.

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Procedure—Inject about 0.2 ■to 0.5■1S *(USP30)* µL each of the *Test Preparation* and the *Standard Preparation,* in duplicate, into the gas chromatograph, record the chromatograms, and determine the peak response ratios. Calculate the percentage of alcohol (v/v) in the specimen under test according to the formula:

$$CD(R_U / R_S)$$

in which C is the labeled concentration of USP Alcohol Determination—Alcohol RS; D is the dilution factor (the ratio of the volume of the *Test Stock Preparation* to the volume of the specimen taken); and R_U and R_S are the peak response ratios obtained from the *Test Preparation* and the *Standard Preparation,* respectively.

System Suitability Test—In a suitable chromatogram, the resolution factor, *R,* between alcohol and the internal standard is not less than 4; the tailing factor of the alcohol peak is not greater than 2.0; and six replicate injections of the *Standard Preparation* show a relative standard deviation of not more than 4.0% in the ratio of the peak of alcohol to the peak of the internal standard.■2S *(USP29)*

BRIEFING

〈**621**〉 **Chromatography,** *USP 29* page 2639, page 3595 of the *First Supplement,* page 265 of the *Second Interim Revision Announcement* pertaining to *USP 29–NF 24,* and page 825 of *PF* 31(3) [May–June 2005]. In the *Chromatographic Reagents* section it is proposed to expand the particle size ranges for the designations L1, L7, and L11. Proposed changes are being made in designation L60. Also, some new column designations are being added.

(BPC: M. Marques) RTS—C44586

Change to read:

SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the ▲detection sensitivity,▲*USP29* ●(Postponed indefinitely)●2 resolution, and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.

▲The detection sensitivity is a measure used to ensure the suitability of a given chromatographic procedure for the complete detection of the impurities in the *Chromatographic purity* or *Related compounds* tests by injecting a volume of a quantitation limit solution equal to that of the *Test solution*. Unless otherwise specified in the individual monograph, the quantitation limit solution may be prepared by dissolving the drug substance Reference Standard in the same solvent as that used for the *Test solution* at a 0.05% concentration level relative to the amount of drug substance in the *Test solution* for drug substances, and a 0.1% level relative to the amount of drug substance in the *Test solution* for drug products. The signal-to-noise ratio for the drug substance peak obtained with the quantitation limit solution should be not less than 10.▲*USP29* ●(Postponed indefinitely)●2

The resolution, *R,* [NOTE—All terms and symbols are defined in the *Glossary of Symbols*] is a function of column efficiency, *N,* and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

Replicate injections of a standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, S_R, if the requirement is 2.0% or less; data from six replicate injections are used if the relative standard deviation requirement is more than 2.0%.

The tailing factor, *T,* a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see *Figure 2*). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.

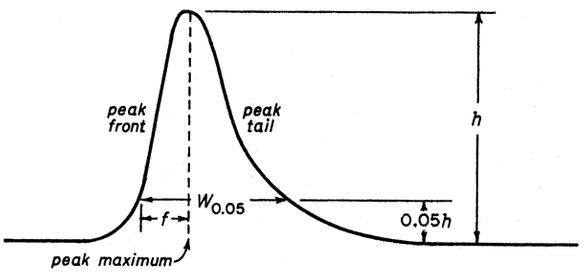

Figure 2. Asymmetrical chromatographic peak

These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see *Procedures* under *Tests and Assays* in the *General Notices*). ~~Adjustments of operating conditions to meet system suitability requirements may be necessary.~~

■If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum ~~specification~~ variation that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when ~~Reference Standards~~ suitable standards (including Reference Standards) are available for all ~~analytes~~ compounds used in the suitability test and only when those

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standards are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure or to circumvent replacing a deteriorated column. ~~The changes described below may require additional validation data unless the user can verify the suitability of the method under the new conditions. This verification consists of assessing the analytical performance characteristics that can be affected by the change (e.g., specificity, linearity, precision, accuracy) to ensure the adequacy of the method. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.~~ The changes described below may require additional validation data. The user should verify the suitability of the method under the new conditions by assessing the relevant analytical performance characteristics potentially affected by the change. *Tables 1* and *2* in the general information chapter *Verification of Compendial Procedures* ⟨1226⟩ provide lists of analytical performance validation characteristics that may require assessment. Multiple adjustments can have a cumulative effect in the performance of the system and should be considered carefully before implementation.

pH of Mobile Phase (HPLC)—The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within ~~0.2~~ ±0.2 units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within ±10%, provided the permitted pH variation (see above) is met.

Ratio of Components in Mobile Phase (HPLC)—~~The amount of the minor~~ The following adjustment limits apply to minor components of the mobile phase (specified at 50% or less). The amount(s) of these component(s) can be adjusted by ±30% relative. ~~or ±2% absolute (i.e., in relation to the total mobile phase), whichever is larger.~~ However, the change in any component cannot exceed ±10% absolute (i.e., in relation to the total mobile phase), nor can the final concentration of any component be reduced to zero. Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.

Binary Mixtures—

SPECIFIED RATIO OF 50 : 50—Thirty percent of 50 is 15% absolute, but this exceeds the maximum permitted change of ±10% absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of 40 : 60 to 60 : 40.

~~SPECIFIED RATIO OF 95 : 5 Thirty percent of 5 is 1.5% absolute. However, because adjustments up to ±2% absolute are allowed, the ratio may be adjusted within the range of 93 : 7 to 97 : 3.~~

SPECIFIED RATIO OF 2 : 98—Thirty percent of 2 is 0.6% absolute. ~~In this case an absolute adjustment of ±2% is not allowed because it would reduce the amount of the first component to zero.~~ Therefore the maximum allowed adjustment is within the range of 1.4 : 98.6 to 2.6 : 97.4.

Ternary Mixtures—

SPECIFIED RATIO OF 60 : 35 : 5—For the second component, 30% of 35 is 10.5% absolute, which exceeds the maximum permitted change of ±10% absolute in any component. Therefore the second component may be adjusted only within the range of 25% to 45% absolute. For the third component, 30% of 5 is 1.5% absolute. ~~Since ±2% absolute is permitted and provides more flexibility, the third component may be adjusted within the range of 3% to 7% absolute.~~ In all cases, a sufficient quantity of the first component is used to give a total of 100%. Therefore, mixture ranges of 50 : 45 : 5 to 70 : 25 : 5 or ~~58 : 35 : 7 to 62 : 35 : 3~~ 58.5 : 35 : 6.5 to 61.5 : 35 : 3.5 would meet the requirement.

~~Detector~~ Wavelength of UV-Visible Detector (HPLC)—Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, ±3 nm.

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Column Length (GC, HPLC): can be adjusted by as much as ~~70%.~~ ±70%.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as ~~±25% 50%.~~ ±25% for HPLC and ±50% for GC.

Film Thickness (Capillary GC): can be adjusted by as much as –50% to 100%.

Particle Size (HPLC): can be reduced by as much as 50%.

Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as ±50%.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. ~~It may be increased to as much as twice the volume specified, provided there are no adverse effects on factors such as baseline, peak shapes, resolution, linearity, and retention times.~~

Column Temperature (HPLC): can be adjusted by as much as ~~±20°.~~ ±10°. Column thermostating is recommended to improve control and reproducibility of retention time.

~~**Column**~~ **Oven Temperature (GC):** can be adjusted by as much as ~~±2%, in terms of absolute temperature.~~ ±10%.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to ±20% is permitted.

~~**Gradient Elution (HPLC)** The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions described in the method. Should this occur, it may be due to excess dwell time, which is the volume between the point at which the two eluants meet and the top of the column.~~ ■2S (*USP29*)

Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.

■Relative retention times may be provided in monographs for informational purposes only, to aid in peak identification. There are no acceptance criteria applied to relative retention times.■2S (*USP29*)

To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals. The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails

■system suitability■2S (*USP29*)
requirements are unacceptable.

Change to read:

CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE—Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

Packings

L1—Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, ~~3~~

■1.5■1S (*USP30*)
to 10 µm in diameter, ■or a monolithic silica rod.■1S (*USP29*)

L2—Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to 50 µm in diameter.

L3—Porous silica particles, 5 to 10 µm in diameter.

L4—Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L5—Alumina of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L6—Strong cation-exchange packing–sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to 50 µm in diameter.

L7—Octylsilane chemically bonded to totally porous silica particles, ~~3~~

■1.5■1S (*USP30*)
to 10 µm in diameter.

L8—An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, 3 to 10 µm in diameter.

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L9—■ ■1S (*USP29*) Irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating, ■3 to 10 µm in diameter.■1S (*USP29*)

L10—Nitrile groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L11—Phenyl groups chemically bonded to porous silica particles, ~~5~~

■1.5■1S (*USP30*)
to 10 µm in diameter.

L12—A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to 50 µm in diameter.

L13—Trimethylsilane chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L14—Silica gel having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating, 5 to 10 µm in diameter.

L15—Hexylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L16—Dimethylsilane chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L17—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to 11 µm in diameter.

L18—Amino and cyano groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L19—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about 9 µm in diameter.

L20—Dihydroxypropane groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L21—A rigid, spherical styrene-divinylbenzene copolymer, 5 to 10 µm in diameter.

L22—A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about 10 µm in size.

L23—An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about 10 µm in size.

L24—A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to 63 µm in diameter.

■[NOTE—Available as YMC-Pack PVA-SIL manufactured by YMC Co., Ltd. and distributed by Waters Corp. (www.waters.com).]■1S (*USP29*)

L25—Packing having the capacity to separate compounds with a molecular weight range from 100–5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26—Butyl silane chemically bonded to totally porous silica particles, ■3■1S (*USP29*) to 10 µm in diameter.

L27—Porous silica particles, 30 to 50 µm in diameter.

L28—A multifunctional support, which consists of a high purity, 100 Å, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.

L29—Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, 5 µm in diameter with a pore volume of 80 Å.

L30—Ethyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L31—A ■hydroxide-selective,■1S (*USP29*) strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of 8.5-µm macroporous particles having a pore size of 2000 Å and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene.

L32—A chiral ligand-exchange packing–L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to 10 µm in diameter.

L33—Packing having the capacity to separate dextrans by molecular size over a range of 4000 to 500,000 Da. It is spherical, silica-based, and processed to provide pH stability.

■[NOTE—Available as TSKgel G4000 SWXL from Tosoh Biosep (www.tosohbiosep.com).]■1S (*USP29*)

L34—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about 9 µm in diameter.

L35—A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of 150 Å.

L36—A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to 5-µm aminopropyl silica.

L37—Packing having the capacity to separate proteins by molecular size over a range of 2,000 to 40,000 Da. It is a polymethacrylate gel.

L38—A methacrylate-based size-exclusion packing for water-soluble samples.

L39—A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40—Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to 20 µm in diameter.

L41—Immobilized α_1-acid glycoprotein on spherical silica particles, 5 µm in diameter.

L42—Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, 5 µm in diameter.

L43—Pentafluorophenyl groups chemically bonded to silica particles by a propyl spacer, 5 to 10 µm in diameter.

L44—A multifunctional support, which consists of a high purity, 60 Å, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45—Beta cyclodextrin bonded to porous silica particles, 5 to 10 µm in diameter.

L46—Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, about 10 µm in diameter.

L47—High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.

■[NOTE—Available as CarboPac MA1 and distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

L48—Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, 15 µm in diameter.

L49—A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to 10 µm in diameter.

■[NOTE—Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.]■1S (*USP29*)

L50—Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm in diameter, and a surface area not less than 350 m^2 per g. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene.

■[NOTE—Available as OmniPac PAX-500 and distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to 10 µm in diameter.

■[NOTE—Available as Chiralpak AD from Chiral Technologies, Inc., (www.chiraltech.com).]■1S (*USP29*)

L52—A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.

■[NOTE—Available as TSK IC SW Cation from Tosoh Biosep (www.tosohbiosep.com).]■1S (*USP29*)

L53—Weak cation-exchange resin consisting of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than 500 µEq/column.

■[NOTE—Available as IonPac CS14 distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter.

■[NOTE—Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).]■1S (*USP29*)

L55—A strong cation-exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.

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■[NOTE—Available as IC-Pak C M/D from Waters Corp. (www.waters.com).]■1S *(USP29)*

L56—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

■[NOTE—Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem).]■1S *(USP29)*

L57—A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about 5 µm in diameter, with a pore size of 120 Å.

■[NOTE—Available as Ultron ES-OVM from Agilent Technologies (www.agilent.com/chem).]■1S *(USP29)*

L58—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.

■[NOTE—Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143) www.bio-rad.com.]■1S *(USP29)*

L59—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa. It is spherical (10 µm), silica-based, and processed to provide hydrophilic characteristics and pH stability.

■[NOTE—Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively) (www.tosohbiosep.com).]■1S *(USP29)*

L60—Spherical, porous silica gel, ~~3 or 5 µm~~

■10 µm or less■1S *(USP30)*
in diameter, the surface of which has been covalently modified with ~~palmitamidopropyl~~

■alkyl amide■1S *(USP30)*
groups and endcapped.

■[NOTE—Available as Supelcosil ABZ from Supelco (http://www.sigmaaldrich.com/Brands/Supelco_Home.html).]■1S *(USP29)*

L61—A hydroxide selective strong anion-exchange resin consisting of a highly cross-linked core of 13 µm microporous particles having a pore size less than 10 Å units and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene with a latex coating composed of 85 nm diameter microbeads bonded with alkanol quaternary ammonium ions (6%).

■[NOTE—Available as Ion Pac AS-11 and AG-11 from Dionex (www.dionex.com).]■1S *(USP29)*

L62—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter.

~~L## (Enoxaparin Sodium, Dowex 1X8)—[To come.]~~

~~L## (Enoxaparin Sodium, Dowex 50WX2)—[To come.]~~

■L## (Dalteparin Sodium, anion-exchange Dowex 1X8)—[To come.]

L## (Dalteparin Sodium, cation-exchange Dowex 50WX2)—[To come.]■2S *(USP29)*

■L## (Glucosamine, Shodex NH2P-50)—Polyamine chemically bonded to cross-linked polyvinyl alcohol polymer, 5 µm in diameter.

[NOTE—Available as Shodex NH2P-50 from Shodex (www.shodex.com).]

L## [Valganciclovir Hydrochloride, Crownpak CR(+)]—A crown ether coated on a 5-µm particle size silica gel substrate. The active site is *(S)*-18-crown-6-ether.

[NOTE—Available as Crownpak CR(+) from Daicel (www.daicel.com).]

L## (Trehalose, Sugar KS-801)—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, 6 to 17 µm in diameter.

[NOTE—Available as Sugar KS-801 from Shodex (www.shodex.com).]

L## (Levalbuterol, Chirobiotic T)—Glycopeptide teicoplanin linked through multiple covalent bonds to a 100-Å units spherical silica.

[NOTE—Available as Chirobiotic T from Astec (www.astecusa.com).]■1S *(USP30)*

Phases

G1—Dimethylpolysiloxane oil.
G2—Dimethylpolysiloxane gum.
G3—50% Phenyl-50% methylpolysiloxane.
G4—Diethylene glycol succinate polyester.
G5—3-Cyanopropylpolysiloxane.
G6—Trifluoropropylmethylpolysiloxane.
G7—50% 3-Cyanopropyl-50% phenylmethylsilicone.
G8—80% Bis(3-cyanopropyl)-20% 3-cyanopropylphenylpolysiloxane (percentages refer to molar substitution).
G9—Methylvinylpolysiloxane.
G10—Polyamide formed by reacting a C_{36} dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00 : 0.90 : 0.20.
G11—Bis(2-ethylhexyl) sebacate polyester.
G12—Phenyldiethanolamine succinate polyester.
G13—Sorbitol.
G14—Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15—Polyethylene glycol (av. mol. wt. of 3000 to 3700).
G16—Polyethylene glycol compound (av. mol. wt. about 15,000). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.
G17—75% Phenyl-25% methylpolysiloxane.
G18—Polyalkylene glycol.
G19—25% Phenyl-25% cyanopropyl-50% methylsilicone.
G20—Polyethylene glycol (av. mol. wt. of 380 to 420).
G21—Neopentyl glycol succinate.
G22—Bis(2-ethylhexyl) phthalate.
G23—Polyethylene glycol adipate.
G24—Diisodecyl phthalate.
G25—Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. ■[NOTE—Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.]■1S *(USP29)*
G26—25% 2-Cyanoethyl-75% methylpolysiloxane.
G27—5% Phenyl-95% methylpolysiloxane.
G28—25% Phenyl-75% methylpolysiloxane.
G29—3,3′-Thiodipropionitrile.
G30—Tetraethylene glycol dimethyl ether.
G31—Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30.
G32—20% Phenylmethyl-80% dimethylpolysiloxane.
G33—20% Carborane-80% methylsilicone.

G34—Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35—A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.

G36—1% Vinyl-5% phenylmethylpolysiloxane.

G37—Polyimide.

G38—Phase G1 containing a small percentage of a tailing inhibitor.

■[NOTE—A suitable grade is available commercially as "SP2100/0.1% Carbowax 1500" from Supelco, Inc. (http://www.sigmaaldrich.com/Brands/Supelco_Home.html).]■1S (*USP29*)

G39—Polyethylene glycol (av. mol. wt. about 1500).

G40—Ethylene glycol adipate.

G41—Phenylmethyldimethylsilicone (10% phenyl-substituted).

G42—35% phenyl-65% dimethylpolysiloxane (percentages refer to molar substitution).

G43—6% cyanopropylphenyl-94% dimethylpolysiloxane (percentages refer to molar substitution).

G44—2% low molecular weight petrolatum hydrocarbon grease and 1% solution of potassium hydroxide.

G45—Divinylbenzene-ethylene glycol-dimethylacrylate.

G46—14% Cyanopropylphenyl-86% methylpolysiloxane.

G47—Polyethylene glycol (av. mol. wt. of about 8000).

G48—Highly polar, partially cross-linked cyanopolysiloxane.■■1S (*USP29*)

Supports

NOTE—Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.

S1A—Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with Na_2CO_3 flux and calcining above 900°. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane ■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*) to mask surface silanol groups.

S1AB—The siliceous earth as described above is both acid- and base-washed. ■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*)

S1C—A support prepared from crushed firebrick and calcined or burned with a clay binder above 900° with subsequent acid-wash. It may be silanized.

S1NS—The siliceous earth is untreated.

S2—Styrene-divinylbenzene copolymer having a nominal surface area of less than 50 m^2 per g and an average pore diameter of 0.3 to 0.4 µm.

S3—Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to 600 m^2 per g and an average pore diameter of 0.0075 µm.

S4—Styrene-divinylbenzene copolymer with aromatic –O and –N groups, having a nominal surface area of 400 to 600 m^2 per g and an average pore diameter of 0.0076 µm.

S5—40- to 60-mesh, high-molecular weight tetrafluorethylene polymer.

S6—Styrene-divinylbenzene copolymer having a nominal surface area of 250 to 350 m^2 per g and an average pore diameter of 0.0091 µm.

S7—Graphitized carbon having a nominal surface area of 12 m^2 per g.

S8—Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9—A porous polymer based on 2,6-diphenyl-*p*-phenylene oxide.

S10—A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11—Graphitized carbon having a nominal surface area of 100 m^2 per g modified with small amounts of petrolatum and polyethylene glycol compound. ■[NOTE—Commercially available as SP1500 on Carbopack B from Supelco (www.sigmaaldrich.com/Brands/Supelco_Home.html).]■1S (*USP29*)

S12—Graphitized carbon having a nominal surface area of 100 m^2 per g.

BRIEFING

〈**730**〉 **Plasma Spectrochemistry,** *USP 29* page 2700. On the basis of comments received, a revision of this chapter is proposed, as written by the Expert Committee for General Chapters. Tables listing primary- and secondary-analysis wavelengths have not been included in this proposal because instrument manufacturers provide analytical wavelength information that is specific to, and most applicable to, each spectrometer design.

(GC: K. Zaidi) RTS—C42042

Change to read:

〈730〉 PLASMA SPECTROCHEMISTRY

~~Plasma-based instrumental techniques that are useful for pharmaceutical analyses fall into two major categories: those based on inductively coupled plasma, and those where a plasma is generated on the surface of the sample. Inductively coupled plasma (ICP) is a high-temperature excitation source that desolvates, vaporizes, atomizes, excites, and ionizes atoms. The excited analyte ions and atoms are subsequently detected by any of a variety of plasma based spectrochemical means, including inductively coupled plasma–atomic emission spectroscopy (ICP–AES), also known as inductively coupled plasma–optical emission spectroscopy (ICP–OES) and inductively coupled plasma–mass spectrometry (ICP–MS). ICP–AES and ICP–MS may be used for either single- or multi-element analysis and provide good general-purpose procedures for either sequential or simultaneous analyses over an extended linear range with good sensitivity.~~

~~An emerging technique in plasma spectrochemistry is laser-induced breakdown spectroscopy (LIBS). In LIBS, a solid, liquid, or gas sample is heated directly by a pulsed laser, and brought to a transient high-energy plasma state where the sample components are reduced to atoms, molecular fragments, and larger clusters. Emissions from the atoms and ions in the sample are collected, typically using fiber optics, and measured using an array detector such as a charge-coupled device (CCD). LIBS can be used for qualitative analysis or against a working standard curve for quantitative analysis. While LIBS is not currently in wide use by the pharmaceutical industry, LIBS is suited for at-line or on-line measurements in a production setting as well as in the laboratory. Because of its potential, it should be considered a viable technique for plasma spectrochemistry in the pharmaceutical laboratory. However, because LIBS is still an emerging technique, details will not be further discussed in this general chapter.~~

~~SAMPLE PREPARATION~~

~~Sample preparation is critical to the success of plasma-based analysis, and it is the first step in performing any analysis via ICP–AES or ICP–MS. Plasma-based techniques are heavily dependent on sample transport into the plasma, and because ICP–AES and ICP–MS share the same sample introduction system, the means by which samples are prepared may be applicable to either technique. The most conventional means by which samples are introduced into the plasma is via solution nebulization. If solution nebulization is employed, solid samples must be dissolved in order to be presented into the plasma for analysis. Samples may be dissolved in any appropriate solvent. There is a strong preference for the use of aqueous or dilute nitric acid solutions, due to minimal interferences with these solvents, when compared to other solvent choices. Hydrogen peroxide, hydrochloric acid, sulfuric acid, perchloric acid, combinations of acids, or various concentrations of acids may all be used to dissolve the sample for~~

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analysis. Dilute hydrofluoric acid may also be used, but great care must be taken to ensure the safety of the analyst, as well as to protect the equipment when using this acid. Additionally, alternative means of dissolving the sample may be employed. These include, but are not limited to, the use of dilute bases, straight or diluted organic solvents, combinations of acids or bases, or combinations of organic solvents.

When analyzing samples that are presented to the plasma via solution nebulization, it is important to consider the potential interferences that may arise from the solvent used. In all cases, when samples are to be analyzed using ICP–MS, use an appropriate internal standard. In cases where sample viscosity differs from the standard viscosity, matrix matching or an appropriate internal standard should also be used for ICP–AES analysis. In either event, the selection of an appropriate internal standard should consider the analyte in question, ionization energy, wavelengths or masses, and the nature of the sample matrix.

Where a sample is not found to be soluble in any acceptable solvent, a variety of digestion techniques may be employed. These include hot-plate digestion, or microwave assisted digestions, including open-vessel and closed-vessel digestions. The decision regarding the type of digestion technique to use is dependent on the nature of the sample being digested, as well as on the analytes of interest. Because some metals are volatile (e.g., mercury and selenium), open-vessel or hot-plate digestions are not appropriate for all analytes.

Use acids, bases, and hydrogen peroxide of ultra high purity. Deionized water must be at least 18 megohm. Check diluents for interferences prior to their use in an analysis. Because it is not always possible to obtain organic solvents that are free of metals, use organic solvents of the highest quality possible with regard to metal contaminants.

SAMPLE INTRODUCTION

There are two ways to introduce the sample into the nebulizer: by using a peristaltic pump or by self-aspiration. The peristaltic pump is used to ensure that the flow rate of sample and standard solution to the nebulizer is the same irrespective of sample viscosity. In some cases, self-aspiration can be used, where a peristaltic pump is not required.

A wide variety of nebulizer types is available, including pneumatic (concentric and cross-flow), grid, and ultrasonic nebulizers. Micronebulizers, high efficiency nebulizers, direct injection high efficiency nebulizers, and flow injection nebulizers are also available. The selection of the nebulizer for a given analysis should consider the sample matrix, analyte, and sensitivity desired. Some nebulizers are better suited for use with solutions containing a high concentration of dissolved solids, while others are better suited for use with organic solutions.

Once a sample leaves the nebulizer, it enters the spray chamber, which is designed to permit only the smallest droplets of sample into the plasma. The spray chamber functions to remove the larger sample droplets generated during the nebulization process, and as a result, typically only 1% to 2% of the sample aerosol reaches the ICP. As with nebulizers, there is more than one type of spray chamber available for use with ICP–AES or ICP–MS. Examples include the Scott double pass spray chamber, as well as cyclonic spray chambers of various configurations. The spray chamber must be compatible with the sample and solvent and must equilibrate and washout in as short a time as possible. When selecting a spray chamber, the nature of the sample matrix, the desired sensitivity, and the analyte should be considered.

In addition to solution nebulization, it is possible to perform analyses using solid samples via laser ablation (LA). In such instances, the sample directly enters the torch. LA–ICP and LA–ICP–MS are better suited for qualitative analyses of pharmaceutical compounds, due to the difficulty in obtaining appropriate standards. Nonetheless, quantitative analyses may be performed if it can be demonstrated that the standards used are adequate. This must be demonstrated through appropriate method validation.

STANDARD PREPARATION

Single- or multi-element standard solutions, whose concentrations are traceable to primary reference standards, such as those of the National Institute of Standards and Technology (NIST), may be purchased for use in the preparation of working standard solutions. Alternatively, standard solutions of elements may be accurately prepared from standard materials and their concentration determined independently, as appropriate. Where possible, standards, blanks, and sample solutions should be matrix matched to minimize matrix interference. In cases where matrix matching is not possible, an appropriate internal standard or the method of standard additions should be used for ICP–AES. Standards and blank solutions to be used for ICP–MS analysis should always contain an appropriate internal standard. In either event, the selection of an appropriate internal standard should consider the analyte in question, their ionization energies, their wavelengths or masses, and the nature of the sample matrix.

ICP

The components that make up the ICP excitation source include the argon gas supply, torch, radio frequency (RF) induction coil, and RF generator. Argon gas is typically used in ICP, although other gases may also be used, depending on the instrumentation available. The use of gases other than argon is not common practice. The plasma torch consists of three concentric quartz tubes designated the inner, the intermediate, and the outer tube. The nebulizer gas flow helps to create a fine aerosol of the sample solution, and the sample is then carried through the inner tube of the torch and into the plasma. The intermediate tube carries the auxiliary gas. The auxiliary gas flow helps to lift the plasma off of the inner and intermediate tubes to prevent melting and the deposition of carbon and salts on the inner tube. The outer tube carries the plasma or coolant gas, which is used to form and sustain the plasma. The tangential flow of the coolant gas through the torch constricts the plasma and prevents the ICP from expanding to fill the outer tube, preventing the torch from melting. An RF induction coil, also called the load coil, surrounds the torch and produces an oscillating magnetic field which, in turn, sets up an oscillating current in the ions and electrons of the argon. In the load coil of the RF generator, the energy transfer between the coil and the argon creates a self-sustaining plasma. Collisions of the ions and electrons of the argon ionize and excite the analyte atoms in the high-temperature plasma. The plasma operates at temperatures of 6,000 to 10,000 K, such that essentially all covalent bonds and analyte-to-analyte interactions have been eliminated.

ICP–AES

An inductively coupled plasma may utilize either an optical or a mass spectral detection system. In the former case, ICP–AES, analyte detection is dependent on the emission wavelength of the analyte in question. Due to differences in technology, a wide variety of ICP–AES systems are available, each with different capabilities, as well as different advantages and disadvantages. Simultaneous systems are capable of analyzing multiple elements at the same time, thereby shortening analysis time. Sequential systems move from one wavelength to the next to perform analyses, and usually provide a larger number of analytical lines to choose from. Charge coupled devices and charge injection devices, with detectors on a chip, make it possible to combine the advantages of both simultaneous and sequential systems, providing the rapid analysis of the simultaneous units with a wider selection of analytical lines as found with sequential units.

In addition, the ICP can be oriented in either axial or radial (also called lateral) configurations. The torch is positioned horizontally in axial plasmas, and the sample is viewed "end-on"; while it is positioned vertically in radial plasmas, and the sample is viewed from the side. Axial viewing of the plasma can provide a more sensitive signal response; however, in some situations where background or sample interference is significant at the wavelength of interest, radial viewing may yield more reliable results. Because of the wide range of elemental concentrations in some real-world samples and because of complex matrix problems, there are many cases where radial is better than axial or vice versa. Methods validated using an instrument with a radial configuration may not be completely transferable to an instrument with an axial configuration, and vice versa.

Additionally, dual-view instrument systems are available, making it possible for the analyst to take advantage of either torch configuration. The selection of torch configuration is dependent on the sample

matrix, analyte in question, analytical wavelength used, cost of instrumentation, required sensitivity, and type of instrumentation available in a given laboratory.

Regardless of torch configuration or detector technology, ICP–AES is a technique which provides a quantitative measurement of the optical emission from excited atoms or ions at specific wavelengths. These measurements are then used to determine the analyte concentration in a given sample. Upon excitation, an atom emits an array of different frequencies of light that is characteristic of the distinct energy transition allowed for that element. The intensity of the light is generally proportional to the analyte concentration. It is necessary to correct for the background signal from the plasma. Sample concentration measurements are usually determined from a working curve of known standards in the concentration range of interest. It is, however, also possible to perform a single-point calibration under certain circumstances, such as with limit tests.

Since there are distinct transitions between atomic energy levels, emission lines have narrow bandwidths. Spectral separation of multiple emission lines requires a high-resolution spectrometer. The decision regarding which spectral line to measure should include an evaluation of potential spectral interferences. All atoms in a sample are excited simultaneously, however, so samples containing multiple elements can lead to spectral overlap. Spectral interference can also be caused by background emission from the sample or plasma. Modern ICP's usually have background correction available and a number of background correction techniques may be applied. Simple background correction typically involves measuring the background emission intensity at some point away from the main peak and subtracting this value from the total signal being measured. Mathematical modeling to subtract the interfering signal as a background correction may also be performed.

The selection of the analytical line is critical to the success of an analysis, regardless of torch configuration or detector type. Though some wavelengths are most often considered to be the primary analytical wavelengths, because there can be a tremendous variety of sample matrices, the selection of the analytical wavelength must be considered in the context of the sample matrix, the composition of the sample itself, the type of instrument being used, and the sensitivity required. Analysts might first choose to start with the wavelengths recommended by the manufacturer of their particular instrument and select alternate wavelengths based on manufacturer recommendations or published wavelength tables.

Forward power, gas flow rates, and torch position may all be optimized to provide the best signal. When organic solvents are used, it is often necessary to use a higher forward power setting than would be used for aqueous solutions, as well as a reduction in the nebulizer gas flow. When using organic solvents, it may also be necessary to bleed small amounts of oxygen into the torch to prevent carbon build-up in the torch.

Calibration

The wavelength accuracy for ICP–AES detection must comply with the manufacturer's applicable operating procedures. The instrument must be standardized for quantification at time of use. Due to the inherent differences between the types of instruments available, there is no general "system suitability" procedure that may be employed. Tests recommended by the instrument manufacturer for a given ICP–AES instrument should be followed. These may include, but are not limited to, use of a multi-element wavelength calibration using a reference solution, internal mercury (Hg) calibration, and peak search. Perform system checks in accordance with the manufacturer's recommendations.

Because ICP–AES is a technique that is generally considered to be linear over a range of 10^6 to 10^8 orders of magnitude, it is not always necessary to continually demonstrate linearity by the use of a standard curve. It is possible to calibrate with a blank and a single standard once a method has been developed and is in routine use. For new methods, it is advisable that suitable linearity be demonstrated throughout the range of test measurements to be performed. An appropriate blank solution and standards that bracket the expected range of the sample concentrations should be assayed and the detector response plotted as a function of analyte concentration. However, it may not always be possible to analyze a bracketing standard when an analysis is performed at or near the detection limit. This is acceptable. The number and concentration of standard solutions used should be based on the analyte in question, the desired sensitivity, and the sample matrix. Use regression analysis of the standard plot to evaluate the linearity of detector response, and individual monographs may require criteria for the residual error of the regression line. Optimally, a correlation coefficient of not less than 0.99, or as indicated in the individual monograph, should be demonstrated for the working standard curve. Here, too, however, the nature of the sample matrix, the analyte(s), the desired sensitivity, and the type of instrumentation available may dictate a poorer correlation coefficient than 0.99. The analyst should use caution when proceeding with such an analysis, and should use additional working standards.

To demonstrate the stability of the system over the analysis time since initial standardization, a solution used in the initial standard curve must be reassayed as a check standard at appropriate intervals throughout the analysis of the sample set. Appropriate intervals may be as deemed adequate by the analyst, based on the analysis being performed. The reassayed standard should agree with its theoretical value to within ±10% for single-element analyses when analytical wavelengths are between 200 and 500 nm, or concentrations are > 1 µg per mL. The reassayed standard should agree with its theoretical value to within ±20% for multi-element analyses, when analytical wavelengths are < 200 nm or > 500 nm, or at concentrations < 1 µg per mL. In cases where an individual monograph provides different guidance regarding the reassayed check standard, the requirements of the monograph take precedence.

Procedure

Follow the procedure as directed in the individual monograph for the instrumental parameters. Due to differences in manufacturers' equipment configurations, the manufacturer's suggested default conditions may be used and modified as needed. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions, and adjustments of operating conditions may be necessary. Alternate conditions must be supported by suitable validation data, and the conditions in the monograph will take precedence for official purposes. Data collected from a single sample introduction are treated as a single result. This result may be the average of data collected from replicate sequential readings from a single solution introduction of the appropriate standard or sample preparations. Sample concentrations are calculated versus the working standard curve generated by plotting the detector response versus the concentration of the analyte in the standard preparations. This calculation is normally performed by the instrument.

The method of standard additions or internal standards may be employed for situations where matrix interferences would result in an inaccurate analyte determination. The method of standard additions involves adding a known concentration of the analyte element to the sample at several concentration levels. The instrument response is plotted against the concentration of the added analyte element, and a linear regression line is drawn through the data points. The absolute value of the *x* intercept multiplied by any dilution factor is the concentration of the analyte in the sample.

ICP–MS

When an inductively coupled plasma utilizes a mass spectral detection system, the technique is referred to as inductively coupled plasma–mass spectrometry (ICP–MS). In this technique, analyte detection is dependent on the masses of the various elemental components of a sample. ICP–MS is an elemental technique, whereby, due to the heat intensity of the plasma source, a sample is, theoretically, reduced to its ionic components. As is the case with ICP–AES, due to differences in technology, a wide variety of ICP–MS instrumentation systems are available.

The systems most commonly in use are quadrupole-based systems. Gaining in interest is time-of-flight ICP–MS. Although still not in widespread use, this approach may see greater use in the future. Additionally, high-resolution instruments are also available.

Regardless of instrument design or configuration, ICP–MS is a technique that provides a quantitative measurement of the components of the sample. Ions are generated from the analyte atoms by the plasma. The analyte ions are then extracted from the plasma using

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the sampling cone. The skimmer cone, located behind the sampling cone "skims" the ions as they emerge from the sampling cone, where they are then passed into the mass spectrometer. The mass spectrometer separates the ions in a magnetic field according to their mass-to-charge *(m/z)* ratios. The ICP–MS has a mass range up to 240 atomic mass units (amu). Depending on the equipment configuration, sample adducts with diluents or their decomposition products, oxides, and multiply charged element ions produced within the plasma may increase the complexity of the resulting mass spectra. Interferences can be minimized by appropriate optimization of operational parameters, including gas flow (nebulizer, plasma, and auxiliary gas flow rates), sample flow, RF power, extraction lens voltage, etc., or through the use of collision or reaction cells, or cool plasma operation, if available on a given instrument. Unless a laboratory is generating or examining isotopes that are not naturally occurring, a list of naturally occurring isotopes will provide the analyst with acceptable isotopes for analytical purposes. Additionally, tables of commonly found interferences and polyatomic isobaric interferences and correction factors may be used.

ICP–MS is generally more sensitive than ICP–AES. The ability of a mass spectrometer to monitor a single ion of a specific mass/charge ratio is a major advantage of ICP–MS for determination of very low analyte concentrations or when elimination of matrix inferences is required. Analytes can often be detected at the parts per trillion (ppt) level using ICP–MS.

The selection of the analytical mass to use is critical to the success of an analysis, regardless of instrument design. Though some masses are often considered to be the primary analytical masses, because there can be a tremendous variety of sample matrices, the recommendation of a specific mass for a given element is not possible. Selection of an analytical mass is always considered in the context of the sample matrix, the type of instrument being used, and the sensitivity required. Analysts might first choose to start with masses recommended by the manufacturer of their particular instrument and select alternate masses based on manufacturer's recommendations or published tables of naturally occurring isotopes.

Optimization of an ICP–MS method is also highly dependent on the plasma parameters and means of sample introduction. Forward power, gas flow rates, and torch position may all be optimized to provide the best signal. When organic solvents are used, it is often necessary to use a higher forward power setting than would be used for aqueous solutions and to reduce the nebulizer flow rate. Additionally, when using organic solvents, it may be necessary to titrate small amounts of oxygen into the auxiliary gas to prevent carbon build-up in the torch. The use of a platinum tipped sampling or skimmer cone may also be required to reduce cone degradation with some organic solvents.

Calibration

The mass spectral accuracy for ICP–MS detection must be in accordance with the applicable operating procedures. The instrument must be standardized for quantification at time of use. Due to the inherent differences between the types of instruments available, there is no general "system suitability" procedure that may be employed. Analysts should refer to the tests recommended by the instrument manufacturer for a given ICP–MS instrument. These may include, but are not limited to, tuning on a reference mass or masses, peak search, and mass calibration. Perform system checks recommended by the instrument manufacturer.

Because ICP–MS is a technique that is generally considered to be linear over a range of 10^6 to 10^8 orders of magnitude, it is not always necessary to continually demonstrate linearity by the use of a standard curve. It is common practice to calibrate with a blank and a single standard, once a method has been developed and is in routine use. For new methods, it is advisable that suitable linearity be demonstrated through the range of test measurements to be performed. An appropriate blank solution and standards that bracket the expected range of the sample concentrations should be assayed and the detector response plotted as a function of analyte concentration. The number and concentration of standard solutions used should be based on the analyte in question, the desired sensitivity, and the sample matrix, and should be left to the discretion of the analyst. Optimally, a correlation coefficient of not less than 0.99, or as indicated in the individual monograph, should be demonstrated for the working standard curve. Here, too, however, the nature of the sample matrix, the analyte, the desired sensitivity, and the type of instrumentation available may dictate a poorer correlation coefficient than 0.99. The analyst should use caution when proceeding with such an analysis and should use additional working standards.

To demonstrate the stability of the system over the analysis time since initial standardization, a solution used in the initial standard curve must be reassayed as a check standard at appropriate intervals through the analysis of the sample set. Appropriate intervals may be established as after every fifth or tenth sample, or as deemed adequate by the analyst, based on the analysis being performed. The reassayed standard should agree with its theoretical value to within $\pm 10\%$ for single element analyses when analytical masses are free of interferences and when concentrations are > 1 ng per mL. The reassayed standard should agree with its theoretical value to within $\pm 20\%$ for multi-elemental analyses, or when concentrations are < 1 ng per mL. In cases where an individual monograph provides different guidance regarding the reassayed check standard, the requirements of the monograph take precedence.

Procedure

Follow the procedure as directed in the individual monograph for the detection mode and instrument parameters. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions, and adjustments of operating conditions may be necessary. Alternate conditions must be supported by suitable validation data, and the conditions in the monograph will take precedence for official purposes. Due to differences in manufacturers' equipment configurations, the analyst may wish to begin with the manufacturer's suggested default conditions and modify them as needed. Data collected from a single sample introduction are treated as a single result. Data collected from replicate sequential readings from a single solution introduction of the appropriate standard or sample preparations should be averaged as a single result. Sample concentrations are calculated versus the working standard curve generated by plotting the detector response versus the concentration of the analyte in the standard preparations. With modern instruments, this calculation is normally performed by the instrument. Data collected from two or three sequential readings from a single solution introduction of the appropriate standard or sample preparations are averaged as a single result. Sample concentrations are calculated versus the working standard curve generated by plotting the detector response versus the concentration of the analyte in the standard preparations. With modern instruments, this calculation is performed by the instrument.

The method of standard additions may be employed for situations where matrix interferences would result in an inaccurate analyte determination. This method involves adding a known concentration of the analyte element to the sample at several concentration levels. The instrument response is plotted against the concentration of the added analyte element and a linear regression line is drawn through the data points. The absolute value of the x intercept multiplied by any dilution factor is the concentration of the analyte in the sample.

GLOSSARY

AUXILIARY GAS: The auxiliary gas is used to "lift" the plasma off of the surface of the torch, thereby preventing melting of the intermediate tube and the formation of carbon and salt deposits on the inner tube.

AXIAL VIEWING: A configuration of the plasma for AES where the plasma is directed toward the spectrometer optical path, also called "end-on."

COLLISION CELL: A design feature on ICP–MS instruments. Collision cells are used to eliminate or minimize interferences from argon and facilitate the analysis of elements that might be affected by those interferences.

COOLANT OR PLASMA GAS: The coolant gas is the main gas supply for the plasma.

~~COOL PLASMA: Plasma conditions used for ICP–MS that result in a plasma that is cooler than normally used for an analysis. This is achieved by using a lower forward power setting and is used to help minimize isotopic interferences caused by argon.~~

~~FORWARD POWER: The number of watts used to ignite and sustain the plasma during an analysis. Forward power requirements may vary, depending on sample matrix and analyte.~~

~~INTERNAL STANDARD: An element in an analysis added to or present in the same concentration in blanks, standards, and samples to act as an intensity reference for the analysis. An internal standard may be used for ICP–AES work and should always be used for quantitative ICP–MS analyses.~~

~~LATERAL VIEWING: See also *Radial Viewing*.~~

~~*m*: The ion mass of interest.~~

~~MULTIPLY CHARGED IONS: Atoms that, when subjected to high ionization energies, can form doubly or triply charged ions (X^{++} or X^{+++}, etc.) such that when detected by MS, the apparent mass will be ½ or $\frac{1}{3}$ that of the atomic mass.~~

~~NEBULIZER: Used to form a consistent sample aerosol that mixes with the argon gas.~~

~~NEBULIZER GAS: One of three regions of argon gas flow in a torch. The nebulizer gas is used to help create a fine mist of the sample when using solution nebulization. This fine mist is then directed through the center tube of the torch and into the plasma.~~

~~PLASMA GAS: See also *Coolant Gas*.~~

~~RADIAL VIEWING: A configuration of the plasma for AES where the plasma is directed orthogonal to the spectrometer optic path, also called "side-on viewing." See also *Lateral Viewing*.~~

~~REACTION CELL: Similar to collision cell. Designed to reduce or eliminate interferences.~~

~~SAMPLING CONE: A metal cone (usually nickel, aluminum, or platinum tipped) with a small opening, through which ionized sample flows after leaving the plasma.~~

~~SEQUENTIAL: A type of detector configuration for AES where discrete emission lines are observed by scanning across the spectral range using a monochromator.~~

~~SIMULTANEOUS: A type of detector configuration for AES where all selected emission lines are observed at the same time, using a polychromator, offering increased analysis speed for multi-element samples.~~

~~SKIMMER CONE: A metal cone, with an opening that is smaller than that of the sampling cone, through which ionized sample flows after leaving the sampling cone and prior to entering the vacuum region of an ICP–MS.~~

~~STANDARD ADDITIONS: A method used to determine the actual analyte concentration in a sample when viscosity effects may cause erroneous results.~~

~~TORCH: A series of three concentric quartz tubes in which the ICP is formed.~~

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■Plasma-based instrumental techniques that are useful for pharmaceutical analyses fall into two major categories: those based on the inductively coupled plasma, and those where a plasma is generated at or near on the surface of the sample. An inductively coupled plasma (ICP) is a high-temperature excitation source that desolvates, vaporizes, and atomizes aerosol samples and ionizes the resulting atoms. The excited analyte ions and atoms can then subsequently be detected by observing their emission lines, a method termed inductively coupled plasma–atomic emission spectroscopy (ICP–AES), also known as inductively coupled plasma–optical emission spectroscopy (ICP–OES); or the excited or ground state ions can be determined by a technique known as inductively coupled plasma–mass spectrometry (ICP–MS). ICP–AES and ICP–MS may be used for either single- or multi-element analysis, and they provide good general-purpose procedures for either sequential or simultaneous analyses over an extended linear range with good sensitivity.

An emerging technique in plasma spectrochemistry is laser-induced breakdown spectroscopy (LIBS). In LIBS, a solid, liquid, or gaseous sample is heated directly by a pulsed laser, or indirectly by a plasma generated by the laser. As a result, the sample is volatilized at the laser beam contact point, and the volatilized constituents are reduced to atoms, molecular fragments, and larger clusters in the plasma that forms at or just above the surface of the sample. Emission from the atoms and ions in the sample is collected, typically using fiber optics or a remote viewing system, and measured using an array detector such as a charge-coupled device (CCD). LIBS can be used for qualitative analysis or against a working standard curve for quantitative analysis. Although LIBS is not currently in wide use by the pharmaceutical industry, it might be suited for at-line or on-line measurements in a production setting as well as in the laboratory. Because of its potential, it should be considered a viable technique for plasma spectrochemistry in the pharmaceutical laboratory. However, because LIBS is still an emerging technique, details will not be further discussed in this general chapter.[1]

SAMPLE PREPARATION

Sample preparation is critical to the success of plasma-based analysis and is the first step in performing any analysis via ICP–AES or ICP–MS. Plasma-based techniques are heavily dependent on sample transport into the plasma, and because ICP–AES and ICP–MS share the same sample introduction system, the means by which samples are prepared may be ap-

[1] Yueh F-Y, Singh JP, Zhang H. Laser-induced breakdown spectroscopy, elemental analysis. In: *Encyclopedia of Analytical Chemistry: Instrumentation and Applications.* New York: Wiley; 2000:2066–2087.

plicable to either technique. The most conventional means by which samples are introduced into the plasma is via solution nebulization. If solution nebulization is employed, solid samples must be dissolved in order to be presented into the plasma for analysis. Samples may be dissolved in any appropriate solvent. There is a strong preference for the use of aqueous or dilute nitric acid solutions, because there are minimal interferences with these solvents compared to other solvent choices. Hydrogen peroxide, hydrochloric acid, sulfuric acid, perchloric acid, combinations of acids, or various concentrations of acids can all be used to dissolve the sample for analysis. Dilute hydrofluoric acid may also be used, but great care must be taken to ensure the safety of the analyst, as well as to protect the quartz sample introduction equipment when using this acid; specifically, the nebulizer, spray chamber, and inner torch tube should be manufactured from hydrofluoric acid-tolerant materials. Additionally, alternative means of dissolving the sample can be employed. These include, but are not limited to, the use of dilute bases, straight or diluted organic solvents, combinations of acids or bases, and combinations of organic solvents.

When samples are introduced into the plasma via solution nebulization, it is important to consider the potential matrix effects and interferences that might arise from the solvent. The use of an appropriate internal standard and/or matching the standard matrix with samples should be applied for ICP–AES and ICP–MS analyses in cases where accuracy and precision are not adequate. In either event, the selection of an appropriate internal standard should consider the analyte in question, ionization energy, wavelengths or masses, and the nature of the sample matrix.

Where a sample is found to be soluble in any acceptable solvent, a variety of digestion techniques can be employed. These include hot-plate digestion and microwave-assisted digestions, including open-vessel and closed-vessel approaches. The decision regarding the type of digestion technique to use depends on the nature of the sample being digested, as well as on the analytes of interest.

Open-vessel digestion is generally not recommended for the analysis of volatile metals, e.g., selenium and mercury. The suitability of a digestion technique, whether open-vessel or closed-vessel, should be supported by spike recovery experiments in order to verify that, within an acceptable tolerance, volatile metals have not been lost during sample preparation. Use acids, bases, and hydrogen peroxide of ultra-high purity, especially when ICP–MS is employed. Deionized water must be at least 18 megohm. Check diluents for interferences before they are used in an analysis. Because it is not always possible to obtain organic solvents that are free of metals, use organic solvents of the highest quality possible with regard to metal contaminants.

It is important to consider the selection of the type, material of construction, pretreatment, and cleaning of analytical labware used in ICP–AES and ICP–MS analyses. The material must be inert and, depending on the specific application, resistant to caustics, acids, and/or organic solvents. For some analyses, diligence must be exercised to prevent the adsorption of analytes onto the surface of a vessel, particularly in ultra-trace analyses. Contamination of the sample solutions from metal and ions present in the container can also lead to inaccurate results.

The use of labware that is not certified to meet Class A tolerances for volumetric flasks is acceptable if the linearity, accuracy, and precision of the method have been experimentally demonstrated to be suitable for the purpose at hand.

SAMPLE INTRODUCTION

There are two ways to introduce the sample into the nebulizer: by a peristaltic pump and by self-aspiration. The peristaltic pump is preferred and serves to ensure that the flow rate of sample and standard solution to the nebulizer is the same irrespective of sample viscosity. In some cases, where a peristaltic pump is not required, self-aspiration can be used.

A wide variety of nebulizer types is available, including pneumatic (concentric and cross-flow), grid, and ultrasonic nebulizers. Micronebulizers, high-efficiency nebulizers, di-

rect-injection high-efficiency nebulizers, and flow-injection nebulizers are also available. The selection of the nebulizer for a given analysis should consider the sample matrix, analyte, and desired sensitivity. Some nebulizers are better suited for use with viscous solutions or those containing a high concentration of dissolved solids, whereas others are better suited for use with organic solutions.

Note that the self-aspiration of a fluid is due to the Bernoulli, or Venturi, effect. Not all types of nebulizers will support self-aspiration. The use of a concentric nebulizer, for example, is required for self-aspiration of a solution.

Once a sample leaves the nebulizer as an aerosol, it enters the spray chamber, which is designed to permit only the smallest droplets of sample solution into the plasma. The spray chamber functions to prevent larger sample from entering the plasma; as a result, typically only 1% to 2% of the sample aerosol reaches the ICP, although some special-purpose nebulizers have been designed that permit virtually all of the sample aerosol to enter the ICP. As with nebulizers, there is more than one type of spray chamber available for use with ICP–AES or ICP–MS. Examples include the Scott double-pass spray chamber, as well as cyclonic spray chambers of various configurations. The spray chamber must be compatible with the sample and solvent and must equilibrate and wash out in as short a time as possible. When a spray chamber is selected, the nature of the sample matrix, the nebulizer, the desired sensitivity, and the analyte should all be considered.

Gas and liquid chromatography systems can be interfaced with ICP–AES and ICP–MS for molecular speciation, ionic speciation, or other modes of separation chemistry, based on elemental emission or mass spectrometry.

Ultimately, the selection of sample introduction hardware should be demonstrated experimentally to provide sufficient specificity, sensitivity, linearity, accuracy, and precision of the analysis at hand.

In addition to solution nebulization, it is possible to analyze solid samples directly via laser ablation (LA). In such instances, the sample enters the torch as a solid aerosol. LA–ICP–AES and LA–ICP–MS are better suited for qualitative analyses of pharmaceutical compounds because of the difficulty in obtaining appropriate standards. Nonetheless, quantitative analyses can be performed if it can be demonstrated through appropriate method validation that the available standards are adequate.[2]

STANDARD PREPARATION

Single- or multi-element standard solutions, whose concentrations are traceable to primary reference standards, such as those of the National Institute of Standards and Technology (NIST), can be purchased for use in the preparation of working standard solutions. Alternatively, standard solutions of elements can be accurately prepared from standard materials and their concentrations, determined independently, as appropriate. Working standard solutions, especially those used for ultra-trace analyses, may have limited shelf life. As a general rule, working standard solutions should be retained for no more than 24 hours unless stability is demonstrated experimentally. The selection of the standard matrix is of fundamental importance in the preparation of element standard solutions. Spike recovery experiments should be conducted with specific sample matrices in order to determine the accuracy of the method. If sample matrix effects cause excessive inaccuracies, standards, blanks, and sample solutions should be matrix matched, if possible, in order to minimize matrix interferences.

In cases where matrix matching is not possible, an appropriate internal standard or the method of standard additions should be used for ICP–AES or ICP–MS. Internal standards can also be introduced through a T connector into the sample uptake tubing. In any event, the selection of an appropriate internal standard should consider the analytes in question, their ionization and excitation energies, their chemical behavior, their wavelengths or masses, and the nature of the sample ma-

[2] For additional information on laser ablation, see Russo R, Mao X, Borisov O, Liu H. Laser ablation in atomic spectrometry. In: *Encyclopedia of Analytical Chemistry: Instrumentation and Applications.* New York: Wiley; 2000.

trix. Ultimately, the selection of an internal standard should be demonstrated experimentally to provide sufficient specificity, sensitivity, linearity, accuracy, and precision of the analysis at hand.

The method of standard additions involves adding a known concentration of the analyte element to the sample at no fewer than two concentration levels plus an unspiked sample preparation. The instrument response is plotted against the concentration of the added analyte element, and a linear regression line is drawn through the data points. The absolute value of the *x*-intercept multiplied by any dilution factor is the concentration of the analyte in the sample.

The presence of dissolved carbon at concentrations of a small percentage in aqueous solutions enhances ionization of selenium and arsenic in an inductively coupled argon plasma. This phenomenon frequently results in a positive bias for ICP–AES and ICP–MS selenium and arsenic quantification measurements, which can be remedied by using the method of standard additions or by adding a small percentage of carbon, such as analytically pure glacial acetic acid, to the linearity standards.

ICP

The components that make up the ICP excitation source include the argon gas supply, torch, radio frequency (RF) induction coil, impedance-matching unit, and RF generator. Argon gas is almost universally used in an ICP. The plasma torch consists of three concentric tubes designated as the inner, the intermediate, and the outer tube. The intermediate and outer tubes are almost universally made of quartz. The inner tube can be made of quartz or alumina if the analysis is conducted with solutions containing hydrofluoric acid. The nebulizer gas flow carries the aerosol of the sample solution into and through the inner tube of the torch and into the plasma. The intermediate tube carries the intermediate (sometimes referred to as the auxiliary) gas. The intermediate gas flow helps to lift the plasma off the inner and intermediate tubes to prevent their melting and the deposition of carbon and salts on the inner tube. The outer tube carries the outer (sometimes referred to as the plasma or coolant) gas, which is used to form and sustain the toroidal plasma. The tangential flow of the coolant gas through the torch constricts the plasma and prevents the ICP from expanding to fill the outer tube, keeping the torch from melting. An RF induction coil, also called the load coil, surrounds the torch and produces an oscillating magnetic field, which in turn sets up an oscillating current in the ions and electrons produced from the argon. The impedance-matching unit serves to couple the RF energy from the generator efficiently to the load coil. The unit can be of either the active or the passive type. An active matching unit adjusts the impedance of the RF power by means of a capacitive network, whereas the passive type adjusts the impedance directly through the generator circuitry. Within the load coil of the RF generator, the energy transfer between the coil and the argon creates a self-sustaining plasma. Collisions of the ions and electrons liberated from the argon ionize and excite the analyte atoms in the high-temperature plasma. The plasma operates at temperatures of 6,000 to 10,000 K, so most covalent bonds and analyte-to-analyte interactions have been eliminated.

ICP–AES

An inductively coupled plasma can use either an optical or a mass spectral detection system. In the former case, ICP–AES, analyte detection is achieved at an emission wavelength of the analyte in question. Because of differences in technology, a wide variety of ICP–AES systems are available, each with different capabilities, as well as different advantages and disadvantages. Simultaneous-detection systems are capable of analyzing multiple elements at the same time, thereby shortening analysis time and improving background detection and

correction. Sequential systems move from one wavelength to the next to perform analyses, and often provide a larger number of analytical lines from which to choose. Array detectors, including charge-coupled devices and charge-injection devices, with detectors on a chip, make it possible to combine the advantages of both simultaneous and sequential systems. These types of detection devices are used in the most powerful spectrometers, providing rapid analysis and a wide selection of analytical lines.

The ICP can be viewed in either axial or radial (also called lateral) mode. The torch is usually positioned horizontally in axially viewed plasmas and is viewed end on, whereas it is positioned vertically in radially viewed plasmas and is viewed from the side. Axial viewing of the plasma can provide higher signal-to-noise ratios (better detection limits and precision); however, it also incurs greater matrix and spectral interferences. Methods validated on an instrument with a radial configuration will probably not be completely transferable to an instrument with an axial configuration, and vice versa.

Additionally, dual-view instrument systems are available, making it possible for the analyst to take advantage of either torch configuration. The selection of the optimal torch configuration will depend on the sample matrix, analyte in question, analytical wavelength(s) used, cost of instrumentation, required sensitivity, and type of instrumentation available in a given laboratory.

Regardless of torch configuration or detector technology, ICP–AES is a technique that provides a qualitative and/or quantitative measurement of the optical emission from excited atoms or ions at specific wavelengths. These measurements are then used to determine the analyte concentration in a given sample. Upon excitation, an atom or atomic ion emits an array of different frequencies of light that are characteristic of the distinct energy transition allowed for that element. The intensity of the light is generally proportional to the analyte concentration. It is necessary to correct for the background emission from the plasma. Sample concentration measurements are usually determined from a working curve of known standards over the concentration range of interest. It is, however, also possible to perform a single-point calibration under certain circumstances, such as with limit tests, if the methodology has been validated for sufficient specificity, sensitivity, linearity, accuracy, precision, ruggedness, and robustness.

Because there are distinct transitions between atomic energy levels, and because the atoms in an ICP are rather dilute, emission lines have narrow bandwidths. However, because the emission spectra from the ICP contain many lines, and because ‘‘wings’’ of these lines overlap to produce a nearly continuous background on top of the continuum that arises from the recombination of argon ions with electrons, a high-resolution spectrometer is required in ICP–AES. The decision regarding which spectral line to measure should include an evaluation of potential spectral interferences. All atoms in a sample are excited simultaneously; however, the presence of multiple elements in some samples can lead to spectral overlap. Spectral interference can also be caused by background emission from the sample or plasma. Modern ICPs usually have background correction available, and a number of background correction techniques can be applied. Simple background correction typically involves measuring the background emission intensity at some point away from the main peak and subtracting this value from the total signal being measured. Mathematical modeling to subtract the interfering signal as a background correction can also be performed with certain types of ICP–AES spectrometers.

The selection of the analytical spectral line is critical to the success of an ICP–AES analysis, regardless of torch configuration or detector type. Though some wavelengths are preferred, the final choice must be made in the context of the

sample matrix, the type of instrument being used, and the sensitivity required. Analysts might choose to start with the wavelengths recommended by the manufacturer of their particular instrument and select alternative wavelengths based on manufacturer recommendations or published wavelength tables.[3,4,5,6,7] Ultimately, the selection of analytical wavelengths should be demonstrated experimentally to provide sufficient specificity, sensitivity, linearity, accuracy, and precision of the analysis at hand.

Forward power, gas flow rates, viewing height, and torch position can all be optimized to provide the best signal. However, it must also be kept in mind that these same variables can influence matrix and spectral interferences.

In general, it is desirable to operate the ICP under robust conditions, which can be gauged on the basis of the MgII / MgI line pair at (280.270 nm / 285.213 nm). If that ratio of intensities is above 6.0 in an aqueous solution, the ICP is said to be *robust,* and is less susceptible to matrix interferences. A ratio of about 10.0 is generally what is sought. Note that the term *robust conditions* is unrelated to *robustness* as applied to analytical method validation. Operation of an instrument with an MgII / MgI ratio greater than 6.0 is not mandated, but is being suggested as a means of optimizing instrument parameters in many circumstances.

The analysis of the Group I elements can be an exception to this strategy. When atomic ions are formed from elements in this group, they assume a noble gas electron configuration, with correspondingly high excitation energy. Because the first excited state of these ions is extremely high, few are excited, so emission intensity is correspondingly low. This situation can be improved by reducing the fractional ionization, which can in turn be achieved by using lower forward power settings in combination with adjusted viewing height or nebulizer gas flow, or by adding an ionization suppression agent to the samples and standards.

When organic solvents are used, it is often necessary to use a higher forward power setting, higher intermediate and outer gas flows, and a lower nebulizer gas flow than would be employed for aqueous solutions, as well as a reduction in the nebulizer gas flow. When using organic solvents, it may also be necessary to bleed small amounts of oxygen into the torch to prevent carbon buildup in the torch.

Calibration

The wavelength accuracy for ICP–AES detection must comply with the manufacturer's applicable operating procedures. Because of the inherent differences among the types of instruments available, there is no general system suitability procedure that can be employed. Calibration routines recommended by the instrument manufacturer for a given ICP–AES instrument should be followed. These might include, but are not limited to, use of a multi-element wavelength calibration with a reference solution, internal mercury (Hg) wavelength calibration, and peak search. The analyst should perform system checks in accordance with the manufacturer's recommendations.

Standardization

The instrument must be standardized for quantification at time of use. However, because ICP–AES is a technique generally considered to be linear over a range of 6 to 8 orders of magnitude, it is not always necessary to continually demonstrate linearity by the use of a standard curve composed of multiple standards. Once a method has been developed and is in routine use, it is possible to calibrate with a blank and a single standard. One-point standardizations are suitable for conducting limit tests on production materials and final products if the methodology has been rigorously validated for suf-

[3] Payling R, Larkins P. *Optical Emission Lines of the Elements.* New York: Wiley; 2000.
[4] Harrison GR. *Massachusetts Institute of Technology Wavelength Tables* [also referred to as *MIT Wavelength Tables*]. Cambridge, MA: MIT Press; 1969.
[5] Winge RK, Fassel VA, Peterson VJ, Floyd MA. *Inductively Coupled Plasma Atomic Emission Spectroscopy: An Atlas of Spectral Information.* New York: Elsevier; 1985.
[6] Boumans PWJM. *Spectrochim Acta A.* 1981;36B:169.
[7] Boumans PWJM. *Line Coincidence Tables for Inductively Coupled Plasma Atomic Emission Spectrometry.* 2nd ed.; Oxford, UK: Pergamon; 1984.

ficient specificity, sensitivity, linearity, accuracy, precision, ruggedness, and robustness. The use of a single-point standardization is also acceptable for qualitative ICP–AES analyses, where the purpose of the experiment is to confirm the presence or absence of elements without the requirement of an accurate quantification.

An appropriate blank solution and standards that bracket the expected range of the sample concentrations should be assayed and the detector response plotted as a function of analyte concentration, as in the case where the concentration of a known component is being determined within a specified tolerance. However, it is not always possible to employ a bracketing standard when an analysis is performed at or near the detection limit. This lack of use of a bracketing standard is acceptable for analyses conducted to demonstrate the absence or removal of elements below a specified limit. The number and concentrations of standard solutions used should be based on the purpose of the quantification, the analyte in question, the desired sensitivity, and the sample matrix. Regression analysis of the standard plot should be employed to evaluate the linearity of detector response, and individual monographs may set criteria for the residual error of the regression line. Optimally, a correlation coefficient of not less than 0.99, or as indicated in the individual monograph, should be demonstrated for the working curve. Here, too, however, the nature of the sample matrix, the analyte(s), the desired sensitivity, and the type of instrumentation available may dictate a correlation coefficient lower than 0.99. The analyst should use caution when proceeding with such an analysis, and should employ additional working standards.

To demonstrate the stability of the system's initial standardization, a solution used in the initial standard curve must be reassayed as a check standard at appropriate intervals throughout the analysis of the sample set. The reassayed standard should agree with its expected value to within $\pm 10\%$, or as specified in an individual monograph, for single-element analyses when analytical wavelengths are between 200 and 500 nm, or concentrations are > 1 µg per mL. The reassayed standard should agree with its theoretical value to within $\pm 20\%$, or as specified in an individual monograph, for multi-element analyses, when analytical wavelengths are < 200 nm or > 500 nm, or at concentrations of < 1 µg per mL. In cases where an individual monograph provides different guidance regarding the reassayed check standard, the requirements of the monograph take precedence.

Procedure

Follow the procedure as directed in the individual monograph for the instrumental parameters. Because of differences in manufacturers' equipment configurations, the manufacturer's suggested default conditions may be used and modified as needed. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions, and adjustments of operating conditions may be necessary. Alternative conditions must be supported by suitable validation data, and the conditions in the monograph will take precedence for official purposes. Data collected from a single sample introduction are treated as a single result. This result might be the average of data collected from replicate sequential readings from a single solution introduction of the appropriate standard or sample solution. Sample concentrations are calculated versus the working curve generated by plotting the detector response versus the concentration of the analyte in the standard solutions. This calculation is often performed directly by the instrument.

ICP–MS

When an inductively coupled plasma uses a mass spectral detection system, the technique is referred to as inductively coupled plasma–mass spectrometry (ICP–MS). In this technique, analytes are detected directly at their atomic masses. Because these masses must be charged to be detected in ICP–MS, the method relies on the ability of the plasma source

to both atomize and ionize sample constituents. As is the case with ICP–AES, a wide variety of ICP–MS instrumentation systems are available.

The systems most commonly in use are quadrupole-based systems. Gaining in interest is time-of-flight ICP–MS. Although still not in widespread use, this approach may see greater use in the future. Additionally, high-resolution sector field instruments are available.

Regardless of instrument design or configuration, ICP–MS provides both a qualitative and a quantitative measurement of the components of the sample. Ions are generated from the analyte atoms by the plasma. The analyte ions are then extracted from the atmospheric-pressure plasma through a sampling cone into a lower-pressure zone, ordinarily held at a pressure near 1 Torr. In this extraction process, the sampled plasma gases, including the analyte species, form a supersonic beam, which dictates many of the properties of the resulting analyte ions. A skimmer cone, located behind the sampling cone, ''skims'' the supersonic beam of ions as they emerge from the sampling cone. Behind the skimmer cone is a lower-pressure zone, often held near a milliTorr. Lastly, the skimmed ions pass a third-stage orifice to enter a zone held near a microTorr, where they encounter ion optics and are passed into the mass spectrometer. The mass spectrometer separates the ions according to their mass-to-charge *(m/z)* ratios. The ICP–MS has a mass range up to 240 atomic mass units (amu). Depending on the equipment configuration, analyte adducts can form with diluents, with argon, or with their decomposition products. Also formed are oxides and multiply-charged analyte ions, which can increase the complexity of the resulting mass spectra. Interferences can be minimized by appropriate optimization of operational parameters, including gas flows (central, intermediate, and outer gas flow rates), sample-solution flow, RF power, extraction-lens voltage, etc., or by the use of collision or reaction cells, or cool plasma operation, if available on a given instrument. Unless a laboratory is generating or examining isotopes that do not naturally occur, a list of naturally occurring isotopes will provide the analyst with acceptable isotopes for analytical purposes. Isotopic patterns also serve as an aid to element identification and confirmation. Additionally, tables of commonly found interferences and polyatomic isobaric interferences and correction factors can be used.

ICP–MS generally offers considerably lower (better) detection limits than ICP–AES, largely because of the extremely low background that it generates. This ability is a major advantage of ICP–MS for determination of very low analyte concentrations or when elimination of matrix interferences is required. In the latter case, some interferences can be avoided simply by additional dilution of the sample solution. In some applications, analytes can be detected below the parts per trillion (ppt) level using ICP–MS. As a general rule, ICP–MS as a technique requires that samples contain significantly less total dissolved solids than does ICP–AES.

The selection of the analytical mass to use is critical to the success of an ICP–MS analysis, regardless of instrument design. Though some masses are often considered to be the primary ones, because of their high natural abundance, an alternative mass for a given element is often used to avoid spectral overlaps (isobaric interferences). Selection of an analytical mass must always be considered in the context of the sample matrix, the type of instrument being used, and the concentrations to be measured. Analysts might choose to start with masses recommended by the manufacturer of their particular instrument and select alternate masses based on manufacturer's recommendations or published tables of naturally occurring isotopes.[8]

Optimization of an ICP–MS method is also highly dependent on the plasma parameters and means of sample introduction. Forward power, gas flow rates, and torch position may all be optimized to provide the best signal. When organic solvents are used, it is often necessary to use a higher forward power setting and a lower nebulizer flow rate than would be used for aqueous solutions. Additionally, when organic solvents are used, it might be necessary to introduce small amounts of ox-

[8] Horlick G, Montaser A. Analytical characteristics of ICPMS. In: Montaser A, Editor. *Inductively Coupled Plasma Mass Spectrometry.* New York: Wiley-VCH; 1998:516–518.

ygen into the central or intermediate gas to prevent carbon buildup in the torch or on the sampler cone orifice. The use of a platinum-tipped sampling or skimmer cone may also be required in order to reduce cone degradation with some organic solvents.

Calibration

The mass spectral accuracy for ICP–MS detection must be in accordance with the applicable operating procedures. Because of the inherent differences between the types of instruments available, there is no general system suitability procedure that can be employed. Analysts should refer to the tests recommended by the instrument manufacturer for a given ICP–MS instrument. These may include, but are not limited to, tuning on a reference mass or masses, peak search, and mass calibration. The analyst should perform system checks recommended by the instrument manufacturer.

Standardization

The instrument must be standardized for quantification at the time of use. Because the response (signal vs. concentration) of ICP–MS is generally considered to be linear over a range of 6 to 8 orders of magnitude, it is not always necessary to continually demonstrate linearity by the use of a working curve. Once a method has been developed and is in routine use, it is common practice to calibrate with a blank and a single standard. One-point standardizations are suitable for conducting limit tests on production materials and final products, provided that the methodology has been rigorously validated for sufficient specificity, sensitivity, linearity, accuracy, precision, ruggedness, and robustness. An appropriate blank solution and standards that bracket the expected range of the sample concentrations should be assayed and the detector response plotted as a function of analyte concentration. The number and concentration of standard solutions used should be based on the analyte in question, the expected concentrations, and the sample matrix, and should be left to the discretion of the analyst. Optimally, a correlation coefficient of not less than 0.99, or as indicated in the individual monograph, should be demonstrated for the working standard curve. Here, too, however, the nature of the sample matrix, the analyte, the desired sensitivity, and the type of instrumentation available might dictate a correlation coefficient lower than 0.99. The analyst should use caution when proceeding with such an analysis and should employ additional working standards.

To demonstrate the stability of the system since initial standardization, a solution used in the initial standard curve must be reassayed as a check standard at appropriate intervals throughout the analysis of the sample set. Appropriate intervals may be established as occurring after every fifth or tenth sample, or as deemed adequate by the analyst, on the basis of the analysis being performed. The reassayed standard should agree with its expected value to within $\pm 10\%$ for single-element analyses when analytical masses are free of interferences and when concentrations are > 1 ng per mL. The reassayed standard should agree with its expected value to within $\pm 20\%$ for multi-element analyses, or when concentrations are < 1 ng per mL. In cases where an individual monograph provides different guidance regarding the reassayed check standard, the requirements of the monograph take precedence.

The method of standard additions should be employed in situations where matrix interferences are expected or suspected. This method involves adding a known concentration of the analyte element to the sample solution at no fewer than two concentration levels. The instrument response is plotted against the concentration of the added analyte element, and a linear regression line is drawn through the data points. The absolute value of the *x*-intercept multiplied by any dilution factor is the concentration of the analyte in the sample.

Procedure

Follow the procedure as directed in the individual monograph for the detection mode and instrument parameters. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating condi-

tions, and adjustments of operating conditions may be necessary. Alternative conditions must be supported by suitable validation data, and the conditions in the monograph will take precedence for official purposes. Because of differences in manufacturers' equipment configurations, the analyst may wish to begin with the manufacturer's suggested default conditions and modify them as needed. Data collected from a single sample introduction are treated as a single result. Data collected from replicate sequential readings from a single introduction of the appropriate standard or sample solutions are averaged as a single result. Sample concentrations are calculated versus the working curve generated by plotting the detector response versus the concentration of the analyte in the standard solutions. With modern instruments, this calculation is often performed by the instrument.

GLOSSARY

AUXILIARY GAS: See *Intermediate (or Auxiliary) Gas.*

AXIAL VIEWING: A configuration of the plasma for AES in which the plasma is directed toward the spectrometer optical path, also called "end-on viewing."

CENTRAL (OR NEBULIZER) GAS: One of three argon gas flows in an ICP torch. The central gas is used to help create a fine mist of the sample solution when solution nebulization is employed. This fine mist is then directed through the central tube of the torch and into the plasma.

COLLISION CELL: A design feature of some ICP–MS instruments. Collision cells are used to reduce interferences from argon species or polyatomic ions and facilitate the analysis of elements that might be affected by those interferences.

COOL PLASMA: Plasma conditions used for ICP–MS that result in a plasma that is cooler than that normally used for an analysis. This condition is achieved by using a lower forward power setting and higher central-gas flow rate, and is used to help reduce isotopic interferences caused by argon and some polyatomic ions.

COOLANT GAS: See *Outer (or Coolant or Plasma) Gas.*

FORWARD POWER: The number of watts used to ignite and sustain the plasma during an analysis. Forward power requirements may vary, depending on sample matrix and analyte.

INTERMEDIATE (OR AUXILIARY) GAS: Gas used to "lift" the plasma off the surface of the torch, thereby preventing melting of the intermediate tube and the formation of carbon and salt deposits on the inner tube.

INTERNAL STANDARD: An element added to or present in the same concentration in blanks, standards, and samples to act as an intensity reference for the analysis. An internal standard should be used for ICP–AES work and must always be used for quantitative ICP–MS analyses.

LATERAL VIEWING: See *Radial Viewing.*

m: The ion mass of interest.

MULTIPLY-CHARGED IONS: Atoms that, when subjected to the high-ionization temperature of the ICP, can form doubly or triply charged ions (X^{++}, X^{+++}, etc.). When detected by MS, the apparent mass of these ions will be ½ or $\frac{1}{3}$ that of the atomic mass.

NEBULIZER: Used to form a consistent sample aerosol that mixes with the argon gas, which is subsequently sent into the ICP.

OUTER (OR COOLANT OR PLASMA) GAS: The main gas supply for the plasma.

PLASMA GAS: See *Outer (or Coolant or Plasma) Gas.*

RADIAL VIEWING: A configuration of the plasma for AES in which the plasma is viewed orthogonal to the spectrometer optic path. Also called "side-on viewing." See also *Lateral Viewing.*

REACTION CELL: Similar to *Collision Cell,* but operating on a different principle. Designed to reduce or eliminate spectral interferences.

SAMPLING CONE: A metal cone (usually nickel-, aluminum-, or platinum-tipped) with a small opening, through which ionized sample material flows after leaving the plasma.

SEQUENTIAL: A type of detector configuration for AES or MS in which discrete emission lines or isotopic peaks are observed by scanning or hopping across the spectral range by means of a monochromator or scanning mass spectrometer.

SIMULTANEOUS: A type of detector configuration for AES or MS in which all selected emission lines or isotopic peaks are observed at the same time by using a polychromator or simultaneous mass spectrometer, offering increased analysis speed for analyses of multi-element samples.

SKIMMER CONE: A metal cone through which ionized sample flows after leaving the sampling cone and before entering the high-vacuum region of an ICP–MS.

STANDARD ADDITIONS: A method used to determine the actual analyte concentration in a sample when viscosity or matrix effects might cause erroneous results.

TORCH: A series of three concentric tubes, usually manufactured from quartz, in which the ICP is formed.■1S *(USP30)*

BRIEFING

⟨**785**⟩ **Osmolality and Osmolarity,** *USP 29* page 2718 and page 845 of *PF* 31(3) [May–June 2005]. It is proposed to correct the molecular weight of vancomycin and the number of decimal places for the molecular weight of sodium chloride in the section on *Osmolarity.* Also, revisions are proposed in the *Procedure* for the section *Measurement of Osmolality,* indicating that the manufacturer's instructions for calibration are to be used.

(GC: H. Pappa) RTS—C43216

In-Process Revision

Change to read:

OSMOLARITY

Osmolarity of a solution is a theoretical quantity expressed in osmoles per L (Osmol per L) of a solution and is widely used in clinical practice because it expresses osmoles as a function of volume. Osmolarity cannot be measured but is calculated theoretically from the experimentally measured value of osmolality.

Sometimes, osmolarity (ξ_c) is calculated theoretically from the molar concentrations:

$$\xi_c = \Sigma \nu_i c_i$$

where ν_i is as defined above, and c_i is the molar concentration of the i^{th} solute in solution. For example, the osmolarity of a solution prepared by dissolving 1 g of vancomycin in 100 mL of 0.9% sodium chloride solution can be calculated as follows:

~~[3 × 10 g/L/1468 (mol. wt. of vancomycin) + 2 × 9 g/L/58.5 (mol. wt. of sodium chloride)] × 1000 = 328 mOsmol/L~~

~~■[3 × 10 g/L/1485.71(mol. wt. of vancomycin) + 2 × 9 g/L/58.5(mol. wt. of sodium chloride)] × 1000 = 328 mOsmol/L■2S *(USP30)*~~

■[3 × 10 g/L/1449.25(mol. wt. of vancomycin) + 2 × 9 g/L/58.44(mol. wt. of sodium chloride)] × 1000 = 329 mOsmol/L■1S *(USP30)*

The results suggest that the solution is slightly hyperosmotic because the osmolality of blood ranges between 285 and 310 mOsmol per kg. However, the solution is found to be hypo-osmotic and has an experimentally determined osmolality of 255 mOsmol per kg.[1] The example illustrates that osmolarity values calculated theoretically from the concentration of a solution should be interpreted cautiously and may not represent the osmotic properties of infusion solutions.

The discrepancy between theoretical (osmolarity) and experimental (osmolality) results is, in part, due to the fact that osmotic pressure is related to osmolality and not osmolarity. More significantly, the discrepancy between experimental results and the theoretical calculation is due to the fact that the osmotic pressure of a real solution is less than that of an ideal solution because of interactions between solute molecules or between solute and solvent molecules in a solution. Such interactions reduce the pressure exerted by solute molecules on a semipermeable membrane, reducing experimental values of osmolality compared to theoretical values. This difference is related to the molal osmotic coefficient ($\Phi_{m,i}$). The example also illustrates the importance of determining the osmolality of a solution experimentally, rather than calculating the value theoretically.

Change to read:

MEASUREMENT OF OSMOLALITY

The osmolality of a solution is commonly determined by the measurement of the freezing point depression of the solution.

Apparatus—The apparatus, an osmometer for freezing point depression measurement, consists of the following: a means of cooling the container used for the measurement; a resistor sensitive to temperature (thermistor), with an appropriate current- or potential-difference measurement device that may be graduated in temperature change or in osmolality; and a means of mixing the sample.

Osmometers that measure the vapor pressures of solutions are less frequently employed. They require a smaller volume of specimen (generally about 5 µL), but the accuracy and precision of the resulting osmolality determination are comparable to those obtained by the use of osmometers that depend upon the observed freezing points of solutions.

Standard Solutions—Prepare *Standard Solutions* as specified in *Table 1,* as necessary.

[1] Kastango, E.S. and Hadaway, L. International Journal of Pharmaceutical Compounding 5, (2001) 465-469.

Table 1. Standard Solutions for Osmometer Calibration[2]

Standard Solutions (Weight in g of sodium chloride per kg of water)	Osmolality (mOsmol/kg) (ξ_m)	Molal Osmotic Coefficient ($\Phi_{m,\,NaCl}$)	Freezing Point Depression (°) ΔT_f
3.087	100	0.9463	0.186
6.260	200	0.9337	0.372
9.463	300	0.9264	0.558
12.684	400	0.9215	0.744
15.916	500	0.9180	0.930
19.147	600	0.9157	1.116
22.380	700	0.9140	1.302

[2] Adapted from the *European Pharmacopoeia,* 4th Edition, 2002, p. 50.

Test Solution—For a solid for injection, constitute with the appropriate diluent as specified in the instructions on the labeling. For solutions, use the sample as is. [NOTE—A solution can be diluted to bring it within the range of measurement of the osmometer, if necessary, but the results must be expressed as that of the diluted solution and must NOT be multiplied by a dilution factor to calculate the osmolality of the original solution,

▲unless otherwise indicated in the monograph.▲*USP30*
The molal osmotic coefficient is a function of concentration. Therefore, it changes with dilution.]

Procedure—~~Set the zero of the apparatus using water. To calibrate the apparatus, choose at least two solutions from *Table 1* such that the osmolalities of the *Standard Solutions* span the expected range of osmolality of the *Test Solution.*~~

~~[■NOTE—If the instrument does not calibrate with multiple standards, calibrate the instrument by the manufacturer's instructions and confirm the instrument calibration with at least two solutions from *Table 1* such that the osmolalities of the *Standard Solutions* span the expected range of osmolality of the *Test Solution*. The instrument reading should be within ± 2 mOsmol/kg from the *Standard Solution* (over the standard range of 100 to 700 mOsmol/kg).]■2S *(USP30)*■ First, calibrate the instrument by the manufacturer's instructions. Confirm the instrument calibration with at least two solutions from *Table 1* such that the osmolalities of the *Standard Solutions* span the expected range of osmolality of the *Test Solution*. The instrument reading should be within ± 2 mOsmol/kg from the *Standard Solution* (over the standard range of 100 to 700 mOsmol/kg).■1S *(USP30)*
Introduce an appropriate volume of each *Standard Solution* into the measurement cell as per the manufacturer's instructions, and start the cooling system. Usually, the mixing device is programmed to operate at a temperature below the lowest temperature expected from the freezing point depression. The apparatus indicates when the equilibrium is attained. Calibrate the osmometer using an appropriate adjustment device such that the reading corresponds to either the osmolality or freezing point depression value of the *Standard Solution* shown in *Table 1.* [NOTE—Some instruments indicate osmolality and some others show freezing point depression.] Before each measurement, rinse the measurement cell at least twice with the solution to be tested. Repeat the procedure with each *Test Solution.* Read the osmolality of the *Test Solution* directly, or calculate it from the measured freezing point depression.

Assuming that the value of the osmotic coefficient is essentially the same whether the concentration is expressed in molality or molarity, the experimentally determined osmolality of a solution can be converted to osmolarity in the same manner in which the concentration of a solution is converted from molality to molarity. Unless a solution is very concentrated, the osmolarity of a solution (ξ_c) can be calculated from its experimentally determined osmolality (ξ_m):

$$\xi_c = 1000\xi_m / (1000 / \rho + \Sigma w_i \nu_i)$$

where w_i is the weight in g; and ν_i is the partial specific volume, in mL per g, of the i^{th} solute. The partial specific volume of a solute is the change in volume of a solution when an additional 1 g of solute is dissolved in the solution. This volume can be determined by the measurement of densities of the solution before and after the addition of the solute. The partial specific volumes of salts are generally very small, around 0.1 mL per g. However, those of other solutes are generally higher. For example, the partial specific volumes of amino acids are in the range of 0.6–0.9 mL per g.

▲It can be shown from the above equation correlating osmolarity with osmolality that,

$$\xi_c = \xi_m (\rho - c)$$

where ρ is the density of the solution, and c is the total solute concentration, both expressed in g per mL. Thus, alternatively, the osmolarity can also be calculated from experimentally determined osmolality from the measurement of density of the solution by a suitable method and the total weight of the solute, after correction for water content, dissolved per mL of the solution.▲*USP30*

BRIEFING

⟨797⟩ Pharmaceutical Compounding—Sterile Preparations, *USP 29* page 2735 and page 413 of the *Pharmacists' Pharmacopeia.* Following entry into official status of this General Chapter in 2004, USP received more than 1500 comments at its five 2004 and 2005 Compounding and Packaging Workshops and also from e-mail. These comments were carefully considered by the Sterile Compounding Expert Committee in the 2000–2005 cycle. In 2004, USP created a web site to inform practitioners of the on-going deliberations of the Committee. This Committee concluded its work at the time of the USP Convention in March 2005, which was taken up again by its successor Committee in the present cycle (2005–2010). The current Committee held its first meeting in July 2005 and considered additional changes based on their own deliberations and further public response. Additional meetings both by telephone and at USP Headquarters in November 2005 resulted in extensive revisions to the official text, which are presented in this *In-Process Revision*. Some of the proposed revisions include new definitions and new sections, as well as revision to the standard published in 2004. Guidance in modifying the standard was sought from other organizations such as the National Institute for Occupational Safety and Health and Food and Drug Administration. There are now 59 sections and subsections in the proposed standard, with major revisions/additions noted in the following: *Introduction*—This section has been re-organized with an addition of new terms and changes to previous ones; *Immediate Use CSPs*—This is a new section to allow exemptions to areas where CSPs are prepared in the case of emergency; *Hazardous Drugs as CSPs*—This is a new section that requires that all compounding personnel be fully trained in handling, storage, and disposing of hazardous drugs; *Radiopharmaceuticals as CSPs*—This new section describes radiopharmaceuticals risk levels and also refers practitioners who compound radiopharmaceuticals to another USP General Chapter *(Radiopharmaceuticals for Positron Emission Tomography Compounding* ⟨823⟩*);Facility Design and Environmental Controls*—This section has been revised to describe environmental design, primary engineering control areas such as buffer room, cleanroom, use of barrier isolator [Compounding Aseptic Isolator (CAI)] and HEPA filters, and the ISO environment for compounding facilities and equipment; *Environment Monitoring*—This section has been revised to discuss total particle count, surface sampling, air sampling, and personnel; *Personnel Cleansing and Garbing*—This section has been revised to provide clear understanding of personnel cleansing and garbing procedures and the disinfecting process.

(SCC: C. Okeke) RTS—C44376

In-Process Revision

⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS

Change to read:

INTRODUCTION

~~This chapter provides procedures and requirements for compounding sterile preparations.~~

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

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

~~a. Preparations prepared according to the manufacturer's labeled instructions and other manipulations when manufacturing sterile products that expose the original contents to potential contamination.~~

~~b. Preparations containing nonsterile ingredients or employing nonsterile components and devices that must be sterilized before administration.~~

~~c. Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess either of the above two characteristics and which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, powders for injection, irrigations, metered sprays, and ophthalmic and otic preparations.~~

■The objective of this chapter is to describe conditions and practices to prevent harm, including death, to patients that could result from the following: 1) microbial contamination (nonsterility), 2) excessive bacterial endotoxins, 3) variability in the intended strength of correct ingredients that exceeds either monograph limits for official articles (see "official" and "article" in the *General Notices and Requirements*) or 10% for nonofficial articles, 4) unintended chemical and physical contaminants, and 5) incorrect types and qualities of ingredients in Compounded Sterile Preparations (CSPs). Nonsterile CSPs are potentially most hazardous to patients when administered into body cavities, central nervous and vascular systems, eyes, and joints; and when used as baths for live organs and tissues. When CSPs contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩), they are potentially most hazardous to patients when administered into the central nervous system.

To achieve these five objectives, this chapter provides practice and quality standards for CSPs of drugs and nutrients. The standards in this chapter pertain to all pre-administration manipulations and procedures of CSPs, including preparation, storage, and transportation. The standards in this chapter do not pertain to the clinical administration of CSPs to patients via application, implantation, infusion, inhalation, injection,

insertion, instillation, and irrigation, which are the routes of administration. The following four specific categories of CSPs are described in this chapter: *Low-Risk Level, Medium-Risk Level,* and *High-Risk Level CSPs;* and *Immediate Use CSPs*. Sterile compounding differs from nonsterile compounding (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ and *Good Compounding Practices* ⟨1075⟩) primarily by requiring the maintenance of sterility when compounding exclusively with sterile ingredients and components, i.e., *Immediate Use CSPs, Low-Risk Level CSPs,* and *Medium-Risk Level CSPs;* and the achievement of sterility when compounding with nonsterile ingredients and components, i.e., *High-Risk Level CSPs*. Some differences between standards for sterile compounding in this chapter and those for nonsterile compounding in chapter ⟨795⟩ include, but are not limited to ISO classified air environments (see *Table 1*); personnel garbing and gloving; personnel training and testing in principles and practices of aseptic manipulations and sterilization; environmental quality specifications and monitoring; and disinfection of gloves and surfaces of ISO Class 5 (see *Table 1*) sources.

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

Class Name		Particle Count	
ISO Class	U.S. FS 209E	ISO, m^3	FS 209E, $ft.^3$
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3520	100
6	Class 1000	35,200	1000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

[*] Adapted from former Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 4644-1 : 1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 μm per m^3 or larger (ISO Class 5) is equivalent to 100 particles per ft^3 (Class 100) (1 m^3 = 35.2 ft^3).

The standards in this chapter are intended to apply to all persons who prepare CSPs and all places where CSPs are prepared, e.g., hospitals and other healthcare institutions, patient treatment clinics, pharmacies, physicians' practice facilities, and other locations and facilities in which CSPs are prepared, stored, and transported. Persons who perform sterile compounding include pharmacists, nurses, pharmacy technicians, and physicians. These terms recognize both that most sterile compounding is performed by or under the supervision of pharmacists in pharmacies and that this chapter applies to all healthcare personnel who prepare, store, and transport CSPs. For the purposes of this chapter, CSPs include any of the following:

(1) Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess any of the characteristics in parts (2) and (3) below and that include the following preparations that must be sterile when they are administered to patients: aqueous bronchial and nasal inhalations, baths and soaks for live organs and tissues, injections (e.g., colloidal dispersions, emulsions, solutions, and suspensions), irrigations for wounds and body cavities, ophthalmic drops and ointments, and tissue implants.

(2) Manufactured sterile products that are prepared either strictly according to the instructions appearing in manufacturers' approved labeling (product package inserts) or that are prepared differently than published in such labeling. [NOTE—The FDA states that "Compounding does not include mixing, reconstituting, or similar acts that are performed in accordance with the directions contained in approved labeling provided by the product's manufacturer and other manufacturer directions consistent with that labeling" (see http://www.fda.gov/cder/fdama/difconc.htm). However, the FDA approved labeling (product package insert) rarely describes environmental quality, e.g., ISO Class air designation, exposure durations to non-ISO classified air, personnel garbing and gloving, and other aseptic precautions by which sterile products are to be prepared for administration. Beyond-use expo-

sure and storage dates or times (see *General Notices and Requirements* and *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩) for sterile products that have been either opened or prepared for administration are not specified in all package inserts for all sterile products. Furthermore, when such durations are specified, they usually refer to chemical stability and not necessarily to microbiological purity or safety.]

(3) The three contamination categories for CSPs described in the section *CSP Microbial Contamination Risk Levels* are assigned primarily according to the potential for microbial contamination during compounding *Low-Risk Level* and *Medium-Risk Level CSPs,* or the potential for not sterilizing *High-Risk Level CSPs,* any of which would subject patients to risk of harm, including death. Therefore *High-Risk Level CSPs* (see the specific criteria described in the *CSP Microbial Contamination Risk Levels* section) must be sterilized before being administered to patients.

ORGANIZATION OF THIS CHAPTER■1S (*USP30*)

The sections in this chapter are organized to facilitate practitioners' understanding of the fundamental accuracy and quality practices of CSPs. They provide a foundation for the development and implementation of essential procedures for the safe preparation of CSPs ~~in the three risk levels,~~

■at *Low-Risk, Medium-Risk,* and *High-Risk Level CSPs;* and *Immediate Use CSPs,*■1S (*USP30*)
which are classified according to the potential for microbial, chemical, and physical contamination. The chapter is divided into the following main sections:

- ~~Responsibilities of all compounding personnel~~
- ~~The basis for the classification of a CSP into a low-, medium, and high-risk level, with examples of CSPs and their quality assurance practices in each of these risk levels~~
- ~~Verification of compounding accuracy and sterilization~~
- ~~Personnel training and evaluation in aseptic manipulation skills, including representative sterile microbial culture medium transfer and fill challenges~~
- ~~Environmental quality and control during the processing of CSPs~~
- ~~Equipment used in the preparation of CSPs~~
- ~~Verification of automated compounding devices for parenteral nutrition compounding~~
- ~~Finished preparation release checks and tests~~
- ~~Storage and beyond-use dating~~
- ~~Maintaining product quality and control after CSPs leave the compounding facility, including education and training of personnel~~
- ~~Packing, handling, storage, and transport of CSPs~~
- ~~Patient or caregiver training~~
- ~~Patient monitoring and adverse events reporting~~
- ~~A quality assurance program for CSPs It is the ultimate responsibility of all personnel who prepare CSPs to understand these fundamental practices and precautions, to develop and implement appropriate procedures, and to continually evaluate these procedures and the quality of final CSPs to prevent harm and fatality to patients who are treated with CSPs.~~

■• Definitions of chapter terminology
- Responsibility of compounding personnel
- CSP microbial contamination risk levels
- Single-dose and multiple-dose containers
- Hazardous drugs as CSPs
- Radiopharmaceuticals as CSPs
- Verification of compounding accuracy and sterility
- Sterilization methods
- Personnel training and evaluation in aseptic manipulation skills
- Environmental quality and control
- Cleaning and disinfecting the sterile compounding areas
- Personnel cleansing and garbing
- Suggested standard operating procedures
- Environmental monitoring
- Processing
- Verification of automated compounding devices for parenteral nutrition compounding
- Finished preparation release checks and tests
- Storage and beyond-use dating
- Maintaining sterility, purity, and stability of dispensed and distributed CSPs
- Packing and transporting CSPs
- Patient or caregiver training
- Patient monitoring and adverse events reporting
- The quality assurance program■1S (*USP30*)

~~It is the ultimate responsibility of all~~

■All■1S (*USP30*)
personnel who prepare CSPs

■are■1S (*USP30*)
to understand these fundamental practices and precautions, to develop and implement appropriate procedures, and to continually evaluate these procedures and the quality of final CSPs to prevent harm, ~~and fatality to patients who are treated with CSPs.~~

■including death, to patients given CSPs.■1S (*USP30*)

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Add the following:

▪DEFINITIONS

Anteroom—An anteroom is an ISO Class 8 (see *Table 1*) or better area where personnel perform hand hygiene and garbing procedures, staging of components, order entry, CSP labeling and other high-particulate generating activities. It is also a transition area that 1) provides assurance that pressure relationships are constantly maintained so that air flows from clean to dirty areas and 2) that reduces the need for the heating, ventilating and air conditioning (HVAC) control system to respond to large disturbances.[1]

Aseptic Processing (see *Microbiological Evaluation of Cleanrooms* ⟨1116⟩)—Aseptic processing is a mode of processing pharmaceutical and medical products that involves the separate sterilization of the product and of the package (containers–closures or packaging material for medical devices) and the transfer of the product into the container and its closure under microbiologic critically controlled conditions.

Beyond-Use Date (see *General Notices and Requirements* and *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩)—For the purpose of this chapter, the beyond-use date is the date or time after which the CSPs shall not be stored or transported. The beyond-use date is determined from the date or time the preparation is compounded.

Biological Safety Cabinet, *Class II* (BSC)—The BSC is a ventilated cabinet for personnel, product, and environmental protection having an open front with inward airflow for personnel protection, downward HEPA filtered laminar airflow for product protection, and HEPA filtered exhausted air for environmental protection.

Buffer Area, Buffer or Core Room, Buffer or Cleanroom Areas, Buffer Room Area, Buffer or Clean Area—This is an ISO Class 7 (see *Table 1*) area where the primary engineering control area (see below) is physically located. Activities that occur in this area include the preparation and staging of components and supplies used when compounding CSPs.

Cleanroom (see *Microbiological Evaluation of Cleanrooms* ⟨1116⟩ and also *Buffer Area*)—A cleanroom is a room in which the concentration of airborne particles is controlled to meet a specified airborne particulate cleanliness class. Microorganisms in the environment are monitored so that a microbial level for air, surface, and personnel gear are not exceeded for a specified cleanliness class.

Compounding Aseptic Isolator (CAI)—The CAI is a form of barrier isolator specifically designed for compounding pharmaceutical ingredients or preparations. It is designed to maintain an aseptic compounding environment within the isolator throughout the compounding and material transfer processes. Air exchange into the isolator from the surrounding environment should not occur unless it has first passed through a microbially retentive filter (HEPA minimum).[2]

Critical Area—A critical area is an ISO Class 5 (see *Table 1*) environment.

Critical Sites—Critical sites include sterile ingredients of CSPs and locations on devices and components used to prepare, package, and transfer CSPs that provide opportunity for exposure to contamination.

Disinfectant—A disinfectant is an agent that frees from infection, usually a chemical agent but sometimes a physical one, and that destroys disease-causing pathogens or other harmful microorganisms but may not kill bacterial spores. It refers to substances applied to inanimate objects.

Labeling (see *General Notices and Requirements* and www.fda.gov/cder/drugsatfda/glossary.htm)—A term that designates all labels and other written, printed, or graphic matter upon an immediate container of an article or preparation or

[1] See *American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc. (ASHRAE), Laboratory Design Guide.*

[2] *CETA Applications Guide for the Use of Compounding Isolators in Compounding Sterile Preparations in Healthcare Facilities,* CAG-001-2005, Controlled Environment Testing Association (CETA), November 8, 2005.

upon; or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term ''label'' designates that part of the labeling upon the immediate container.

Media-Fill Test (see *Microbiological Evaluation of Cleanrooms* ⟨1116⟩)—A media fill test is used to qualify aseptic technique of compounding personnel or processes and to ensure that the processes used are able to produce sterile product without microbial contamination. During this test, a microbiological growth medium such as Soybean–Casein Digest Medium (SCDM) is substituted for the actual drug product to simulate admixture compounding.[3] The issues to consider in the development of a media fill test are the following: media-fill procedures, media selection, fill volume, incubation, time and temperature, inspection of filled units, documentation, interpretation of results, and possible corrective actions required.

Multiple-Dose Container (see *General Notices and Requirements* and *Containers for Injections* under *Injections* ⟨1⟩)—A multiple-dose container is a multiple-unit container for articles or preparations intended for parenteral administration only and usually contains antimicrobial preservatives. The beyond-use date for an opened or entered (e.g., needle-punctured) multiple-dose container with antimicrobial preservatives is 28 days (see *Antimicrobial Effectiveness Testing* ⟨51⟩), unless otherwise specified by the manufacturer.

Negative Pressure Room—A room that is at a lower pressure compared to adjacent spaces and, therefore, the net flow of air is *into* the room.[1]

Pharmacy Bulk Package (see *Containers for Injections* under *Injections* ⟨1⟩)—The pharmacy bulk package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for infusion or, through a sterile transfer device, for the filling of empty sterile syringes. The closure shall be penetrated only one time after constitution with a suitable sterile transfer device or dispensing set, which allows measured dispensing of the contents. The pharmacy bulk package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

Where a container is offered as a *Pharmacy Bulk Package,* the label shall (a) state prominently ''Pharmacy Bulk Package—Not for Direct Infusion,'' (b) contain or refer to information on proper techniques to help assure safe use of the product, and (c) bear a statement limiting the time frame in which the container may be used once it has been entered, provided it is held under the labeled storage conditions.

Primary Engineering Control—It is a device or room that provides an ISO Class 5 (see *Table 1*) environment for the exposure of critical sites when compounding CSPs. Such devices include, but may not be limited to, laminar airflow workbenches (LAFWs), biological safety cabinets (BSCs), and compounding aseptic isolators (CAIs).

Preparation—For the purposes of this chapter, a preparation, or a CSP, is a sterile drug or nutrient compounded in a licensed pharmacy or other healthcare-related facility pursuant to the order of a licensed prescriber; the article may or may not contain sterile products.

Product—For the purposes of this chapter, a product is a commercially manufactured sterile drug or nutrient that has been evaluated for safety and efficacy by the U.S. Food and Drug Administration (FDA). Products are accompanied by full prescribing information, which is commonly known as the FDA-approved manufacturer's labeling or product package insert.

Positive Pressure Room—A positive pressure room is one that is at a higher pressure compared to adjacent spaces and, therefore, the net airflow is *out of* the room.[1]

Single-Dose Container (see *General Notices and Requirements* and *Containers for Injections* under *Injections* ⟨1⟩)—A single-dose container is a single-unit container for articles (see *General Notices and Requirements*) or preparations intended for parenteral administration only. It is intended for a single use. A single-dose container is labeled as such. Examples of

[3] Swarbrick J, Boylan J, *Encyclopedia of Pharmaceutical Technology,* Vol 7.

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single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Sterilizing Grade Filter—A sterile grade filter is a filter that will remove all microorganisms from a fluid stream, producing a sterile effluent. Such filters typically have a nominal porosity of 0.2 µm.

Sterilization by Filtration—Passage of a fluid or solution through a sterilizing grade filter to produce a sterile effluent.

Terminal Sterilization—Terminal sterilization is the application of a lethal process, e.g., steam under pressure or autoclaving, to sealed containers for the purpose of achieving a predetermined sterility assurance level (SAL) of usually less than 10^{-6}, i.e., or a probability of less than one in one million of a nonsterile unit.[4]

Unidirectional Flow (see U.S. Food and Drug Administration, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice)—An airflow moving in a single direction, in a robust and uniform manner, and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.■1S (*USP30*)

Change to read:

RESPONSIBILITY OF COMPOUNDING PERSONNEL

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

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

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

1. Compounding personnel are adequately skilled, educated, instructed, and trained to correctly perform and document the following activities in their sterile compounding duties:
   a. Perform antiseptic hand cleansing and disinfection of nonsterile compounding surfaces;
   b. Select and appropriately don protective ~~gloves, goggles, gowns, masks, and hair and shoe covers;~~ ■garb;■1S (*USP30*)
   c. ~~Use laminar flow clean-air hoods, barrier isolators, and other contamination control devices that are appropriate for the risk level;~~ ■Maintain or achieve sterility of CSPs in ISO Class 5 (see *Table 1*) primary engineering devices, and protect personnel and compounding environments from contamination by radioactive, cytotoxic, and chemotoxic drugs (see *Hazardous Drugs as CSPs* section and *Radiopharmaceuticals as CSPs* section);■1S (*USP30*)
   d. Identify, weigh, and measure ingredients; and
   e. Manipulate sterile products aseptically, sterilize high-risk level CSPs, and label and quality inspect CSPs.
2. Ingredients have their correct identity, quality, and purity.
3. Opened or partially used packages of ingredients for subsequent use in CSPs are properly stored under restricted access conditions in the compounding facility. Such packages cannot be used when visual inspection detects unauthorized breaks in the container, closure, and seal; when the contents do not possess the expected appearance, aroma, and texture; when the contents do not pass identification tests specified by the compounding facility; and when either the beyond-use or expiration date has been exceeded.
4. To minimize the generation of bacterial endotoxins, water-containing CSPs that are nonsterile during any phase of the compounding procedure are sterilized within 6 hours after completing the preparation.
5. Sterilization methods achieve sterility of CSPs while maintaining the labeled strength of active ingredients and the physical integrity of packaging.
6. Measuring, mixing, sterilizing, and purifying devices are clean, appropriately accurate, and effective for their intended uses.
7. Potential harm from added substances and differences in rate and extent of bioavailability of active ingredients for other than oral route of administration are carefully evaluated before such CSPs are dispensed and administered.
8. Packaging selected for CSPs is appropriate to preserve the sterility and strength until the beyond-use date.
9. While being used, the compounding environment maintains the sterility or the presterilization purity, whichever is appropriate, of the CSP.
10. Labels on CSPs list the names and amounts or concentrations of ~~all ingredients~~ ■active ingredients and the labels or labeling (see *Labels and Labeling* in *Preservation, Packaging, Storage, and Labeling* section in the *General Notices and Requirements*) of injections list the names and amounts or concentrations of all ingredients (see *Injections* ⟨1⟩).■1S (*USP30*)

[4] U.S. Food and Drug Administration, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, September 2004 (http://www.fda.gov/cder/guidance/5882fnl.htm).

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Before being dispensed, and/or administered, the clarity of solutions is visually confirmed; also, the identity and amounts of ingredients, procedures to prepare and sterilize CSPs, and specific release criteria are reviewed to ensure their accuracy and completeness.

11. Beyond-use dates are assigned on the basis of direct testing or extrapolation from reliable literature sources and other documentation (see *Stability Criteria* and *Beyond-Use Dating* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).
12. Procedures for measuring, mixing, dilution, purification, sterilization, packaging, and labeling conform to the correct sequence and quality established for the specified CSP.
13. Deficiencies in compounding, labeling, packaging, and quality testing and inspection can be rapidly identified and corrected.
14. When time and personnel availability so permit, compounding manipulations and procedures are separated from postcompounding quality inspection and review before CSPs are dispensed and administered.

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

Change to read:

CSP MICROBIAL CONTAMINATION RISK LEVELS

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

The characteristics described below for low-risk, medium-risk, and high-risk CSPs are intended as a guide to the breadth and depth of care necessary in compounding, but they are neither exhaustive nor prescriptive. The licensed healthcare professionals who supervise compounding are responsible for determining the procedural and environmental quality practices and attributes that are necessary for the risk level they assign to specific CSPs.

These risk levels apply to the quality of CSPs immediately after the final aseptic mixing or filling or immediately after the final sterilization, unless precluded by the specific characteristics of the preparation. ~~, such as lipid-based emulsions where administration must be completed within 12 hours of preparation~~

■■1S (*USP30*)
Upon subsequent storage and shipping of freshly finished CSPs, an increase in the risks of chemical degradation of ingredients, contamination from physical damage to packaging, and permeability of plastic and elastomeric packaging is expected. In such cases, compounding personnel

■are to■1S (*USP30*)
consider the potential additional risks to the integrity of CSPs when assigning beyond-use dates. The pre-administration ~~exposure~~

■■1S (*USP30*)
duration and temperature limits specified in the following low-risk, medium-risk, and high-risk level sections apply in the absence of direct ~~testing results or appropriate information sources that justify different limits for specific CSPs. For a summary of the criteria according to risk levels, please see the *Appendix*.~~

■sterility testing results that justify different limits for specific CSPs.■1S (*USP30*)

Low-Risk Level CSPs

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

Low-Risk Conditions—

1. The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 (see *Table 1*) or better air quality using only sterile ingredients, products, components, and devices.
2. The compounding involves only transfer, measuring, and mixing manipulations ~~with closed or sealed packaging systems that are performed promptly and attentively.~~

   ■using no more than three commercially manufactured sterile products and entries into one container package (e.g., bag, vial) of sterile product to make the CSP.■1S (*USP30*)
3. Manipulations are limited to aseptically opening ampuls, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices, ~~and packages of other sterile products,~~

   ■package containers of other sterile products, and containers for storage and dispensing.■1S (*USP30*)
4. For a low-risk preparation, in the absence of passing a sterility test

   ■(see *Sterility Tests* ⟨71⟩),■1S (*USP30*)
   the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 48 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 14 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20° or colder.

Examples of Low-Risk Compounding—

1. Single

   ■volume■1S (*USP30*)
   transfers of sterile dosage forms from ampuls, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers. The ~~content of ampuls require sterile filtration~~

   ■solution content of ampuls should be passed through a sterile filter■1S (*USP30*)
   to remove any particles.
2. Simple aseptic measuring and transferring with not more than three (3) manufactured products including an infusion or diluent solution to compound drug admixtures and nutritional solutions.

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

1. Routine disinfection and air quality testing of the direct compounding environment to minimize microbial surface contamination and maintain ISO Class 5 (see *Table 1*) air quality.
2. Visual confirmation that compounding personnel are properly donning and wearing appropriate items and types of protective garments and goggles.
3. Review of all orders and packages of ingredients to ensure that the correct identity and amounts of ingredients were compounded.

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4. Visual inspection of CSPs to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and the accuracy and thoroughness of labeling.

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed at least annually by each person authorized to compound in a low-risk level under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of low-risk level CSPs. Once begun, this test is completed without interruption. Within an ISO Class 5 ~~air quality environment, (see *Table 1*)~~

■(see *Table 1*) air quality environment,■1S (*USP30*)
three sets of four 5-mL aliquots of sterile Soybean–Casein Digest Medium are transferred with the same sterile 10-mL syringe and vented needle combination into separate sealed, empty, sterile 30-mL clear vials (i.e., four 5-mL aliquots into each of three 30-mL vials). Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials, then the vials are incubated as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

Medium-Risk Level CSPs

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

Medium-Risk Conditions—

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

■4. For a medium-risk preparation, in the absence of passing a sterility test (see *Sterility Tests* ⟨71⟩), the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 9 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20° or colder.■1S (*USP30*)

Examples of Medium-Risk Compounding—

1. Compounding of total parenteral nutrition fluids using manual or automated devices during which there are multiple injections, detachments, and attachments of nutrient source products to the device or machine to deliver all nutritional components to a final sterile container.
2. Filling of reservoirs of injection and infusion devices with ~~multiple~~ ■more than three■1S (*USP30*) sterile drug products and evacuation of air from those reservoirs before the filled device is dispensed.
3. ~~Filling of reservoirs of injection and infusion devices with volumes of sterile drug solutions that will be administered over several days at ambient temperatures between 25° and 40°.~~

■■1S (*USP30*)
3. Transfer of volumes from multiple ampuls or vials into ~~a single, final sterile container or product.~~ ■one or more final sterile containers.■1S (*USP30*)

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

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed

■at least annually■1S (*USP30*)
under conditions that closely simulate the most challenging or stressful conditions encountered during compounding. This test is completed without interruption within an ISO Class 5 ~~air quality environment.(see *Table 1*)~~

■(see *Table 1*) air quality environment.■1S (*USP30*)
Six 100-mL aliquots of sterile Soybean–Casein Digest Medium are aseptically transferred by gravity through separate tubing sets into separate evacuated sterile containers. The six containers are then arranged as three pairs, and a sterile 10-mL syringe and 18-gauge needle combination is used to exchange two 5-mL aliquots of medium from one container to the other container in the pair. For example, after a 5-mL aliquot from the first container is added to the second container in the pair, the second container is agitated for 10 seconds, then a 5-mL aliquot is removed and returned to the first container in the pair. The first container is then agitated for 10 seconds, and the next 5-mL aliquot is transferred from it back to the second container in the pair. Following the two 5-mL aliquot exchanges in each pair of containers, a 5-mL aliquot of medium from each container is aseptically injected into a sealed, empty, sterile 10-mL clear vial, using a sterile 10-mL syringe and vented needle. Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials, then the vials are incubated as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

High-Risk Level CSPs

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

High-Risk Conditions—

1. Nonsterile ingredients, including manufactured products for routes of administration other than those listed under *c.* in the *Introduction* are incorporated or a nonsterile device is employed before terminal sterilization.
2. ~~Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see *Table 1*). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.~~

■Sterile contents of commercially manufactured products, CSPs that lack effective antimicrobial preservatives, and sterile surfaces of devices and containers for the preparation, transfer, sterilization, and packaging of CSPs are exposed to air quality worse than ISO Class 5 (see *Table 1*) for more than 1 hour (see *Immediate Use CSPs* section).■1S (*USP30*)

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3. ~~Nonsterile preparations are exposed for at least 6 hours before being sterilized.~~

■Before sterilization, nonsterile procedures such as weighing and mixing are conducted in air quality worse than ISO Class 7 (see *Table 1*), compounding personnel are improperly garbed and gloved (see *Personnel Cleansing and Garbing*); or water-containing preparations are stored for more than 6 hours.■1S (*USP30*)

4. It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients (see *Ingredient Selection* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).
5. For a

■sterilized■1S (*USP30*)
high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 3 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20° or colder.

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

■containers to remove particulate matter. Sterilization of high-risk level CSPs by filtration shall be performed with a sterile 0.22-µm porosity filter entirely within an ISO Class 5 (see *Table 1*) or superior air quality environment.■1S (*USP30*)

Examples of High-Risk Compounding—

1. Dissolving nonsterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized.
2. ~~Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see *Table 1*). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.~~

■Exposing the sterile ingredients and components used to prepare and package CSPs to room air quality worse than ISO Class 5 (see *Table 1*) for more than 1 hour (see *Immediate Use CSPs* section).■1S (*USP30*)

3. Measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.
4. Assuming, without appropriate evidence or direct determination, that packages of bulk ingredients contain at least 95% by weight of their active chemical moiety and have not been contaminated or adulterated between uses.

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

Example of a Media-Fill Test Procedure CSPs Sterilized by Filtration—This, or an equivalent test, is performed under conditions that closely simulate the most challenging or stressful conditions encountered when compounding high-risk level CSPs.

■[NOTE—Sterility tests for autoclaved CSPs are not required unless they are prepared in batches of more than 25 units.]■1S (*USP30*)

This test is completed without interruption in the following sequence:

1. Dissolve 3 g of nonsterile commercially available Soybean–Casein Digest Medium in 100 mL of nonbacteriostatic water to make a 3%

■nonsterile■1S (*USP30*)
solution.
2. Draw 25 mL of the medium into each of three 30-mL sterile syringes. Transfer 5 mL from each syringe into separate sterile 10-mL vials. These vials are the ~~controls and they generate exponential microbial growth,~~

■positive controls to generate exponential microbial growth, which is■1S (*USP30*)
indicated by visible turbidity upon incubation.
3. Under aseptic conditions and using aseptic techniques, affix a sterile 0.2-µm porosity filter unit and a 20-gauge needle to each syringe. Inject the next 10 mL from each syringe into three separate 10-mL sterile vials. Repeat the process for three more vials. Label all vials, affix sterile adhesive seals to the closure of the nine vials, and incubate them at 25° to 35°. Inspect for microbial growth over 14 days as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

Add the following:

■IMMEDIATE USE CSPs

For the purpose of emergency or immediate patient care, CSPs are exempted from the requirements described in this chapter for *Low-Risk Level, Medium-Risk Level,* and *High-Risk Level CSPs* when all of the following criteria are met:

1. Only simple aseptic measuring and transfer manipulations are performed with not more than three (3) sterile nonhazardous commercial drug and diagnostic radiopharmaceutical drug products, including an infusion or diluent solution.
2. Unless required for the preparation, the preparation procedure occurs continuously without delays or interruptions and does not exceed 1 hour.
3. At no point during preparation and prior to administration are critical surfaces and ingredients of the CSP directly exposed to contact contamination such as human touch,

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cosmetic flakes or particulates, blood, human body substances (excretions and secretions e.g., nasal and oral), and nonsterile inanimate sources.

4. Administration begins not later than one (1) hour following the start of preparing the CSP.
5. When the CSP is not administered by the person who prepared it, or its administration is not witnessed by the person who prepared it, the CSP shall bear a label listing patient identification information such as name and identification number(s), the names and amounts of all ingredients, the name or initials of the person who prepared the CSP, and the exact 1-hour beyond-use time and date.
6. If administration has not begun within one (1) hour following the start of preparing the CSP, the CSP is promptly and safely discarded. *Immediate Use CSPs* shall not be stored for later use.

CSPs containing three (3) or fewer commercial sterile drug products that are stored in excess of one (1) hour before beginning to be administered must comply with the *Low-Risk Level* standards; CSPs containing more than three (3) commercial sterile drug products and those requiring complex manipulations and/or preparation methods must comply with the *Medium-Risk Level* standards; and CSPs prepared from nonsterile ingredients or components must comply with the *High-Risk Level* standards in this chapter. Because of known safety risks of hazardous drugs to healthcare workers and other nonpatients who may be exposed to them, hazardous drugs such as cancer chemotherapy drugs and all those on the National Institute for Occupational Safety and Health list (NIOSH)[5] shall not be prepared as *Immediate Use CSPs*. Hazardous drugs must be prepared using suitable ISO Class 5 (see *Table 1*) environment containment equipment and/or devices in a manner fully compliant with the standards in this chapter including the *Hazardous Drugs as CSPs* section. Personnel who prepare and administer *Immediate Use CSPs* are responsible for recognizing the potential harm to patients that may result when such CSPs are microbially contaminated and administered over long durations. Compounding in worse than ISO Class 5 (see *Table 1*) conditions increases the likelihood of microbial contamination, and administration durations exceeding a few hours increase the potential for clinically significant microbial colonization; thus, for patient harm.▪1S (*USP30*)

[5] NIOSH, see Appendix A at http://www.cdc.gov/niosh/docs/2004-165/.

Add the following:

▪SINGLE-DOSE AND MULTIPLE-DOSE CONTAINERS

Opened or needle-punctured single-dose containers such as ampuls, bags, bottles, syringes, and vials of sterile products and CSPs shall be used within 1 hour if opened in worse than ISO Class 5 (see *Table 1*) air quality (see *Immediate Use CSPs* section), and any remaining contents must be discarded. Single-dose vials exposed to ISO Class 5 (see *Table 1*) or cleaner air may be used up to 6 hours after initial needle puncture. Opened single-dose ampuls shall not be stored for any time period.

Multiple-dose containers (e.g., vials) are formulated for removal of portions on multiple occasions because they contain antimicrobial preservatives. The beyond-use date after initially entering or opening (e.g., needle-punctured) multiple-dose containers is 28 days (see *Antimicrobial Effectiveness Testing* ⟨51⟩), unless otherwise specified by the manufacturer.▪1S (*USP30*)

Add the following:

▪HAZARDOUS DRUGS AS CSPs

Although the potential therapeutic benefits of compounded sterile preparations (CSPs) outweigh the risks of their adverse effects in ill patients, exposed healthcare workers risk similar adverse effects with no therapeutic benefit. Occupational exposure to hazardous drugs (see "Sample list of drugs that should be handled as hazardous" in Appendix A of NIOSH Publication No. 2004-165: *Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care*

Settings at http://www.cdc.gov/niosh/docs/2004-165/) can result in (1) acute effects, such as skin rashes; (2) chronic effects, including adverse reproductive events; and (3) possibly cancer.

Hazardous drugs shall only be prepared for administration under conditions that protect the healthcare workers and other personnel in the preparation and administration area. Hazardous drugs shall be stored separately from other inventory in a manner to prevent contamination and personnel exposure. Such storage is preferably within a containment area such as a negative pressure room. The storage area must have sufficient general exhaust ventilation, at least 12 air exchanges per hour (ACPH)[6] to dilute and remove any airborne contaminants. Hazardous drugs shall be handled with caution using appropriate chemotherapy gloves during distribution, receiving, stocking, inventorying, preparing for administration, and disposal.

Hazardous drugs shall be prepared in an ISO Class 5 (see *Table 1*) environment with protective engineering controls in place, and following aseptic practices specified for the appropriate contamination risk levels defined in this chapter. Access shall be limited to areas where drugs are stored and prepared to protect persons not involved in drug preparation. All hazardous drugs shall be prepared in a Class II or III biological safety cabinet (BSC), or a compounding aseptic isolator (CAI) that meets or exceeds the standards for CAI in this chapter. When other primary engineering controls, e.g., closed-system vial-transfer devices (CSTD) are used, this shall be within the BSC or CAI to provide backup containment and ISO Class 5 (see *Table 1*) environment. The ISO Class 5 (see *Table 1*) BSC or CAI shall be placed in an ISO Class 7 (see *Table 1*) room that is physically separated, i.e., a different room, from other preparation areas, and optimally has no less than 0.01-inch water column negative pressure[1] to adjacent positive pressure ISO Class 7 (see *Table 1*), or better, anterooms, thus providing inward airflow to contain any airborne drug. If a compounding isolator that meets the requirements of this chapter is used outside of a cleanroom, the room must maintain a minimum negative pressure of 0.01 inch water column and have a minimum of 12 air changes per hour (ACPH). Note that an anteroom leading to a positive pressure room may be ISO Class 8 (see *Table 1*) but an anteroom leading to a negative pressure room shall meet at least ISO Class 7 (see *Table 1*) criteria so that air drawn into the negative pressure environment is of the same ISO Class 7 (see *Table 1*) quality. A pressure indicator shall be installed that can be readily monitored for correct room pressurization. The BSC and CAI optimally shall be 100% vented to the outside air through HEPA filtration (see the Ventilated cabinet section at http://www.cdc.gov/niosh/docs/2004-165/). In facilities that prepare a very low volume of hazardous drugs (e.g., less than 5 preparations/week), the use of two tiers of containment, e.g., CSTD within a BSC or CAI that are located in a non-negative pressure room is acceptable. In addition, containment of the finished hazardous product shall be maintained throughout the administration/disposal phase utilizing needleless or closed administration systems.

Appropriate personnel protective equipment (PPE) shall be worn when compounding in a BSC or CAI, and when using CSTD devices. Appropriate PPE may include gowns, face masks, eye protection, hair covers, shoe covers or dedicated shoes, double gloving, and complying with manufacturers' recommendations when using CAI (http://www.cdc.gov/niosh/docs/2004-165/).

All personnel who compound hazardous drugs shall be fully trained in the storage, handling, and disposal of these drugs. This training shall occur prior to preparing or handling hazardous CSPs, and its effectiveness shall be verified by testing specific hazardous drugs preparation techniques; such verification shall be documented for each person at least annually. This training must include didactic overview of hazardous drugs including mutagenic, teratogenic, and carcinogenic properties, and it shall include ongoing training for each new hazardous drug that enters the marketplace. Compounding personnel of

[6] Guidelines for Environmental Infection Control in Health-Care Facilities, Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC), MMWR, vol. 52, no. RR-10, June 6, 2003, figure 3, pg. 12.

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reproductive capability must confirm in writing that they understand the risks of handling hazardous drugs. The training shall include at least the following: (1) safe aseptic manipulation practices; (2) negative pressure techniques when utilizing BSC or CAI; (3) correct use of CSTD devices; (4) containment, clean-up, and disposal procedures for breakages and spills; and (5) treatment of personnel contact and inhalation exposure.

[NOTE—Because standards of assay and unacceptable quantities of contamination of each drug have not been established in the literature, the following paragraph is a recommendation only. Future standards will be adopted as these assay methods are developed and proven.] Ongoing quality assurance shall be an integral part of hazardous drug preparation. In order to assure containment, especially in operations preparing large volumes of hazardous drugs, environmental sampling to detect uncontained hazardous drugs needs to be performed routinely: e.g., initially as a benchmark and at least every 6 months. This sampling shall include surface wipe sampling of the working area of BSC and CAI, counter tops where finished preparations are placed, areas adjacent to BSC and CAI, including the floor directly under the working area, and patient administration areas. Common marker hazardous drugs that can be assayed include cyclophosphamide, ifosfamide, methotrexate and fluorouracil. If any measurable contamination (cyclophosphamide levels greater than 1.00 ng/cm^2 has been found to cause human uptake) is found by any of these quality assurance procedures, practitioners shall make the decision to identify, document, and contain the cause of contamination. Such action may include retraining, thorough cleaning, and improving engineering controls.

Disposal of all hazardous drug wastes shall comply with all applicable federal and state regulations. All personnel who perform routine custodial waste removal and cleaning activities in storage and preparation areas for hazardous drugs shall be trained in appropriate procedures to protect themselves and prevent contamination. The NIOSH Publication No. 2004-165 at www.cdc.gov/niosh/docs/2004-165/ and the references under the heading, Sterile Hazardous Preparations at http://www.ashp.org/SterileCpd/ are recommended sources for education and training in principles and practices of safety with hazardous drugs.■1S (*USP30*)

Add the following:

▪RADIOPHARMACEUTICALS AS CSPs

Compounding of radiopharmaceuticals for positron emission tomography (PET) shall be performed as specified in the general test chapter *Radiopharmaceuticals for Positron Emission Tomography—Compounding* ⟨823⟩. In the case of PET compounding, chapter ⟨823⟩ supersedes this chapter.

For the purposes of this chapter, the following shall be designated *Low-Risk Level CSPs*: (1) radiopharmaceutical dosage units with volumes of 15 mL and less and expiration times of 18 hours and shorter, such as those prepared from eluates from technetium-99m/molybdenum 99 generator systems; and (2) commercially manufactured cyclotron radiopharmaceuticals that contain preservatives and bear expiration times of 72 hours or shorter. These radiopharmaceuticals shall be compounded using appropriately shielded vials and syringes in a properly functioning and certified vertical LAFW, Class II Type B2 BSC, or other suitable containment device (e.g., CAI) located in an ISO Class 8 (see *Table 1*) or cleaner air environment to permit compliance with special handling, shielding, and negative air flow requirements. Radiopharmaceutical vials, designed for multi-use, compounded with technetium-99m, exposed to ISO Class 5 (see *Table 1*) environment and punctured by needles with no direct contact contamination may be used up to the time indicated by manufacturer's recommendations. Storage and transport of properly shielded vials of radiopharmaceutical CSPs may occur in a limited access ambient environment without a specific ISO Class designation.

Technetium-99m/molybdenum-99 generator systems shall be stored and eluted (operated) under conditions recommended by manufacturers and applicable state and federal

regulations. Such generator system shall be eluted in an ISO Class 8 (see *Table 1*) or cleaner air environment to permit special handling, shielding, and air flow requirements. To limit acute and chronic radiation exposure of inspecting personnel to a level that is as low as reasonably achievable (ALARA), direct visual inspection of radiopharmaceutical CSPs containing high concentrations or doses of radioactivity shall be avoided.■1S (*USP30*)

Change to read:

VERIFICATION OF COMPOUNDING ACCURACY AND ~~STERILIZATION~~

■STERILITY■1S (*USP30*)

The compounding procedures and sterilization methods for CSPs correspond to correctly designed and verified written documentation in the compounding facility. Verification requires ~~planned testing designed to demonstrate effectivenes of all procedures critical to the~~

■planned testing, monitoring, and documentation to demonstrate adherence to environmental quality requirements, personnel practices, and procedures critical to achieving and maintaining sterility,■1S (*USP30*)
accuracy, and purity of finished CSPs. For example, sterility testing (see *Test for Sterility of the Product To Be Examined* under *Sterility Tests* ⟨71⟩) may be applied to specimens of low- and medium-risk CSPs, and standard nonpathogenic bacterial cultures may be added to nondispensable specimens of high-risk CSPs before terminal sterilization for subsequent evaluation by sterility testing. Packaged and labeled CSPs are visually inspected for physical integrity and expected appearance, including final fill amount. ~~To ensure that the identities and concentrations of ingredients are accurate, and in the absence of reliable observations and data to confirm and extrapolate those parameters, samples of CSPs are assayed.~~

■The accuracy of identities, concentrations, amounts, and purities of ingredients in CSPs is confirmed by reviewing labels on packages, observing and documenting correct measurements with approved and correctly standardized devices, and reviewing information in labeling and certificates of analysis provided by suppliers. When the correct identity, purity, strength, and sterility of ingredients and components of CSPs cannot be confirmed (e.g., in the case of unlabeled syringes, opened ampuls, punctured stoppers of vials and bags, or containers of ingredients with incomplete labeling), such ingredients and components shall be discarded immediately.

Some individual ingredients, such as bulk drug substances, are not labeled with expiration dates when they are stable indefinitely in their commercial packages under their labeled storage conditions. However, despite retaining full chemical stability, such ingredients may gain or lose moisture during storage and use. Changes in moisture content may require testing (see *Loss on Drying* ⟨731⟩) to determine the correct amount to weigh for accurate content of active chemical moieties in CSPs (see *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩).

Although not required, a quantitative stability-indicating chemical assay is recommended to ensure compounding accuracy of CSPs, especially those that contain drug ingredients with a narrow therapeutic plasma concentration range.■1S (*USP30*)

Sterilization Methods

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

■(e.g., see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩■1S (*USP30*)
—and, preferably, verified wherever possible—to achieve sterility in the particular CSPs. General guidelines for matching CSPs and components to appropriate sterilization methods include the following:

1. CSPs have been ascertained to remain physically and chemically stable when subjected to the selected sterilization method.
2. Glass and metal devices may be covered tightly with aluminum foil, then exposed to dry heat in an oven at a mean temperature of 250° for ~~2 hours~~

   ■30 minutes■1S (*USP30*)
   to achieve sterility and depyrogenation (see *Dry-Heat Sterilization* under *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩and *Bacterial Endotoxins Test* ⟨85⟩). Such items are either used immediately or stored until use in an environment suitable for compounding low- and medium-risk CSPs.
3. Personnel ascertain from appropriate information sources that the sterile microporous membrane filter used to sterilize CSP solutions, either during compounding or administration, is chemically and physically compatible with the CSP.

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~~STERILIZATION BY FILTRATION~~

▪Sterilization of High-Risk Level CSPs by Filtration▪1S (*USP30*)

Commercially available sterile filters must be approved for human-use applications in sterilizing pharmaceutical fluids. ~~Both filters that must be sterilized before processing CSPs and those filters that are commercially available, disposable, sterile, and pyrogen-free have a nominal porosity of 0.2 µm, which includes 0.22 µm porosity.~~

▪Sterile filters used to sterilize CSPs shall be pyrogen-free and have a nominal porosity of 0.2 µm or 0.22 µm.▪1S (*USP30*) They should be certified by the manufacturer to retain at least 10^7 microorganisms of a strain of *Brevundimonas (Pseudomonas) diminuta* on each cm^2 of upstream filter surface ~~under conditions similar to those in which the CSPs will be sterilized. In emergency situations when sterile 0.2-µm porosity membranes are not available, filters of the same composition and 0.45-µm nominal porosity may be used. Sterilizing filters with 0.2-µm and 0.45-µm nominal porosities will not remove bacterial endotoxins and viruses by physical retention.The~~

▪area under conditions similar to those in which the CSPs will be sterilized (see *High-Risk Conditions* in *High-Risk Level CSPs* section).▪1S (*USP30*)

~~The supervising health care professional~~

▪The compounding supervisor▪1S (*USP30*) must ensure, directly or from appropriate documentation, that the filters are chemically and physically stable at the pressure and temperature conditions to be used

▪and have enough capacity to filter volumes,▪1S (*USP30*) and that the filters will achieve sterility and maintain prefiltration pharmaceutical quality, ~~of the specific CSP. The filter dimensions and material~~

▪including strength of ingredients, of the specific CSP. The filter dimensions and liquid material to be sterile-filtered▪1S (*USP30*) must permit the sterilization process to be completed rapidly without the replacement of the filter during the process. When CSPs are known to contain excessive particulate matter, a prefilter or larger porosity membrane is placed upstream from the sterilizing filter to remove gross particulate contaminants in order to maximize the efficiency of the sterilizing filter.

~~When filter devices are assembled from separate nonsterile components by compounding personnel, such devices shall be identified to be sterile and ascertained to be effective under relevant conditions before they are used to sterilize CSPs. For example, sterility can be identified using biological indicators (see *Biological Indicators* ⟨1035⟩). Filter units used to sterilize CSPs~~

▪Filter units used to sterilize CSPs must▪1S (*USP30*) also be subjected to the manufacturer's recommended integrity test, such as the bubble point test.

~~When commercially available sterile disposable filter devices are used, the Compounding personnel may accept the written certification from suppliers that the filters retain at least 10^5 cfu of *Brevundimonas (Pseudomonas) diminuta* on each cm^2 of filter surface.~~

▪▪1S (*USP30*)

Compounding personnel must ascertain that selected filters will achieve sterilization of the particular CSPs being sterilized. Large deviations from usual or expected chemical and physical properties of CSPs,

▪for example, water-miscible alcohols,▪1S (*USP30*) may cause undetectable damage to filter integrity and shrinkage of microorganisms to sizes smaller than filter porosity.

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

▪▪1S (*USP30*)

~~STEAM STERILIZATION~~

▪Sterilization of High-Risk Level CSPs by Steam▪1S (*USP30*)

The process of thermal sterilization employing saturated steam under pressure, or autoclaving, is the preferred method to terminally sterilize aqueous preparations that have been verified to maintain their full chemical and physical stability under the conditions employed (see *Steam Sterilization* under *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩). To achieve sterility, ~~it is necessary that all materials~~

▪all materials are to▪1S (*USP30*) be exposed to steam at 121°, under a pressure of about one atmosphere or 15 psi, for the duration verified by testing to achieve sterility of the items, which is usually 20 to 60 minutes for CSPs. An allowance must be made for the time required for the material to reach 121° before the sterilization exposure duration is timed.

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

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

▪Sterilization of High-Risk Level CSPs by Dry Heat

Dry heat sterilization is usually done as a batch process in an oven designed for sterilization. Heated filtered air should be evenly distributed throughout the chamber by a blower device. The oven should be equipped with a system for controlling temperature and exposure period. Sterilization by dry heat requires higher temperatures and longer exposure times than

sterilization by steam. Dry heat should only be used for those materials that cannot be sterilized by steam, when the moisture would either damage or be impermeable to the materials. During sterilization sufficient space should be left between materials to allow for good circulation of the hot air. The effectiveness of dry heat sterilization shall be verified using appropriate biological indicators (see *Biological Indicators* ⟨1035⟩) and temperature sensing devices.■1S (*USP30*)

Change to read:

PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS

Personnel who prepare CSPs must be ~~provided with appropriate training from~~

■trained conscientiously and skillfully by■1S (*USP30*)
expert personnel, audio–video instructional sources, and professional publications in the theoretical principles and practical skills of aseptic manipulations

■and in achieving and maintaining ISO Class 5 (see *Table 1*)

environmental conditions■1S (*USP30*)
before they begin to prepare CSPs. Compounding personnel shall perform didactic review and pass written and media-fill testing of aseptic manipulative skills initially; at least annually thereafter for low- and medium-risk level compounding; and semiannually for high-risk level compounding. Compounding personnel who fail written tests, or whose media-fill test vials result in gross microbial colonization, must be immediately reinstructed and re-evaluated by expert compounding personnel to ensure correction of all aseptic practice deficiencies.

Media-Fill Challenge Testing—The skill of personnel to aseptically prepare CSPs may be evaluated using sterile fluid bacterial culture media-fill ~~validation,~~

■verification,[7]■1S (*USP30*)
(i.e., sterile bacterial culture medium transfer via a sterile syringe and needle). Media-fill testing is used to assess the quality of the aseptic skill of compounding personnel. Media-fill tests represent the most challenging or stressful conditions actually encountered by the personnel being evaluated when they prepare particular risk level CSPs and when sterilizing high-risk level CSPs.

Commercially available sterile fluid culture media, such as Soybean–Casein Digest Medium (see *Sterility Tests* ⟨71⟩), shall be able to promote exponential colonization of bacteria that are most likely to be transmitted to CSPs from the compounding personnel and environment. Media-filled vials are

■generally■1S (*USP30*)
incubated ~~at 25° to 35°~~

■within a range of 20° to 35°■1S (*USP30*)
for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

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

■■1S (*USP30*)

[7] FDA Guideline on Guidance for Industry Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, September 2004 (http://www.fda.gov/cder/guidance/5882fnl.htm).

Change to read:

ENVIRONMENTAL QUALITY AND CONTROL

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

~~Critical Site Exposure~~

■Exposure of Critical Sites■1S (*USP30*)

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

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

■Critical sites include ingredients of CSPs and locations on devices and components used to prepare, package, and transfer CSPs that provide opportunity for exposure to contamination. The risk of critical sites becoming contaminated increases with the duration of exposure, the potency and concentration of the contaminants, and the spatial area of the critical sites. Critical sites for low-, medium-, and high-risk level CSPs must not be exposed to air quality worse than ISO Class 5 (see *Table 1*).■1S (*USP30*)

The size of the critical site affects the risk of contamination entering the product: the greater the exposed area, the greater the risk. ~~An open~~

■For example, an open ampul,■1S (*USP30*)
vial, or bottle exposes to contamination a critical site of much larger area than the tip of a 26-gauge needle. Therefore, the risk of contamination when entering an open

■ampul,■1S (*USP30*)
vial, or bottle is much greater than during the momentary exposure of a needle tip.

The nature of a critical site also affects the risk of contamination. The relatively rough, permeable surface of an elastomeric closure retains microorganisms and other contaminants, after swabbing with ~~an alcohol~~

■a 70% isopropyl alcohol (IPA)■1S (*USP30*)
pad, more readily than does the smoother glass surface of the neck of an ampul. Therefore, the surface disinfection can be expected to be more effective for an ampul.

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~~Once the ampul is open, the critical site of exposure is greatly increased, creating a pathway with the potential for introduction of glass, fiber, and dust into the fluid contained in the ampul.~~

■1S (*USP30*)
The prevention or elimination of

■physical contact contamination and■1S (*USP30*)
airborne particles must be given high priority. Airborne contaminants,

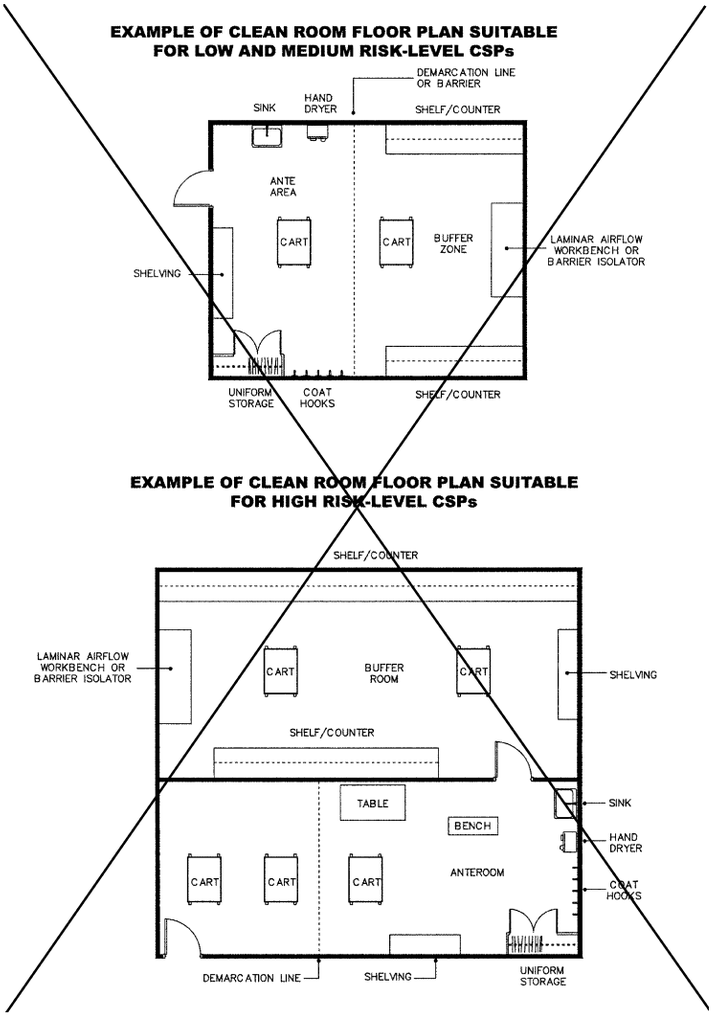
■especially those generated by sterile compounding personnel,■1S (*USP30*)
are much more likely to reach critical sites than contaminants that are adhering to the floor or other surfaces below the work level. Further, particles that are relatively large or of high density settle from the airspace more quickly, and thus ~~can be removed from the vicinity of critical sites.~~

■they must be precluded from ISO Class 5 (see *Table 1*) environments in which critical sites are exposed.■1S (*USP30*)

~~Clean Rooms and Barrier Isolators~~

■ISO Class 5 Air Sources, Cleanrooms, Buffer Zones, and Anterooms■1S (*USP30*)

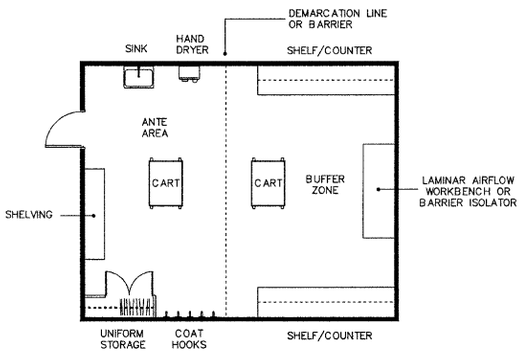
~~In general, sterile product preparation facilities utilize laminar airflow workbenches (LAFWs) to provide an adequate critical site environment. A discussion of the necessary facilities and proper procedures for preparing sterile products using LAFWs in clean rooms is presented below. The use of alternative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



~~Fig. 1~~

■The most common sources of ISO Class 5 (see *Table 1*) air quality for exposure of critical sites are horizontal and vertical LAFWs and CAIs. A cleanroom (see *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨1116⟩) is a compounding environment that is supplied with high-efficiency particulate air (HEPA), or HEPA-filtered air, that meets ISO Class 7 (see *Table 1*), the access to which is limited to personnel trained and authorized to perform sterile compounding and facility cleaning. A buffer zone is an area that provides at least ISO Class 7 (see *Table 1*) air quality. An anteroom or ante-area provides at least ISO Class 8 air quality. *Figure 1* illustrates placement of LAFWs in cleanrooms used for low-risk and medium-risk level (top) and high-risk level (bottom) sterile compounding. The floor plans depicted in *Figure 1* are suggestions only, not restrictive or prescriptive requirements. Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and cleanrooms is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring (see the *Environmental Monitoring* section). It is the responsibility of each compounding facility to ensure that each source of ISO Class 5 (see *Table 1*) environment for exposure of critical sites and sterilization by filtration is properly located, operated, maintained, monitored, and verified.

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



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

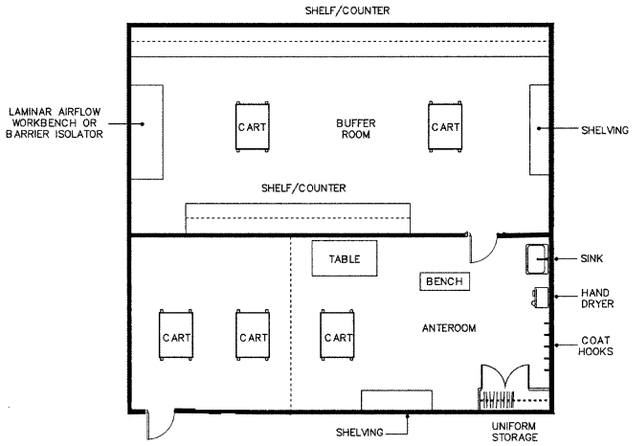


Figure 1■1S (*USP30*)

~~**Environmental Controls**~~

▪**Facility Design and Environmental Controls**▪1S (*USP30*)

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

▪Compounding facilities are physically designed and environmentally controlled to minimize airborne contamination contacting critical sites. Primary engineering controls typically include, but are not limited to, LAFWs, BSCs, and CAIs, which provide an ISO Class 5 (see *Table 1*) environment for the exposure of critical sites. Primary engineering controls must maintain ISO Class 5 (see *Table 1*) or better conditions for 0.5-µm particles (dynamic operating conditions) while compounding CSPs. Secondary engineering controls such as cleanrooms and anterooms generally provide a buffer zone or buffer room as a core for the location of the primary engineering control. Buffer zones or cleanrooms are designed to maintain at least ISO Class 7 (see *Table 1*) conditions for 0.5-µm particles under dynamic conditions and ISO Class 8 (see *Table 1*) conditions for 0.5-µm and larger particles under dynamic conditions for the anterooms and ante-areas. Airborne contamination control is achieved in the primary engineering control through the use of HEPA filters. The airflow in the primary engineering control is typically unidirectional (laminar flow) and because of the particle collection efficiency of the filter, the "first air" at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination. HEPA-filtered air should be supplied in critical areas (ISO Class 5, see *Table 1*) at a velocity sufficient to sweep particles away from the compounding area and maintain unidirectional airflow during operations. Proper design and control prevents turbulence and stagnant air in the critical area. In situ air pattern analysis via smoke studies should be conducted at the critical area to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions.[7] The principles of HEPA filtered unidirectional airflow in the work environment must be understood and practiced in the compounding process in order to achieve the desired environmental conditions. Policies and procedures for maintaining and working within the primary engineering control area must be written and followed. The policies and procedures will be determined by the scope and risk levels of the aseptic compounding activities utilized during the preparation of the CSPs. The CSP work environment is designed to have the cleanest work surfaces (primary engineering controls) located in a buffer area. The buffer area should maintain at least ISO Class 7 (see *Table 1*) conditions for 0.5-µm and larger particles under dynamic operating conditions. The room should be segregated from surrounding, unclassified spaces to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment and this segregation should be continuously monitored. For rooms providing a physical separation, through the use of walls, doors and pass-throughs, a minimum differential positive pressure of 0.02 to 0.05 inches water column is required. For cleanrooms or buffer zones not physically separated from the anteroom, the principle of displacement airflow should be employed. This concept utilizes a low pressure differential, high airflow principle. Using displacement airflow typically requires an air velocity of 40 feet per minute (fpm) or more from the buffer room across the line of demarcation into the ante-area. The displacement concept is not applied to high risk compounding applications.[8] The primary engineering control should be placed within a buffer room in such a manner as to avoid conditions that could adversely affect its operation. For example, strong air currents from opened doors, personnel traffic, or air streams from the HVAC systems can disrupt the unidirectional airflow in open-faced workbenches. The operators may also create disruptions

[8] ISO 14644-4 : 2001 Cleanrooms and associated controlled environments—Design, construction, and start-up, *Case Postale 56,* CH-1211 Geneve 20, Switzerland, tel. +41 22 749 01 11.

in airflow by their own movements and by the placement of objects onto the work surface. The primary engineering control should be placed out of the traffic flow and in a manner to avoid disruption from the HVAC system and room cross-drafts. Room air exchanges are typically expressed as air changes per hour (ACPH). Adequate HEPA filtered airflow supplied to the cleanroom and anteroom is required to maintain cleanliness classification during operational activity through the number of air changes per hour. Factors that should be considered when determining air-change requirements include number of personnel working in the room, compounding processes that generate particulates, as well as temperature effects. An ISO Class 7 (see *Table 1*) cleanroom supplied with HEPA filtered air shall receive an ACPH of not less than 30. The primary engineering control is a good augmentation to generating air changes in the air supply of a room but cannot be the sole source of HEPA filtered air. If the room has an ISO Class 5 (see *Table 1*) recirculating device, a minimum of 15 ACPH through the room supply HEPA filters is adequate providing the combined ACPH is not less than 30. More air changes may be required based on the number of personnel and processes. HEPA filtered supply air is introduced at the ceiling with low-wall mounted returns, creating a general top-down dilution of room air with HEPA filtered make-up air. Ceiling mounted returns are not recommended. All HEPA filters should be efficiency tested using the most penetrating particle size and should be leak tested at the factory and then leak tested again in situ after installation.[9] Activities and tasks carried out within the buffer area should be limited to only those necessary when working within a controlled environment. Only the furniture, equipment, supplies, and other material required for the compounding activities to be performed should be brought into the room. They should be nonpermeable, nonshedding, cleanable, and resistant to disinfectants. Whenever such items are brought into the room, they should first be cleaned and disinfected. Whenever possible, equipment and other items used in the buffer area should not be taken out of the room except for calibration, servicing, or other activities associated with the proper maintenance of the item. The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area should be smooth, impervious, free from cracks and crevices, and nonshedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate. The surfaces should be resistant to damage by disinfectant agents. Junctures of ceilings to walls should be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic, and they should be caulked around each perimeter to seal them to the support frame. Walls may be constructed of flexible material (e.g., heavy gauge polymer), panels locked together and sealed, or of epoxy-coated gypsum board. Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. Dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills, should be avoided. The exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls should be sealed. The buffer area shall not contain sources of water (sinks) or floor drains. Work surfaces should be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are easily cleaned and disinfected. Carts should be of stainless steel wire, nonporous plastic, or sheet metal construction with good quality, cleanable casters to promote mobility. Storage shelving, counters, and cabinets should be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and disinfectable. Their number, design, and manner of installation should promote effective cleaning and disinfection. Placement of devices (e.g., computers and printers) and objects (e.g., carts and cabinets) that are not essential to compounding in buffer zones and

[9] By definition (IEST RP CC 001.4), HEPA filters are a minimum of 99.97% efficient when tested using 0.3-µm thermally generated particles and a photometer or rated at their most penetrating particle size using a particle counter.

cleanrooms is dictated by their effect on the required environmental quality of air atmospheres and surfaces, which must be verified by monitoring.■ IS (*USP30*)

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

Class Name		Particle	
ISO Class	U.S. FS 209E	ISO, m³	FS 209E, ft.³
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3520	100
6	Class 1000	35,200	1000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

[a] Adapted from Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO 4644-1:1999, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 µm per m³ or larger (ISO Class 5) is equivalent to 100 particles per ft³ (Class 100).

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

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

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

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

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

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

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

CSP Environment

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

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

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

▪Placement of Primary Engineering Controls Within ISO Class 7 Buffer Areas

Primary engineering controls (LAFWs, BSCs, and CAIs) are located within a restricted access ISO Class 7 (see *Table 1*) buffer area within a cleanroom with the exception below (see *Figure 1*). Only authorized personnel and materials required for compounding and cleaning are permitted in the buffer area. Presterilization procedures for high-risk level CSPs, such as weighing and mixing, shall be completed in an ISO Class 8 (see *Table 1*) or better environment.

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CAIs must be placed in an ISO Class 7 (see *Table 1*) cleanroom *unless* they meet all of the following conditions: The isolator must provide isolation from the room and maintain ISO Class 5 (see *Table 1*) during dynamic operating conditions including transferring ingredients, components, and devices into and out of the isolator and during preparation of CSPs. Particle counts sampled approximately 6 to 12 inches upstream of the critical exposure site must maintain ISO Class 5 (see *Table 1*) levels during compounding operations. It is incumbent on the compounding personnel to obtain documentation from the manufacturer that the CAI will meet this standard when located in worse than ISO Class 7 (see *Table 1*) environments.

Additional Personnel Requirements

Food, drinks, and materials exposed in patient-care and treatment areas, must not enter anterooms, ante-areas, and buffer areas where components and ingredients of CSPs are present. When compounding activities require the manipulation of a patient's blood-derived or other biological material (e.g., radiolabeling a patient's or a donor's white-blood cells), the manipulations must be clearly separated from routine paths and equipment used in CSP preparation activities, and they must be controlled by specific standard operating procedures in order to avoid any cross-contamination. Packaged compounding supplies and components, such as needles, syringes, tubing sets, and small- and large-volume parenterals, should be uncartoned and wiped down with a disinfectant that does not leave a residue (e.g., 70% IPA) when possible in an anteroom-type area, of ISO Class 8 (see *Table 1*) air quality, before being passed into the buffer areas. Personnel hand hygiene and garbing procedures are also performed in the anteroom or ante-area, which may contain a sink that enables hands-free use with a closed system of soap dispensing to minimize the risk of extrinsic contamination. There shall be some demarcation designation that separates the anteroom, or ante-area, from the buffer area. Adequate provision for performing antiseptic hand cleansing utilizing an alcohol-based surgical hand scrub with persistent activity followed by the donning of sterile gloves should be provided after entry into the buffer area. ■1S (*USP30*)

~~**Cleaning and Sanitizing the Workspaces**~~

■Cleaning And Disinfecting The Sterile Compounding Areas■1S (*USP30*)

~~The cleaning, sanitizing, and organizing of the direct and contiguous compounding areas (DCCA) is the responsibility of trained operators (pharmacists and technicians) following written procedures and is performed at the beginning of each shift.~~

■The cleaning and disinfecting practices and frequencies in this section apply to direct and contiguous compounding areas (DCCAs), which include ISO Class 5 (see *Table 1*) compounding areas for exposure of critical sites as well as buffer rooms, anterooms, and ante-areas (see *Table 2*). Trained compounding personnel are responsible for developing and practicing written procedures for cleaning and disinfecting the DCCAs. These procedures shall be conducted at the beginning of each work shift and when there are spills or environmental quality breaches. ■1S (*USP30*)

Before compounding is performed, all items are removed from the DCCA and all surfaces are cleaned of loose material and residue from spills, followed by an application of a residue-free ~~sanitizing agent, that is left on for a time sufficient to exert its antimicrobial effect.[10]~~

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

■disinfecting agent (e.g., IPA), that is left on for a time sufficient to exert its antimicrobial effect. Work surfaces in the ISO Class 7 (see *Table 1*) buffer areas and ISO Class 8 (see *Table 1*) anterooms or ante-areas are cleaned and disinfected at least daily, and dust and debris are removed when necessary from storage sites for compounding ingredients and supplies, using a method that does not degrade the ISO Class 7 or 8 (see *Table 1*) air quality (see *Disinfectants and Antiseptics* ⟨1072⟩).

~~[10] Approved by the pharmacist in charge.~~

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Table 2. Minimum Frequency of Cleaning and Disinfecting Sterile Compounding Areas

Site	Minimum Frequency
ISO Class 5 (see *Table 1*) Primary Engineering Control (e.g., LAFW, BSC, CAI)	At the beginning of each shift
Counters and easily cleanable work surfaces	Daily
Floors	Daily
Walls	Monthly
Ceilings	Monthly
Storage shelving	Monthly

■1S (*USP30*)

Floors in the buffer or clean area are cleaned by mopping once daily when no aseptic operations are in progress. Mopping may be performed by trained and supervised custodial personnel using approved agents described in the written procedures. Only approved cleaning and ~~sanitizing~~

■disinfecting■1S (*USP30*)
agents are used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Their schedules of use and methods of application are in accord with written procedures. All cleaning tools, such as wipers, sponges, and mops, are nonshedding and dedicated to use in the buffer or clean area. Floor mops may be used in both the buffer or clean area and anteroom area, but only in that order. Most wipers are discarded after one use. If cleaning tools are reused, their cleanliness is maintained by thorough rinsing and disinfecting after use and by storing in a clean environment between uses. Trash is collected in suitable plastic bags and removed with minimal agitation.

In the anteroom area,

■walls, ceilings, and shelving shall be cleaned monthly.■1S (*USP30*)
Supplies and equipment removed from shipping cartons are wiped with a ~~sanitizing agent, such as sterile 70% isopropyl alcohol (IPA)[2], which is checked periodically for contamination. Alternatively, if supplies are planned to be~~

■disinfecting agent, such as IPA. The IPA shall be delivered from a wash or spray bottle, the discharge opening of which must not contact any objects or materials before contacting the surfaces to be disinfected. Wiping with small IPA swabs that are commercially available in individual foil-sealed packages is preferred for disinfecting stoppers on bags and vials before they are pierced with sterile needles and for necks of ampuls before they are broken. The surface of IPA swabs for disinfecting stoppers must not contact any other object before contacting the stoppers. After IPA is sprayed or wiped on a surface to be disinfected, allow the IPA to remain for at least 30 seconds before the surface is contacted to prepare CSPs. Alternatively, if supplies are■1S (*USP30*)
received in sealed pouches, the pouches can be removed as the supplies are introduced into the buffer or clean area without the need to ~~sanitize~~

■disinfect■1S (*USP30*)
the individual supply items. No shipping or other external cartons may be taken into the buffer or clean area.

Cleaning and ~~sanitizing of the anteroom area is performed at least weekly~~

■disinfecting of counters and other easily cleanable surfaces of the anteroom area is performed at least daily■1S (*USP30*)
by trained and supervised custodial personnel, in accordance with written procedures. However, floors are cleaned and ~~sanitized~~

■disinfected■1S (*USP30*)
daily, always proceeding from the buffer or clean area to the anteroom area. ~~Storage shelving is emptied of all supplies and cleaned and sanitized at planned intervals, preferably monthly.~~

■Storage shelving, emptied of all supplies, walls, and ceilings are cleaned and disinfected at planned intervals, monthly if not more frequently.■1S (*USP30*)

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

■■1S (*USP30*)

Personnel Cleansing and ~~Gowning~~

■Garbing■1S (*USP30*)

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

~~Prior to entering the buffer or clean area, operators should remove outer lab jackets or the like, makeup, and jewelry and should thoroughly scrub hands and arms to the elbow. After drying hands and arms they should properly don clean, nonshedding uniform components, including hair covers, shoe covers, knee-length coats or coveralls, and appropriate protective gloves, in that order. The coats should fit snugly at the wrists and be zipped or snapped closed in the front. Shoe covers should be donned so that feet then touch the floor only on the clean side of the bench or other demarcation. Face masks should be donned just before beginning activities in the DCCA to minimize airborne contaminants from coughing, sneezing, and talking.~~

~~When preparing CSPs in a vertical flow LAFW with a transparent shield between the face of the operator and sterile components, or when using an isolator, wearing a face mask is optional, but head and facial hair must be covered.~~

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

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

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~~ing protracted compounding activities, personnel should intermittently resanitize their gloves with sterile 70% isopropyl alcohol.~~

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

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

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

■The careful cleansing of hands and arms, and correct donning of personal protective equipment (PPE) by compounding personnel, constitute the first major step in preventing microbial contamination in CSPs. Personnel must also be thoroughly competent and highly motivated to perform flawless aseptic manipulations with ingredients, devices, and components of CSPs. Squamous cells are normally shed from the human body at a rate of 10^6 or more per hour, and those skin particles are laden with microorganisms.[10,11] When persons are afflicted with rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, as well as when they wear sheddable cosmetics, they shed these particles at even higher rates. Particles shed from compounding personnel pose an increased risk of microbial contamination of critical sites of CSPs. Therefore, compounding personnel with such afflictions as mentioned above shall be excluded from working in ISO Class 5 and ISO Class 7 (see *Table 1*) compounding areas until their condition is remedied. Personnel wearing cosmetics that may shed and could contact critical sites shall not be permitted to prepare CSPs until the cosmetics are sufficiently removed from the skin.

Before entering the clean area, compounding personnel must remove the following: personal outer garments (e.g., bandannas, coats, hats, jackets, scarves, sweaters, vests); all cosmetics, because they shed flakes and particles; and all hand, wrist, and other body jewelry that can interfere with the effectiveness of PPE (e.g., fit of gloves and cuffs of sleeves, or visible body piercing above the neck). The wearing of artificial nails or extenders is prohibited while working in the sterile compounding environment. Natural nails must also be kept neat and trimmed. Personnel must don the following PPE and perform hand hygiene in an order that proceeds from the dirtiest to cleanest activities. Garbing activities considered the dirtiest include donning of dedicated shoes or shoe covers, head and facial hair covers (e.g., beard covers in addition to face masks), and face mask/eye shield. Eye shields are optional unless working with irritants like germicidal disinfecting agents.

After donning dedicated shoes or shoe covers, head and facial hair covers, and face masks, perform a hand hygiene procedure by removing debris from underneath fingernails using a nail cleaner under running warm water followed by vigorous hand washing. Wash hands and arms to the elbows for at least 30 seconds with either a plain (nonantimicrobial) soap, or antimicrobial soap, and water while in the anteroom/ante-area. The use of antimicrobial scrub brushes is not recommended as they can cause skin irritation and skin damage. Hands and forearms will be completely dried using either a lint-free disposable towels or an electronic hand dryer. After completion of hand washing, don nonshedding disposable gowns with sleeves that fit snugly around the wrists.

Once inside the clean area, prior to donning sterile, powder-free gloves, antiseptic hand cleansing must be performed using an alcohol-based surgical hand scrub with persistent activity[12] (e.g., alcohol-based preparations containing either 0.5%

[10] Agalloco J, Akers JE. Aseptic Processing: A Vision of the Future. Pharmaceutical Technology, 2005. Aseptic Processing supplement, s16.

[11] Eaton T. Microbial Risk Assessment for Aseptically Prepared Products. Am Pharm Rev. 2005; 8 (5, Sep/Oct): 46–51.

[12] *Guideline for Hand Hygiene in Health care Settings,* MMWR, October 25, 2002, vol. 51, No. RR-16 available on the Internet at http://www.cdc.gov/handhygiene/.

or 1.0% chlorhexidine gluconate) following manufacturers' recommendations. Allow hands to dry thoroughly before donning sterile gloves.

Sterile gloves shall be the last item donned before compounding begins. Gloves become contaminated when they contact nonsterile surfaces during compounding activities. Disinfection of contaminated gloves may be accomplished by applying 70% IPA to all contact surface areas of the gloves and letting the gloves dry thoroughly. Only use gloves that have been tested for compatibility with alcohol disinfection by the manufacturer. Routine application of 70% IPA should occur throughout the compounding day and whenever nonsterile surfaces (e.g. vials, counter tops, chairs, and carts) are touched. Gloved hands shall also be routinely inspected for holes, punctures, or tears and replaced immediately if detected, along with performing antiseptic hand cleansing as indicated above. Compounding personnel must be trained and evaluated in the avoidance of touching critical sites with contaminated gloves.

When compounding personnel must temporarily exit the ISO Class 7 (see *Table 1*) environment during a work shift, the exterior gown, if not visibly soiled, may be removed and retained in the ISO Class 8 (see *Table 1*) anteroom/ante-area, to be re-donned during that same work shift only. However, shoe covers, hair and facial hair covers, face mask/eye shield, and gloves must be replaced with new ones before re-entering the ISO Class 7 (see *Table 1*) clean environment along with performing proper hand hygiene.

During high-risk compounding activities that precede terminal sterilization, such as weighing and mixing, compounding personnel shall be garbed and gloved the same as when performing compounding in an ISO Class 5 (see *Table 1*) environment. Properly garbed and gloved compounding personnel who are exposed to air quality that is either known or suspected to be worse than ISO Class 8 (see *Table 1*) must re-garb PPE along with washing their hands properly, performing antiseptic hand cleansing with a waterless alcohol-based surgical scrub, and donning sterile gloves upon re-entering the ISO Class 7 (see *Table 1*) clean area. When CAIs[2] are the source of the ISO Class 5 (see *Table 1*) environment, the garbing and gloving requirements for compounding personnel should be as described above, unless the isolator manufacturer can provide written documentation based on validated environmental testing that any component(s) of PPE or personnel cleansing are not required.■1S (*USP30*)

SUGGESTED STANDARD OPERATING PROCEDURES

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

1. Access to the buffer or clean area is restricted to qualified personnel with specific responsibilities or assigned tasks in the area.
2. All cartoned supplies are decontaminated in the anteroom area by removing them from shipping cartons and wiping or spraying with a disinfecting agent, such as ~~sterile IPA, while being transferred to a clean, sanitized~~

   ■IPA, while being transferred to a clean, disinfected■1S (*USP30*)

   cart or other conveyance for introduction into the buffer or clean area. Individual pouched supplies need not be wiped because the pouches can be removed as these supplies are introduced into the buffer or clean area.
3. Supplies required frequently or otherwise needed close at hand but not necessarily needed for the scheduled operations of the shift are decontaminated and stored on the shelving in the anteroom area.
4. Carts used to bring supplies from the storeroom cannot be rolled beyond the demarcation line in the anteroom area, and carts used in the buffer or clean area cannot be rolled outward beyond the demarcation line unless cleaned and ~~sanitized~~

   ■disinfected■1S (*USP30*)

   before returning.
5. Generally, supplies required for the scheduled operations of the shift are prepared and brought into the buffer or clean area, preferably on one or more movable carts. Supplies that are required for back-up or general support of operations may be stored on the designated shelving in the buffer or clean area, but avoid excessive accumulation of supplies.
6. Objects that shed particles cannot be brought into the buffer or clean area, including pencils, cardboard cartons, paper towels, and cotton items. Only nonshedding paper-related products (boxes, work records, and so forth) can be brought into the buffer or clean area.
7. Traffic flow in and out of the buffer or clean area must be minimized.
8. Personnel preparing to enter the buffer or clean area must remove all jewelry from hands and arms.
9. Personnel entering the buffer or clean area must first scrub hands and arms with soap, including using a scrub brush on the fingers and nails. ~~An air dryer or disposable nonshedding towels are used to dry hands and arms after washing.~~

   ■■1S (*USP30*)
10. Personnel entering the buffer or clean area ~~, after scrubbing, should don attire as described under *Personnel Cleansing and Gowning*.~~

    ■must scrub and should don attire as described in the *Personnel Cleansing and Garbing* section.■1S (*USP30*)

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11. No chewing gum,

■drinks,■1S (*USP30*)
candy, or food items may be brought into the buffer or clean area or anteroom area.

12. At the beginning of each compounding activity session, and after liquids are spilled, the surfaces of the direct compounding environment are first cleaned with *Purified Water* to remove water soluble residues. Immediately thereafter, the same surfaces are ~~sanitized with sterile 70% isopropyl alcohol,~~

■disinfected with IPA■1S (*USP30*)
or other effective antimicrobial agents, using a nonlinting wipe.

13. When LAFWs or ~~are used as the ISO Class 5 air quality environment, (see *Table 1*),~~

■CAIs are used as the ISO Class 5 (see *Table 1*) air quality environment,■1S (*USP30*)
their blowers must be operated continuously during compounding activity, including during interruptions of less than 8 hours. When the blower is turned off and before other personnel enter to perform compounding activities, only one person can enter the contiguous buffer area for the purposes of turning on the blower (for at least 30 minutes) and of ~~sanitizing~~

■disinfecting■1S (*USP30*)
the work surfaces.

14. Traffic in the area of the DCCA is minimized and controlled. The DCCA is shielded from all less clean air currents that are of higher velocity than the clean laminar airflow.
15. Supplies to be utilized in the DCCA for the planned procedures are accumulated and then decontaminated by wiping or spraying the outer surface with IPA or removing the outer wrap at the edge of the DCCA as the item is introduced into the aseptic work area.
16. After proper introduction into the DCCA of supply items required for and limited to the assigned operations, they are so arranged that a clear, uninterrupted path of HEPA-filtered air will bathe all critical sites at all times during the planned procedures. That is, no objects may be placed ~~behind~~

■between the first air from HEPA filters and■1S (*USP30*)
an exposed critical site in a horizontal position or above in the vertical LAFW.

17. All supply items are arranged in the DCCA so as to reduce clutter and to provide maximum efficiency and order for the flow of work.
18. All procedures are performed in a manner designed to minimize the risk of touch contamination. Gloves are ~~sanitized~~

■disinfected■1S (*USP30*)
with adequate frequency with an approved disinfectant.

19. All rubber stoppers of vials and bottles and the necks of ampuls are ~~sanitized~~

■disinfected■1S (*USP30*)
with IPA prior to the introduction of a needle or spike for the removal of product.

20. After the preparation of every admixture, the contents of the container are thoroughly mixed and then inspected for the presence of particulate matter, evidence of incompatibility, or other defects.
21. After procedures are completed, used syringes, bottles, vials, and other supplies are removed, but with a minimum of exit and re-entry into the DCCA to minimize the risk of introducing contamination into the aseptic workspace.

~~Environmental Monitoring~~

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

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

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

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

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

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

■■1S (*USP30*)

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Add the following:

▪ENVIRONMENTAL MONITORING

Assessment and verification of the adequacy of the aseptic compounding environment is essential. Environmental monitoring programs are designed to promptly identify potential sources of contamination, allowing for implementation of corrective actions in order to minimize the possibility of CSP contamination. This program provides information, which demonstrates that the engineering controls, disinfecting procedures, and employee work practices create an environment within the compounding area that consistently maintains acceptably low microbial levels. The compounding area includes the ISO Class 5 (see *Table 1*) primary engineering controls. ISO Class 7 (see *Table 1*) buffer room (cleanroom) and ISO Class 8 (see *Table 1*) anteroom or ante-area. The value of an environmental monitoring program lies in the consistent, quantitative assessment of environmental conditions in these areas over time.

Sampling Plan

The evaluation of environmental quality is performed by measuring the number of airborne viable particles (microorganisms) in the ISO classified air environments within the compounding area and the total number of particles (nonviable and viable). The environmental quality of the ISO classified areas as it pertains to microbial bioburden is evaluated by assessing the number of viable and nonviable particles in the air.

An environmental sampling plan shall be developed for monitoring airborne viable particles. Selected sampling sites should include multiple locations within each ISO Class 5 (see *Table 1*) environment and in the ISO Class 7 and 8 (see *Table 1*) areas. The plan should include location, method of sampling, volume of air sampled, frequency of sampling, time of day as related to activity in the compounding area, and action levels.

Monitoring of the data generated by the program can detect changes in the microbial bioburden; such changes may be allowed for indication of changes in the state-of-control within the environment. It is recommended that compounding personnel refer to *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨1116⟩ and the *CDC Guidelines for Environmental Infection Control in Healthcare Facilities–2003*[7,13] for more information. Although ⟨1116⟩ is an informational chapter and not applicable to controlled environments for use by licensed pharmacies, it can provide valuable information in helping compounding sites establish a robust environmental monitoring program. Changes in the microbial bioburden found during monitoring can allow for detection and resolution of problems in the system before loss of control of the environment.

Growth Media

A general microbiological growth medium such as Soybean–Casein Digest Medium (also known as trypticase soy broth or agar (TSA) should be used to support the growth of bacteria. Malt extract agar (MEA) or some other media that supports the growth of fungi should also be used. Media used for surface sampling must be supplemented with additives to neutralize the effects of disinfecting agents (e.g., TSA with lecithin and polysorbate 80).

Air Sampling

Evaluation of airborne microorganisms in the controlled air environments (LAFWs, CAIs, BSCs, buffer or clean areas, and anterooms/areas) is performed by properly trained individuals using suitable electric air samplers. Impaction is the preferred method of active air sampling.

Use of settling plates for qualitative air sampling cannot be relied upon and shall not be used solely to determine the quality of air in the controlled environment. The settling of parti-

[13] CDC Guideline for Environmental Infection Control in Health-Care Facilities, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5210a1.htm).

cles by gravity onto culture plates is highly dependent on the particle size and is strongly influenced by air movement. Given the unpredictable and uncontrollable nature of ambient particle movement, pharmacists or technicians cannot directly relate the number of colony-forming units (cfu) on a settling plate to the concentrations of the corresponding particles in the sampled environment.

Samples collected by gravity on settling plates are not suitable substitutes for volumetric air samples and should not be used to determine the relative air concentrations of different microorganisms because of the method's collection bias.

Air sampling shall be performed at locations that are prone to contamination during compounding activities and during other activities like staging, labeling, gowning, and cleaning. Locations should include zones of air backwash turbulence within laminar airflow workbench and other areas where air backwash turbulence may enter the compounding area (doorways, in and around ISO Class 5 (see *Table 1*) engineering controls and environments).

The instructions in the manufacturer's user manual for verification and use of these electric air samplers that actively collect volumes of air for evaluation must be followed. A sufficient volume of air should be tested per location in order to maximize sensitivity. These air sampling devices need to be serviced and calibrated as recommended by the manufacturer. Consideration should be given to the overall effect the chosen sampling method will have on the unidirectional airflow within a compounding environment.

Collection Methods—There are a number of different manufacturers of electric air sampling equipment. It is important that compounding personnel refer to the manufacturers' recommended procedures when using the equipment to perform active air sampling procedures. It is recommended that compounding personnel also refer to *Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms* under *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨1116⟩, which can provide more information on the use of active air samplers and the volume of air that should be sampled to detect environmental bioburden excursions.

Sampling Frequency—Active electronic air sampling that is designed not to interrupt airflow while sampling shall be performed and the results evaluated at least monthly for low- and medium-risk level compounding operations and at least weekly for high-risk level compounding operations. More frequent sampling will provide earlier detection of loss of environmental control.

Surface Sampling

Surface sampling is recommended but not required. Surface sampling can be an important component of the microbial environmental monitoring program in controlled environments. It is also useful to evaluate cleaning procedures and employee work practices. Surface sampling should only be performed when no compounding activity is occurring on or near the surface to be tested. For these reasons, sampling is often performed at the end of a shift or the end of the work day. Surface sampling may be performed in all ISO classified areas and can be accomplished using contact plates and/or swabs. Sample areas should be defined on the sample plan or form. The sample size usually ranges from 24 to 30 cm^2. Contact plates are filled with general growth medium and neutralizing agents such as lecithin and polysorbate 80. Swabs should contain a transport medium and are most appropriate for irregular surfaces.

Collection Methods—To sample using a contact plate, gently touch the area with the agar surface and roll the plate across the surface to be sampled. The contact plates should be incubated as stated in the subsection *Sampling Plate Incubation Period.* The contact plate will leave a media residue behind. Therefore, immediately after sampling with the contact plate the sampled area should be thoroughly cleaned and disinfected prior to resuming compounding.

To sample an area with a swab, rub the swab in a twisting motion across the surface within a defined surface area template. After collection of the sample, the swab is placed in an appropriate media containing a neutralizer, processed by appropriate means, and plated to the desired nutrient agar. Results should be reported as cfu per surface area.

Sampling Frequency—Surface sampling should be performed when no other activities are occurring in critical areas and the results evaluated at least monthly for low- and medium-risk level compounding operations and at least weekly for high-risk level compounding operations. More frequent sampling will provide earlier detection of loss of environmental control.

Glove Fingertips Sampling

Personnel monitoring is required because direct touch contamination is the most likely source of introducing microorganisms into CSPs. Contact agar plates are used to sample gloved fingertips after compounding CSPs immediately after exiting the ISO Class 5 (see *Table 1*) environment. Glove fingertip sampling must occur outside of the ISO Class 5 (see *Table 1*) environment. Do not disinfect gloves with IPA immediately prior to sampling. Disinfecting gloves immediately before sampling will provide false negative results. The minimum sampling schedule is provided in *Table 3.* Plates filled with nutrient agar with neutralizing agents added are used when sampling personnel fingertips. Personnel should "touch" the agar with the fingertips of both hands in a manner to create a slight impression in the agar. The gloves must be discarded and hand hygiene performed after performing this procedure.

When a finger plate result for personnel monitoring after proper incubation exceeds the action limit, a review of hand hygiene and garbing procedures as well as glove and surface disinfection procedures and work practices should occur.

Air and Surface Sampling Frequencies

The sampling frequency table *(Table 3)* details the required sampling intervals for each of the respective CSP risk level compounding areas. If two or more risk levels of compounding (e.g., medium- and high-risk level) activity should occur in a pharmacy, then the more stringent frequency of sampling must be performed routinely. If compounding occurs in multiple locations within an institution (e.g., main pharmacy and satellites), environmental monitoring is required for each individual compounding area.

Table 3. Environmental Monitoring Sampling Schedule

	Low-Risk Level CSPs	Medium-Risk Level CSPs	High-Risk Level CSPs
Required air sampling	Once a month	Once a month	Weekly
Required glove fingertips[a]	Weekly	Weekly	Daily
Recommended ISO surface sampling	Weekly	Weekly	Daily

[a] At least one individual or 10% of the compounding personnel, whichever is larger, to be sampled.

Sampling Plate Incubation Period

At the end of the designated sampling or exposure period for all environmental monitoring activities (air, surface, or personnel), the plates are recovered, covers secured, inverted and incubated at a temperature and for a time period conducive to multiplication of microorganisms. Trypticase soy broth or agar (TSA) should be incubated at between 33° and 37° for 2 days. Malt extract agar (MEA) or other suitable fungal media should be incubated at between 26° and 30° for 7 days.

Action Limits, Documentation, and Data Evaluation

The greatest value of viable microbial monitoring in the air and on surfaces of the aseptic environment are realized when normal baseline cfu counts are determined over a period of time. Environmental monitoring data shall be collected and trended as a means of evaluating the overall control of the compounding environment.

The number of discrete colonies of microorganisms are counted and reported as cfu and documented on an environmental monitoring form. Counts from air monitoring need to be transformed into cfu/cubic meter of air and evaluated for adverse trends.

Action levels shall be determined based on baseline data gathered. *Table 4* should only be used as a guideline or as interim levels until baseline data has been gathered. Determining the baseline cfu counts permits identification of an increasing trend of microbial cfu. An increasing trend in cfu counts should prompt a re-evaluation of the adequacy of cleaning procedures, operational procedures, personnel work practices, and air filtration efficiency within the aseptic compounding location. When action levels are exceeded, an investigation into the source of the contamination shall be conducted. Sources could include heating, ventilating, and air conditioning (HVAC) systems, damaged HEPA filters, and changes in personnel garbing habits or working practices. Eliminate the source of the problem, clean the affected area, and then resample.

Table 4. Action Levels (Counts) of Microbial Colony-Forming Units (cfu) per Cubic Meter of Air or Contact Plate[a]

ISO Class of Sampled Location	Sampled Sources and Their Action Levels (Counts) of Microbial cfu		
	Active Air[b] (required)	Glove Fingertip (required)	Inanimate Surfaces (recommended)
5	> 3	> 3	> 3
7	> 20	not required	> 20
8	> 100	not required	> 100

[a] The cfu action levels are adapted from those in *Microbiological Evaluation of Cleanrooms and Other Controlled Environments* ⟨1116⟩.
[b] At least one cubic meter, m^3, or 1000 liters, L, of air must be sampled.

Nonviable Particle Facility Environmental Monitoring Program

A program to monitor nonviable particles differs from that of viable particles in that it is intended to directly measure the performance of the engineering controls used to create the various levels of air cleanliness, e.g., ISO Class 5, ISO Class 7, or ISO Class 8 (see *Table 1*).

Engineering Control Performance Verification

Primary (e.g., LAFWs, BSCs, and CAIs) and secondary (e.g., buffer and ante rooms/areas) engineering controls are essential components of the overall contamination control strategy for aseptic compounding. As such, it is imperative that they perform as designed and the resulting levels of contamination are within acceptable limits. Certification procedures

such as those outlined in the CETA Certification Guide for Sterile Compounding Facilities (CAG-003-2005) should be performed by a qualified individual no less than every 6 months and whenever the device or room is relocated, altered, or major service to the facility is performed.

Total Particle Counts—Certification that each ISO classified area, e.g., ISO Class 5, ISO Class 7, and ISO Class 8 (see *Table 1*) is within established guidelines shall be performed no less than every 6 months and whenever the LAFW, BSC, or CAI is relocated or the physical structure of the buffer room or anteroom/area has been altered. Testing shall be performed by qualified operators using current, state-of-the-art electronic equipment with the following results:

- Not more than 3,520 particles 0.5 µm size and larger per cubic meter of air (ISO Class 5, see *Table 1*) for any LAFW, BSC, and CAI;
- Not more than 352,000 particles of 0.5 µm size and larger per cubic meter of air (ISO Class 7, see *Table 1*) for any buffer room;
- Not more than 3,520,000 particles of 0.5 µm size and larger per cubic meter of air (ISO Class 8, see *Table 1*) for any anteroom/area.

All certification records shall be maintained and reviewed by the supervising pharmacist or other designated employee to ensure that the controlled environments comply with the proper air cleanliness, room pressures, and air changes per hours. (Refer to Cleanrooms, CAIs, and *Table 1* in the *Environmental Quality and Control* section.)

Pressure Differential Monitoring

A pressure gauge or velocity meter shall be installed to monitor the pressure differential or airflow between the cleanroom and anteroom and the anteroom and the general pharmacy area. The results should be reviewed and documented on a daily basis in a log. The pressure between the ISO Class 7 (see *Table 1*) and general pharmacy area should not be less than 5 Pa (0.02-inch water column, w.c.). Facilities used to compound low-risk CSPs utilizing directional airflow should maintain a minimum velocity of 0.2 m/s (40 fpm).■1S (*USP30*)

Change to read:

PROCESSING

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

~~Aseptic Technique~~

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

■■1S (*USP30*)

Components

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

STERILE INGREDIENTS AND COMPONENTS

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

NONSTERILE INGREDIENTS AND COMPONENTS

If any nonsterile components, including containers, devices, and ingredients, are used to make a CSP, such CSPs must be ~~compounded at a high-risk level.~~

■high-risk.■1S (*USP30*)
Nonsterile active ingredients and added substances, or excipients, for CSPs should preferably be official *USP* or *NF* articles. When nonofficial ingredients are used, they must be accompanied by certificates of analysis from their suppliers to aid compounding personnel in judging the identity, quality, and purity in relation to the intended

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use in a particular CSP. Physical inspection of a package of ingredients is necessary in order to detect breaks in the container, looseness in the cap or closure, and deviation from the expected appearance, aroma, and texture of the contents.

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

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

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

Equipment

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

Change to read:

FINISHED PREPARATION RELEASE CHECKS AND TESTS

All high-risk level CSPs ~~for administration by injection into the vascular and central nervous systems~~

■■ IS (*USP30*)
that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, and vials), or in multiple-dose vials for administration to multiple patients, or are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized are tested to ensure that they are sterile (see *Sterility Tests* ⟨71⟩) and do not contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩).

■Inspection of Solution Dosage Forms and Review of Compounding Procedures

All CSPs that are intended to be solutions must be visually examined for the presence of particulate matter and not administered or dispensed when such matter is observed. The prescription orders, written compounding procedure, preparation records, and expended materials used to make CSPs at all contamination risk levels are inspected for accuracy of correct identities and amounts of ingredients, aseptic mixing and sterilization, packaging, labeling, and expected physical appearance before they are administered or dispensed.■ IS (*USP30*)

Physical Inspection

Finished CSPs are individually inspected in accordance with written procedures after compounding. If not distributed promptly, these ~~products~~

■CSPs■ IS (*USP30*)
are individually inspected just prior to leaving the storage area. Those ~~products~~

■CSPs■ IS (*USP30*)
that are not immediately distributed are stored in an appropriate location as described in the written procedures. Immediately after compounding and as a condition of release, each ~~product~~

■CSP■ IS (*USP30*)
unit, where possible, should be inspected against lighted white or black background or both for evidence of visible particulates or other foreign matter. Prerelease inspection also includes container–closure integrity and any other apparent visual defect. ~~Products~~

■CSPs■ IS (*USP30*)
with observed defects should be immediately discarded or marked and segregated from acceptable products in a manner that prevents their administration. When ~~products~~

■CSPs■ IS (*USP30*)
are not distributed promptly after preparation, a predistribution inspection is conducted to ensure that a CSP with defects, such as precipitation, cloudiness, and leakage, which may develop between the time of release and the time of distribution, is not released.

Compounding Accuracy Checks

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

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

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nel or port. These volume accuracy checks and the following additional safety and accuracy checks in this section must be included in the standard operating procedures manual of the CSP facility.

Sterility Testing

All high-risk level CSPs ~~for administration by injection into the vascular and central nervous systems~~

■■1S (*USP30*)
that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized must be tested to ensure that they are sterile (see *Sterility Tests* ⟨71⟩) before they are dispensed or administered. The *Membrane Filtration* method is the method of choice where feasible (e.g., components are compatible with the membrane). A method not described in the *USP* may be used if verification results demonstrate that the alternative is at least as effective and reliable as the *USP Membrane Filtration* method or the *USP Direct Inoculation of the Culture Medium* method where the *Membrane Filtration* method is not feasible.

~~In such a case, a written procedure requiring daily observation of the media and requiring an immediate recall if there is any evidence of microbial growth must be available.~~

■When high-risk level CSPs are dispensed before receiving the results of their sterility tests, there shall be a written procedure requiring daily observation of the incubating test specimens and immediate recall of the dispensed CSPs when there is any evidence of microbial growth in the test specimens.■1S (*USP30*)
In addition, the patient and the physician of the patient to whom a potentially contaminated CSP was administered are notified of the potential risk. Positive sterility test results should prompt a rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes.

Bacterial Endotoxin (Pyrogen) Testing

All high-risk level CSPs, ~~for administration by injection into the vascular and central nervous systems~~

■except those for inhalation and ophthalmic administration,■1S (*USP30*)
that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, vials), or in multiple-dose vials for administration to multiple patients, or exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized must be tested to ensure that they do not contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩

■and *Pyrogen Test* ⟨151⟩).■1S (*USP30*)
In the absence of a bacterial endotoxins limit in the official monograph or other CSP formula source, the CSP must not exceed the amount of USP Endotoxin Units (EU per hour per kg of body weight or m^2 of body surface area) specified in the above chapter for the appropriate route of administration.

Identity and Strength Verification of Ingredients

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

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

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

■■1S (*USP30*)

Change to read:

STORAGE AND BEYOND-USE DATING

Beyond-use dates for compounded preparations are usually assigned based on professional experience, which should include careful interpretation of appropriate information sources for the same or similar formulations (see *Stability Criteria and Beyond-Use Dating* in the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩). Beyond-use dates for CSPs are rarely based on preparation-specific chemical assay results, which are used with the Arrhenius equation to determine expiration dates (see *General Notices and Requirements*) for manufactured products. The majority of CSPs are aqueous solutions in which hydrolysis of dissolved ingredients is the most common chemical degradation reaction. The extent of hydrolysis and other heat-catalyzed degradation reactions at any particular time point in the life of a CSP represents the thermodynamic sum of exposure temperatures and durations. Such lifetime stability exposure is represented in the mean kinetic temperature calculation (see *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩). Drug hydrolysis rates increase exponentially with arithmetic temperature increase; thus, exposure of a beta-lactam antibiotic solution for 1 day at controlled room temperature (see *General Notices and Requirements*) will have an equivalent effect on the extent of hydrolysis of approximately 3 to 5 days in cold temperatures (see *General Notices and Requirements*).

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

Determining Beyond-Use Dates

■Beyond-use dates and expiration dates are not the same (see *General Notices and Requirements*). Expiration dates for the chemical and stability of manufactured sterile products are determined from results of rigorous analytical and performance testing, and they are specific for a particular formulation in its container and at stated exposure conditions of illumination and temperature.■1S (*USP30*)

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

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

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

To ensure consistent practices in determining and assigning beyond-use dates, the pharmacy should have written policies and procedures governing the determination of the beyond-use dates for all compounded products. When attempting to predict a theoretical beyond-use date, a compounded or an admixed product should be considered as a unique system that has physical and chemical properties and stability characteristics that differ from its components. For example, antioxidant, buffering, or antimicrobial properties of a sterile vial for injection (SVI) might be lost upon its dilution, with the potential of seriously compromising the chemical stability of the SVI's active ingredient or the physical or microbiological stability of the SVI formulation in general. Thus, the properties stabilized in the SVI formulation usually cannot be expected to be carried over to the compounded or admixed product. Product-specific, experimentally determined stability data evaluation protocols are preferable to published stability information. Pharmacists should consult the general information chapter under *Pharmaceutical Stability* ⟨1150⟩ for the appropriate stability parameters to be considered when initiating or evaluating a product-specific stability study.

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

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

■When manufactured multiple-dose vials (MDVs; see *Preservation, Packaging, Storage,* and *Labeling* in the *General Notices and Requirements*) of sterile ingredients are used in CSPs, the stoppers of the MDVs are inspected for physical integrity and disinfected by wiping with an IPA swab before each penetration with a sterile withdrawal device. When contaminants or abnormal properties are suspected or observed in MDVs, such MDVs shall be discarded. The beyond-use date after initially entering or opening (e.g., needle-punctured) multiple-dose containers is 28 days (see *Antimicrobial Effectiveness Testing* ⟨51⟩), unless otherwise specified by the manufacturer.

Proprietary Bag and Vial Systems

Sterility storage and stability beyond-use times for attached and activated (activated is defined as allowing contact of the previously separate diluent and drug contents) container pairs of drug products for intravascular administration, such as ADD-Vantage® and Mini Bag Plus® are as indicated by the

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manufacturers. In other words, follow manufacturers' instructions for handling and storing ADD-Vantage®, Mini Bag Plus®, Add A Vial®, Add-Ease® products, and any others.■1S (*USP30*)

Monitoring Controlled Storage Areas

To ensure that product potency is retained through the manufacturer's labeled expiration date, pharmacists must monitor the drug storage areas within the pharmacy. Controlled temperature ~~storage areas in the pharmacy (refrigerators, 2° to 8°; freezers, –20° to –10°; and incubators, 30° to 35°; etc.)~~

■areas in compounding facilities include the following: controlled room temperature, 15°to 30° with mean kinetic temperature 25°; cold temperature, 2° to 8°; freezing temperature, –10° and colder (see *General Notices)* if needed to achieve freezing; and microbial culture media at the media-specific temperature range. A controlled temperature area■1S (*USP30*) should be monitored at least once daily and the results documented on a temperature log. Additionally, pharmacy personnel should note the storage temperature when placing the product into or removing the product from the storage unit in order to monitor any temperature aberrations. Suitable temperature recording devices may include a calibrated continuous recording device or a National Bureau of Standards calibrated thermometer that has adequate accuracy and sensitivity for the intended purpose and should be properly calibrated at suitable intervals. If the pharmacy uses a continuous temperature recording device, pharmacy personnel should verify at least once daily that the recording device itself is functioning properly.

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

Change to read:

~~MAINTAINING PRODUCT QUALITY AND CONTROL AFTER THE CSP LEAVES THE PHARMACY~~

■MAINTAINING STERILITY, PURITY, AND STABILITY OF DISPENSED AND DISTRIBUTED CSPs■1S (*USP30*)

~~Sterile Preparations for Institutional Use~~

~~This section pertains to the responsibilities of the pharmacy for maintaining product quality and control after the CSP leaves the pharmacy for distribution and use within the organized health care system to which the pharmacy belongs. The pharmacy is responsible for the quality of all CSPs prepared by or dispensed from the pharmacy, throughout the life cycle of the CSP, regardless of where the CSP exists physically within the organized health care system.~~

■This section summarizes the responsibilities of pharmacy departments for maintaining quality and control of CSPs that are dispensed and administered within their parent healthcare organizations.[14]

Compounding personnel shall ensure proper storage and security of CSPs prepared by or dispensed from the compounding facility, until either their beyond-use dates are reached or they are administered to patients.■1S (*USP30*)
In fulfilling this general responsibility, the ~~pharmacy~~

■compounding facility■1S (*USP30*)
is responsible for the proper packaging, handling, transport, and storage of CSPs prepared by or dispensed from it, including the appropriate education, training, and supervision of ~~pharmacy~~

■compounding■1S (*USP30*)
personnel assigned to these functions. The ~~pharmacy~~

■compounding facility■1S (*USP30*)
should assist in the education and training of ~~nonpharmacy~~

■noncompounding■1S (*USP30*)
personnel responsible for carrying out any aspect of these functions.

Establishing, maintaining, and assuring compliance with comprehensive written policies and procedures encompassing these responsibilities is a further responsibility of the ~~pharmacy~~

■compounding facility.■1S (*USP30*)
Where ~~nonpharmacy~~

■noncompounding■1S (*USP30*)
personnel are assigned tasks involving any of these responsibilities, the policies and procedures encompassing those tasks should be developed by ~~the pharmacy in consultation with other institutional departments as appropriate.~~

■compounding supervisors. The quality and control activities related to distribution of CSPs are summarized in the following five subsections.■1S (*USP30*)
Activities or concerns that should be addressed as the ~~pharmacy~~

■compounding facility■1S (*USP30*)
fulfills these responsibilities are as follows.

Packaging, Handling, and Transport

Inappropriate processes or techniques involved with packaging, handling, and transport can adversely affect ~~product quality and package integrity. While pharmacy~~

■quality and package integrity of CSPs. While compounding■1S (*USP30*)
personnel routinely perform many of the tasks associated with these functions, some tasks, such as transport, handling, and placement into storage, may be fulfilled by ~~nonpharmacy~~

■noncompounding■1S (*USP30*)
personnel who are not under the direct administrative control of the ~~pharmacy~~

■compounding facility.■1S (*USP30*)

[14] Accrediting organizations require that sterile drug and nutrient compounding be controlled by the pharmacy departments of its accredited institutions.

Under these circumstances, appropriate written policies and procedures are established by the ~~pharmacy~~

■compounding facility■1S (*USP30*)
with the involvement of other departments or services whose personnel are responsible for carrying out those CSP-related functions for which the ~~pharmacy~~

■compounding facility■1S (*USP30*)
has a direct interest. The performance of the ~~nonpharmacy~~

■noncompounding■1S (*USP30*)
personnel is monitored for compliance to established policies and procedures.

The critical requirements that are unique to CSPs and that are necessary to ensure ~~product~~

■CSP■1S (*USP30*)
quality and packaging integrity must be addressed in written procedures. For example, techniques should be specified to prevent the depression of syringe plungers or dislodging of syringe tips during handling and transport. Additionally, disconnection of system components (for example, where CSPs are dispensed with administration sets attached to them) must be prevented throughout the ~~life cycle of the product.~~

■beyond-use date of the CSP.■1S (*USP30*)
Foam padding or inserts are particularly useful where CSPs are transported by pneumatic tube systems. Regardless of the methods used, the ~~pharmacy~~

■compounding facility■1S (*USP30*)
has to evaluate their effectiveness and the reliability of the intended protection. Evaluation should be continuous, for example, through a surveillance system, including a system of problem reporting to the ~~pharmacy~~

■compounding facility.■1S (*USP30*)
Inappropriate transport and handling can adversely affect the quality of certain CSPs having unique stability concerns. For example, the physical shaking that might occur during pneumatic tube transport, or undue exposure to heat or light, have to be addressed on a product-specific basis. Alternate transport modes or special packaging measures might be needed for the proper assurance of quality of these CSPs. The use of tamper-proof closures and seals on CSP ports can add an additional measure of security to ensure product integrity regardless of transport method used.

Chemotoxic and other hazardous CSPs require safeguards to maintain the integrity of the CSP and to minimize the exposure potential of these products to the environment and to personnel who may come in contact with them.

■Transportation by pneumatic tube should be discouraged because of potential breakage and contamination.■1S (*USP30*)
Special requirements associated with the packaging, transport, and handling of these agents include the prevention of accidental exposures or spills and the training of personnel in the event of an exposure or spill. Examples of special requirements of these agents also include exposure-reducing strategies such as the use of Luer lock syringes and connections, syringe caps, the capping of container ports, sealed plastic bags, impact-resistant containers, and cautionary labeling. ~~Appropriate cushioning for pneumatic tube transport should be selected and evaluated to ensure that the products so conveyed can withstand the stresses induced by the system. Pneumatic transport of nonevaluated packaging alternatives should be avoided. Additional references should be consulted as necessary for further information on handling chemotoxic and other hazardous drugs.~~

■■1S (*USP30*)

Use and Storage

The pharmacy

■or other compounding facility■1S (*USP30*)
is responsible for ensuring that CSPs in the patient-care setting maintain their quality until administered. The immediate labeling of the CSP container will display prominently and understandably the requirements for proper storage and expiration dating. Delivery and patient-care-setting personnel must be properly trained to deliver the CSP to the appropriate storage location. Outdated and unused CSPs must be returned to the pharmacy ~~for disposal or possible reuse.~~

■or other compounding facility for disposition.■1S (*USP30*)
Written procedures have to exist to ensure that storage conditions in the patient-care setting are suitable for the CSP-specific storage requirements. Procedures include daily monitoring and documentation of drug storage refrigerators to ensure temperatures between 2° and 8° and the monthly inspection of all drug storage locations by pharmacy personnel. Inspections must confirm compliance with appropriate storage conditions, separation of drugs and food, proper use of multiple-dose containers, and the avoidance of using single-dose products as multiple-dose containers. CSPs, as well as all other drug products, must be stored in the patient-care area in such a way as to secure them from unauthorized personnel, visitors, and patients.

~~Administration~~

■Readying for Administration■1S (*USP30*)

Procedures essential for generally ensuring ~~product~~

■■1S (*USP30*)
quality, especially sterility assurance, when readying a CSP for its subsequent administration include proper hand-washing, aseptic technique, site care, and change of administration sets. Additional procedures may also be essential for certain ~~products,~~

■CSPs,■1S (*USP30*)
devices, or techniques. Examples where such special procedures are needed include in-line filtration, the operation of automated infusion control devices, and the replenishment of ~~drug products~~

■CSPs■1S (*USP30*)
into the reservoirs of implantable or portable infusion pumps.

■When CSPs are likely to be exposed to warmer than 30° for more than 1 hour during their administration to patients, the maintenance of their sterility and stability must be confirmed from either relevant and reliable sources or direct testing.■1S (*USP30*)

Redispensed CSPs

~~The pharmacy must have the sole authority for determining whether a CSP not administered as originally intended can be used for an alternate patient or under alternate conditions. All CSPs that are not used as originally intended must be returned to the pharmacy for appropriate disposition, which may include redispensing, but only if adequate continuing quality can be fully ensured.~~

■The pharmacy or other compounding facility must have the sole authority to determine when unopened, returned CSPs may be redispensed. Returned CSPs may be redispensed only

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when personnel responsible for sterile compounding can ensure that such CSPs are sterile, pure, and stable (contain labeled strength of ingredients).■1S (*USP30*)
The following may provide such assurance: the CSP was maintained under continuous refrigeration and protected from light, if required; and no evidence of tampering or any readying for use outside the pharmacy exists. ~~, and there is sufficient time remaining until the originally assigned beyond-use time and date will be reached~~

■Assignment of new storage times and beyond-use dates that exceed the original dates for returned CSPs is permitted only when there is supporting evidence from sterility testing and quantitative assay of ingredients.■1S (*USP30*)
Thus, initial preparation and thaw times should be documented and reliable measures should have been taken to prevent and detect tampering. Compliance with all procedures associated with maintaining product quality is essential. The CSP must not be redispensed if there is not adequate assurance that product quality and packaging integrity (including the connections of devices, where applicable) were continuously maintained between the time the CSP left and the time that it was returned. ~~to the pharmacy~~

■■1S (*USP30*)
Additionally, CSPs must not be redispensed if redispensing cannot be supported by the originally assigned beyond-use time.

Education and Training

The assurance of CSP quality and packaging integrity is highly dependent upon the proper adherence of all personnel to the pertinent written procedures. The ~~pharmacy~~

■compounding personnel■1S (*USP30*)
must design, implement, and maintain a formal education, training, and competency assessment program that encompasses all the functions and tasks addressed in the foregoing sections and all personnel to whom such functions and tasks are assigned. This program includes the assessment and documentation of procedural breaches, administration mishaps, side effects, allergic reactions, and complications associated with dosage or administration, such as extravasation. This program should be coordinated with the institution's adverse-event and incident reporting programs.

Add the following:

■ACRONYMS

ACD	automated compounding devices
ACPH	air changes per hour
ALARA	as low as reasonably achievable
ASHRAE	American Society of Heating, Refrigerating and Air-Conditioning Engineers
BSC	biological safety cabinet
CAI	compounding aseptic isolator
CDC	Centers for Disease Control and Prevention
CETA	Controlled Environment Testing Association
cfu	colony-forming units
CSPs	compounded sterile preparations
CSTD	closed-system vial-transfer devices
DCCA	direct and contiguous compounding areas
EU	Endotoxin Unit
FDA	Food and Drug Administration
FPM	feet per minute
HEPA	high efficiency particulate air
HICPAC	Healthcare Infection Control Practices Advisory Committee
HPLC	high performance liquid chromatography
HVAC	heating, ventilation, and air conditioning
IPA	isopropyl alcohol
LAFW	laminar airflow workbenches
MDVs	multiple-dose vials
MEA	malt extract agar
MMWR	Morbidity and Mortality Weekly Report
NBS	National Bureau of Standards
NIOSH	National Institute for Occupational Safety and Health
PET	positron emission tomography
PPE	personal protective equipment
QA	quality assurance
SAL	sterility assurance level
SCC	Sterile Compounding Expert Committee
SCDM	Soybean–Casein Digest Medium
SOP	standard operating procedures
SVI	sterile vial for injection
TLC	thin-layer chromatography
TSA	trypticase soybroth or agar
USP	United States Pharmacopeia■1S (*USP30*)

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Change to read:

~~APPENDIX~~

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

APPENDIX *(Continued)*

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

APPENDIX *(Continued)*

CRITERIA	LOW RISK LEVEL	MEDIUM RISK LEVEL	HIGH RISK LEVEL
CSP Work Environment	• Appropriate solid surfaces • Limited (but necessary) furniture, fixtures, etc. • Anteroom area • Buffer zone	See low-risk level.	See low-risk level.
Equipment	• Written policies and procedures that address calibration, routine maintenance, personnel training	See low-risk level.	See low-risk level.
Components	• Written policies and procedures that address Sterile components	See low-risk level.	Sterile and nonsterile drug components must meet the compendial standards if available • Written policies and procedures that address — Sterile components — Nonsterile components
Processing: Aseptic Technique	• Written policies and procedures that address specific training and performance evaluation • Critical operations are carried out in a Direct Compounding Common Area (DCCA)	See low-risk level.	See low-risk level.
Environmental Control	• Policies and procedures that address — Cleaning and sanitizing the workspaces (DCCA) — Personnel and gowning — Standard operating procedures	See low-risk level.	See low-risk level.
Verification Procedures • Sterility Testing	Not required	Not required	Yes, recommended
Verification Procedures • Environmental Monitoring	• Certification of LAFW and barrier isolates every six (6) months • Certification of the buffer room/zone and anteroom/zone every six (6) months • Bacterial monitoring using an appropriate manner at least monthly	See low-risk level.	See low-risk level.
Verification Procedures • Personnel Training and Education	Initially and annually thereafter • Didactic review • Written testing • Media fill testing	See low-risk level.	See low-risk level.

APPENDIX

■Principle Competencies, Conditions, Practices, and Quality Assurances That Are Required (▶ "shall" or "must") and Recommended (• "should" or "is advised") in USP Chapter ⟨797⟩

NOTE—This tabular appendix selectively abstracts and condenses the full text of ⟨797⟩ for rapid reference only. Compounding personnel are responsible for the full text and all official USP terminology, content, and conditions therein.

⟨797⟩ Section	**Competencies, Conditions, and Practices**
INTRODUCTION	• Chapter purpose is to prevent harm and death to patients treated with CSPs. ▶ Chapter pertains to preparation, storage, and transportation, but not administration, of CSPs. ▶ Personnel and facilities to which ⟨797⟩ applies; therefore, for whom and at which facility the standards may be enforced by regulatory and accreditation authorities. ▶ Types of preparations designated to be CSPs according to their physical forms, and their sites and routes of administration to patients.
DEFINITIONS	▶ Several that are important to ⟨797⟩.
Pharmacy Bulk Package	▶ One penetration of the closure with sterile devices in ISO Class 5 or cleaner air to obtain multiple single doses. ▶ Labeled "Pharmacy Bulk Package—Not for Direct Infusion." ▶ Beyond-use time after initial entry is that stated by the manufacturer.
RESPONSIBILITY OF COMPOUNDING PERSONNEL	▶ Practices and quality assurance procedures required to prepare, store, and transport CSPs that are sterile, and acceptably accurate, pure, and stable.
CSP MICROBIAL CONTAMINATION RISK LEVELS	▶Proper training and evaluation of personnel, proper cleansing and garbing of personnel, proper cleaning and disinfecting of compounding work environments, and proper maintenance and monitoring of controlled environmental locations (all of which are detailed in their respective sections).
Low-Risk Level CSPs	▶ Aseptic manipulations within an ISO Class 5 environment using three or fewer sterile products and entries into any container. ▶ In absence of passing sterility test, store not more than 48 hours at controlled room temperature, 14 days at cold temperature, and 45 days in solid frozen state at –20° or colder. ▶ Media-fill test at least annually by compounding personnel.

APPENDIX

■Principle Competencies, Conditions, Practices, and Quality Assurances That Are Required (▶ "shall" or "must") and Recommended (● "should" or "is advised") in USP Chapter ⟨797⟩

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⟨797⟩ Section	Competencies, Conditions, and Practices
Medium-Risk Level CSPs	▶ Aseptic manipulations within an ISO Class 5 environment using prolonged and complex mixing and transfer, or more than three sterile products and entries into any container, or pooling ingredients from multiple sterile products to prepare multiple CSPs. ▶ In absence of passing sterility test, store not more than 30 hours at controlled room temperature, 9 days at cold temperature, and 45 days in solid frozen state at –20° or colder. ▶ Media-fill test at least annually by compounding personnel.
High-Risk Level CSPs	▶ Confirmed presence of nonsterile ingredients and devices, or confirmed or suspected exposure of sterile ingredients for more than 1 hour to air quality inferior to ISO Class 5 before final sterilization. ▶ Sterilization method verified to achieve sterility for the quantity and type of containers. ▶ Meet allowable limits for bacterial endotoxins. ▶ Maintain acceptable strength and purity of ingredients and integrity of containers after sterilization. ▶ In absence of passing sterility test, store not more than 24 hours at controlled room temperature, 3 days at cold temperature, and 45 days in solid frozen state at –20° or colder. ▶ Media-fill test at least semiannually by compounding personnel.
IMMEDIATE USE CSPs	▶ Fully comply with all six specified criteria.
SINGLE-DOSE AND MULTIPLE-DOSE CONTAINERS	▶ Beyond-use date 28 days, unless specified otherwise by the manufacturer, for closure sealed multiple-dose containers after initial opening or entry. ▶ Beyond-use time of 6 hours, unless specified otherwise by the manufacturer, for closure sealed single-dose containers in ISO Class 5 or cleaner air after initial opening or entry. ▶ Beyond-use time of 1 hour for closure sealed single-dose containers after being opened or entered in worse than ISO Class 5 air. ▶ Storage of opened single-dose ampuls is not permitted.

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APPENDIX

■Principle Competencies, Conditions, Practices, and Quality Assurances That Are Required (▶ "shall" or "must") and Recommended (• "should" or "is advised") in USP Chapter ⟨797⟩

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⟨797⟩ Section	Competencies, Conditions, and Practices
HAZARDOUS DRUGS AS CSPs	▶ Appropriate personnel protective equipment. ▶ Appropriate primary engineering controls (BSCs and CAIs) for concurrent personnel protection and exposure of critical sites are in a separate ISO Class 7 room with at least 0.01-inch water column negative pressure. ▶ Segregated drug storage is in a room with at least 12 air changes per hour (ACPH). ▶ CAIs that maintain ISO Class 5 environment within the compounding chamber when located in air quality worse than ISO Class 7 must be located in rooms with a minimum of 0.01-inch water column negative pressure and 12 air changes per hour (ACPH). ▶ Annual documentation of full training of personnel regarding storage, handling, and disposal of hazardous drugs. • Total external exhaust of primary engineering controls. • Negative pressure in drug storage rooms. • Assay of surface wipe samples every 6 months.
RADIOPHARMACEUTICALS AS CSPs	▶ Positron Emission Tomography is according to USP chapter ⟨823⟩. ▶ Appropriate primary engineering controls and radioactivity containment and shielding. ▶ Location of primary engineering controls permitted in ISO Class 8 controlled environment. ▶ Technetium-99m/molybdenum-99 generators used according to manufacturer, state, and federal requirements.
VERIFICATION OF COMPOUNDING ACCURACY AND STERILITY	▶ Review labels and document correct measurements, aseptic manipulations, and sterilization procedures to confirm correct identity, purity, and strength of ingredients in, and sterility of CSPs.
Sterilization Methods	▶ Verify methods achieve sterility while maintaining appropriate strength, purity, quality, and packaging integrity. ▶ Prove sterility of High-risk level batches of more than 25 units by USP chapter ⟨71⟩ or superior sterility testing. • Prove effectiveness for High-risk level of 25 units or less by USP chapter ⟨71⟩, equivalent, or superior sterility testing.

APPENDIX

■Principle Competencies, Conditions, Practices, and Quality Assurances That Are Required (▶ "shall" or "must") and Recommended (• "should" or "is advised") in USP Chapter ⟨797⟩

NOTE—This tabular appendix selectively abstracts and condenses the full text of ⟨797⟩ for rapid reference only. Compounding personnel are responsible for the full text and all official USP terminology, content, and conditions therein. *(Continued)*

⟨797⟩ Section	Competencies, Conditions, and Practices
Sterilization of High-Risk Level CSPs by Filtration	▶ Nominal 0.2-µm porosity sterile membranes that are chemically and physically compatible with the CSP. ▶ Complete rapidly without filter replacement. ▶ Subject filter to manufacturer's recommended integrity test, e.g., bubble point test, after filtering CSPs.
Sterilization of High-Risk Level CSPs by Steam	▶ Test to verify the mass of containers to be sterilized will be sterile after the selected exposure duration in the particular autoclave. ▶ Ensure live steam contacts all ingredients and surfaces to be sterilized. ▶ Pass solutions through a 1.2-µm or smaller porosity filter into final containers to remove particulates before sterilization.
PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS	▶ Pass didactic and media-fill testing initially, followed by annually.
ENVIRONMENTAL QUALITY AND CONTROL Exposure of Critical Sites	▶ ISO Class 5 or better air. ▶ Preclude direct contact (e.g., touch and secretions) contamination.
Facility Design and Environmental Controls	▶ Primary engineering controls provide unidirectional (i.e., laminar) HEPA air at a velocity sufficient to prevent airborne particles from contacting critical sites. ▶ Cleanrooms for nonhazardous and nonradioactive CSPs are supplied with HEPA that enters from ceilings with return vents low on walls, and provide not less than 30 air changes per hour. ▶ Buffer rooms or zones maintain 0.02- to 0.05-inch water column positive pressure, and do not contain sinks or drains. ▶ Air velocity from buffer rooms or zones to anterooms or ante-areas is at least 40 feet per minute. • Surfaces and essential furniture in buffer rooms or zones and cleanrooms are nonporous, smooth, nonshedding, impermeable, cleanable, and resistant to disinfectants.

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⟨797⟩ Section	**Competencies, Conditions, and Practices**
Placement of Primary Control within ISO Class 7 Buffer Areas	▶ Primary engineering controls for nonhazardous and nonradioactive CSPs are located in cleanrooms, except for CAIs that are proven to maintain ISO Class 5 air when particle counts are sampled 6 to 12 inches upstream of critical site exposure areas during performance of normal inward and outward transfer of materials, and compounding manipulations when such CAIs are located in air quality worse than ISO Class 7. ▶ Food, drinks, and items exposed in patient care areas, and unpacking of bulk supplies and personnel cleansing and garbing are prohibited from buffer areas or rooms. ▶ Demarcation designation between buffer areas or rooms and anterooms or ante-areas. ▶ Antiseptic hand cleansing and sterile gloves in buffer areas or rooms.
Cleaning and Disinfecting the Sterile Compounding Areas	▶ Trained personnel write detailed procedures including cleansers, disinfectants, and nonshedding wipe and mop materials. ▶ Work surfaces in ISO Class 7 and 8 areas cleaned at least daily. ▶ Floors in ISO Class 7 and 8 areas cleaned daily when no compounding occurs. ▶ IPA (70% isopropyl alcohol) remains on surfaces to be disinfected for at least 30 seconds before such are used to prepare CSPs. ▶ Emptied shelving, walls, and ceilings in anterooms and ante-areas cleaned at least monthly.

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⟨797⟩ Section	Competencies, Conditions, and Practices
Personnel Cleansing and Garbing	▶ Personnel with rashes, sunburn, weeping sores, conjunctivitis, active respiratory infection, and sheddable cosmetics are prohibited from preparing CSPs. ▶ Compounding personnel remove personal outer garments; cosmetics; artificial nails; hand, wrist, and body jewelry that can interfere with the fit of gowns and gloves; and visible body piercing above the neck. ▶ Order of compounding garb and cleansing in anteroom or ante-area: shoes or shoe covers, head and facial hair covers, face mask, fingernail cleansing, hand and forearm washing and drying; nonshedding gown. ▶ Order of cleansing and gloving in buffer room or area: hand cleansing with a persistently active alcohol-based product containing 0.5% to 1.0% chlorhexidine gluconate, allow hands to dry; sterile gloves. ▶ Routinely disinfect gloves with IPA after contacting nonsterile objects. ▶ Inspect gloves for holes and replace when breaches are detected. ▶ Personnel repeat proper procedures after they are exposed to direct contact contamination or worse than ISO Class 8 air. ▶ These requirements are exempted only for Immediate Use CSPs and CAIs for which manufacturers provide written documentation based on validated testing that such personnel practices are not required to maintain sterility in CSPs.
STANDARD OPERATING PROCEDURES	▶ All facilities are required to have these, and they must include at least the items enumerated in this section.
ENVIRONMENTAL MONITORING Sampling Plan	▶ Plan includes locations, methods, air volumes, frequency, and time of day sampling occurs in ISO Class 5, 7, and 8 controlled environments.
Growth Media	• Typical media to support bacterial and fungal growth in contact samples.
Air Sampling	▶ At least monthly by active electronic air sampling in controlled ISO Class 5, 7, and 8 areas for preparing Low- and Medium-risk level CSPs, and at least weekly in those areas where High-risk level CSPs are prepared. • Improve environmental controls and aseptic personnel practices when $\geq$3, $\geq$20, and $\geq$100 microbial cfu per m^3 air are detected in, respectively, ISO Class 5, 7, and 8 controlled environments.

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⟨797⟩ Section	Competencies, Conditions, and Practices
Surface Sampling	• Surfaces in primary engineering controls using sterile contact agar plates or swabs. • At least monthly in ISO Class 5, 7, and 8 areas for preparing Low- and Medium-risk level CSPs, and at least weekly in those areas where High-risk level CSPs are prepared. • Improve cleaning, disinfecting, and personnel aseptic practices when $\geq$3, $\geq$5, and $\geq$100 microbial cfu per 24 to 30 cm^2 area are detected in, respectively, ISO Class 5, 7, and 8 controlled environments.
Personnel Monitoring	▶ Fingertips of gloves of at least one member or 10% of compounding personnel, whichever is greater, using sterile agar plates weekly when compounding Low- and Medium-risk level CSPs, and daily when compounding High-risk level CSPs. • Improve cleaning, disinfecting, and personnel aseptic practices when $\geq$3 microbial cfu are detected per sample.
Total Particle Counts	▶ Active electronic air sampling in ISO Class 5, 7, and 8 controlled areas at least every 6 months, and when primary engineering controls are relocated and physical structures are changed in cleanrooms, buffer rooms or zones, and anterooms or ante-areas.
Pressure Differential Monitoring	• Pressure differential between ISO Class 7 cleanrooms and surrounding uncontrolled environment is not less than 0.02-inch water column.
FINISHED PREPARATION RELEASE CHECKS AND TESTS Inspection of Solution Dosage Forms and Review of Compounding Procedures	▶ Review procedures and documents to ensure sterility, purity, correct identities and amounts of ingredients, and stability. ▶ Visually inspect for abnormal particulate matter and color, and intact containers and seals.
Sterility Testing	▶ High-risk level CSPs prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2° to 8° and 6 hours at warmer than 8° before being sterilized.
Bacterial Endotoxin (Pyrogen) Testing	▶ High-risk level CSPs, excluding those for inhalation and ophthalmic administration, prepared in batches of more than 25 identical containers, or exposed longer than 12 hours at 2° to 8° and 6 hours at warmer than 8° before being sterilized.

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⟨797⟩ Section	Competencies, Conditions, and Practices
Identity and Strength Verification of Ingredients	▶ Written procedures to verify correct identity, quality, amounts, and purities of ingredients used in CSPs. ▶ Written procedures to ensure labels of CSPs contain correct names and amounts or concentrations of ingredients, total volumes, beyond-use dates, storage conditions, and route(s) of administration.
STORAGE AND BEYOND-USE DATING Determining Beyond-Use Dates	▶ Use the general criteria in USP ⟨795⟩ in the absence of direct stability-indicating assays or authoritative literature that supports longer or shorter durations.
MAINTAINING STERILITY, PURITY, AND STABILITY OF DISPENSED AND DISTRIBUTED CSPs	▶ Written procedures for proper packaging, storage, and transportation conditions to maintain sterility, quality, purity, and strength of CSPs.
Redispensed CSPs	▶ When sterility, and acceptable purity, strength, and quality can be ensured. ▶ Assignment of sterility storage times and stability beyond-use dates that occur later than those of originally dispensed CSPs must be based on results of sterility testing and quantitative assay of ingredients.
PACKAGING AND TRANSPORTING CSPs	▶ Packaging maintains physical integrity, sterility, stability, and purity of CSPs. ▶ Modes of transport that maintain appropriate temperatures and prevent damage to CSPs.
PATIENT OR CAREGIVER TRAINING	▶ Multiple component formal training program to ensure patients and caregivers understand the proper storage, handling, use, and disposal of CSPs.
PATIENT MONITORING AND ADVERSE EVENTS REPORTING	▶ Written standard procedures describe means for patients to ask questions and report concerns and adverse events with CSPs, and for compounding supervisors to correct and prevent future problems. • Adverse events and defects with CSPs reported to FDA's MedWatch and USP's MEDMARX programs.■1S (*USP30*)

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GENERAL CHAPTERS

General Information

BRIEFING

〈**1065**〉 **Ion Chromatography,** *USP 29* page 2898. On the basis of comments received, it is proposed to revise the *Apparatus* section to specify the use of a metal-free tubing system for trace metal analysis. In addition, it is proposed to clarify wording in the *Direct UV Detection* and *Photometric Detection* subsections under *Detectors*.

(GC: H. Pappa) RTS—C43030

Change to read:

APPARATUS

IC instruments closely resemble conventional HPLC instruments. Typical components include an autosampler, a high-pressure pump, an injection valve with a sample loop of suitable size (typically 10 to 250 µL), a guard column, an analytical column, an optional suppressor or other forms of a post-column reaction system, a flow-through detector, and a data system ranging in complexity from an integrator to a computerized data system (*Figure 1*). Because mobile phases generally consist of dilute acids, alkalis, or salt solutions, the components in contact with the mobile phase and the sample are typically made from inert materials, such as polyetheretherketone. Conventional HPLC systems also may be used provided that their components are compatible with the mobile phase and injected sample solutions.

■A metal-free tubing system should be used for trace metal analysis.■1S (*USP30*)

Following suitable preparation, the sample is introduced via the injection valve. After the optional chemical suppression or other post-column reaction on the column effluent, the analyte species are detected using conductivity, amperometry, UV/VIS, or other detection modes. Because IC uses a predominantly ionic mobile phase, a suppressor is often necessary prior to conductometric detection, although nonsuppressed conductometric detection has been successfully used in pharmaceutical analysis.

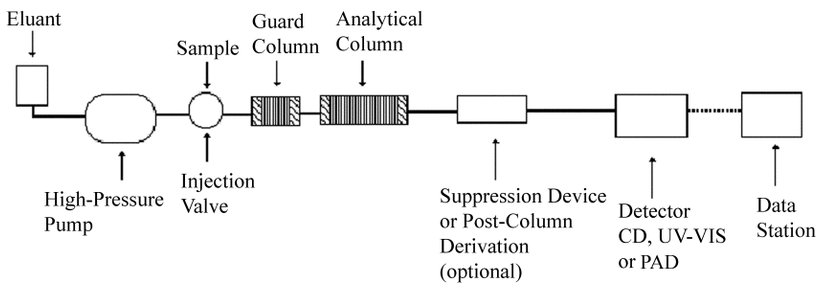

Figure 1. Components of a typical IC system illustrated schematically; CD = conductivity detector and PAD = pulsed amperometric detector.

Stationary and Mobile Phases

As IC has developed and matured as an instrumental technique, the number of ion-exchange materials developed for IC has increased, facilitated by the understanding of the processes taking place at the surface of the stationary phase. In contrast to the silica-based column packing prevalent in classical HPLC, organic polymers are predominately used as support materials for IC. Such materials have a higher stability with respect to extremes in pH and in many cases are compatible with organic solvents. Typically, separation of anions requires the use of polymer-based anion exchangers and dilute bases as mobile phases. However, for cation separations, the stability over the entire pH range that is typical of organic polymers is not necessary, because dilute acids serve as mobile phases. Therefore, silica-based cation exchangers that exhibit a significantly higher chromatographic efficiency are commonly used for the separation of cations.

Depending on the separation mode (ion exchange, ion exclusion, or ion-pair), different types of stationary phases are used. For ion exchange, the stationary phase is either an anion or a cation exchanger. Typically, a strong cation exchanger is used for the ion-exclusion separation of organic acids, and a reversed-phase stationary phase is used when ion-pair is the separation mode. The ion-exchange capacity of a resin is defined as the number of ion-exchange sites per weight equivalent of the column packing and is typically expressed in terms of mEq per g of resin. With ion exchange, the retention times for the analyte ions increase with increasing ion-exchange capacity of the resin. This effect can be partly compensated for by using mobile phases of higher ionic strength. Styrene/divinylbenzene copolymers, polymethacrylate, and polyvinyl resins are the substrate materials used in the manufacturing process of the polymer-based ion exchangers. Organic polymers are functionalized directly at their surface, with the exception of latex-based ion exchangers, where the totally porous latex particle acts as an ion-exchange material. Surface-functionalized, ''pellicular'' substrates show a much higher chromatographic efficiency compared with the fully functionalized resins.

With ion exchange, a mobile phase consisting of mono- or divalent ionic species, alone or mixed at an optimum ratio, is used to accomplish the separation. In ion-exclusion methods, particularly for organic acids, the mobile phase consists of mineral acids to maintain

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organic acids in their undissociated forms. Often, the nature of the analyte dictates the mobile phase and the detection mode used. Typical mobile phases used in IC are described below in the section on detectors.

Detectors

Conductivity detection is by far the most commonly employed mode of detection in IC. Although the original IC development work included the use of low-capacity ion-exchange resins for efficient chromatographic separation and conductometric detection of ions in a chemically suppressed mobile phase, the advances in column technologies as well as instrumentation development allow the use of high-capacity ion exchange today.

In suppressed IC, the background conductance of the ionic mobile phase is significantly reduced as it flows through the suppression device. For example, dilute NaOH, about 10 to 50 mM, used as the mobile phase in IC of anions is converted to H_2O (poor conductivity) when the column effluent containing NaOH flows through a suppressor device present in an acidic form. The analyte ionic species in the column effluent are converted from their sodium or other metal salt forms to highly conducting acid forms (due to higher equivalent conductance of hydrogen ions compared to other cations). Analogous reactions occur in the hydroxide form suppressor in IC of cations, wherein the acidic mobile phase is converted to water, and the analyte cations are converted to highly conducting hydroxide forms (due to higher equivalent conductance of hydroxide ions compared to other anions).

The reduced background conductance and the enhanced signal due to the ionic species result in an enhanced signal-to-noise ratio for the conductometric detection of ions in suppressed IC. This results in reduced background noise and increasing sensitivity and reproducibility of the analysis. The commonly used chemical suppression devices fall into three broad categories. In the first type, the reactions occur across an ion-exchange membrane with the regenerant ions furnished by either a chemical or as products of electrolysis of water. In the second type, the suppression reactions occur in a packed bed of high-exchange capacity resin material, with regeneration either by a chemical or by electrolysis of water. In the third type, although not commonly used, the suppression reactions occur as the eluant stream mixes with the flowing stream of high-capacity resin material.

For pharmaceutical analyses, suppressed conductometric detection may be used for detection of trace ions in high purity waters. The commonly used mobile phases for the separation of anions by suppressed IC include hydroxide ions or a mixture of bicarbonate and carbonate ions. The common mobile phases for separation of cations usually consist of mineral acids or methanesulfonic acid.

Ion-chromatographic analyses also can be performed without chemical suppression, in which case the analytical column effluent flows directly to a conductivity detector. The typical eluants used in nonsuppressed IC are phthalic acid and *p*-hydroxybenzoic acid for the determination of anions and methanesulfonic acid for the determination of cations. The equivalent conductance values of chloride, sulfate, and other common anions are significantly greater than that of the eluant anion, and therefore, a positive peak is detected as the anions are carried through the detector. The equivalent conductance values of sodium, potassium, calcium, magnesium, and other common cations are significantly lower than that of the cation (H^+) in the eluant. In this instance, a negative peak is detected as the cations are carried through the detector.

Nonsuppressed IC is easier to perform, and it is a useful technique for determining ions of weak acids such as cyanide and sulfide, which are nonconductive after chemical suppression but show a higher baseline noise. Pharmaceutical analyses can be performed in the nonsuppressed mode because the quantification limits are usually in the upper mg per L to low percentage levels. While suppressor-based methodologies must often be implemented on the instrument systems specifically designed for this purpose, IC may be performed without the suppressor on an existing HPLC. This is possible because the commonly used eluants in IC include dilute bases or acids that are compatible for use on existing HPLC instruments. When this approach is considered, analysts are encouraged to consult the instrument manufacturer for applicability of the instrument for the IC analysis.

OTHER DETECTORS

Other commonly used detection modes in IC include pulsed amperometry, direct UV detection, or post-column derivatization followed by UV/VIS detection.

Pulsed Amperometric Detection Mode (PAD)—PAD uses a specialized mode of the conventional amperometric technique. This type of detector is commonly used for the detection of electroactive species, e.g., organic compounds such as carbohydrates, sugar alcohols, amino acids, and organic sulfur species. In PAD, analytes are detected by an oxidative desorption process at the surface of an electrode located in the column effluent stream. Following the detection process, a series of potentials are applied for fixed time periods to clean the electrode surface. Unlike conventional amperometry that suffers from electrode surface fouling, a rapidly repeating sequence of different working potentials, referred to as waveform, helps the removal of the products of redox reactions from the electrode surface. For details of application of IC using PAD in the analysis of mono- and oligosaccharides of glycoproteins, see *Glycoprotein Glycan Analysis* ⟨1084⟩.

Direct

■and Indirect■1S *(USP30)*

UV Detection—Direct UV Detection is used for inorganic and organic ions that possess a UV chromophore. These include organic acids, bromide, iodide, nitrate, nitrite, thiosulfate, and cyano-metal complexes. Analogous to the inverse conductometric detection of cations, UV detection may also be performed indirectly. This method is called indirect photometric chromatography (IPC).

Photometric Detection—Photometric detection involves ~~derivatization~~

■chelation■1S *(USP30)*
of the

■metal ions in■1S *(USP30)*
column effluent with a color-forming reagent prior to detection with a visible wavelength. A classic example is the separation of metal ions in which the column effluent is ~~derivatized~~

■chelated■1S *(USP30)*
with 4-(2-pyridylazo)-resorcinol followed by detection at 510 to 530 nm.

BRIEFING

⟨1118⟩ Monitoring Devices—Time, Temperature, and Humidity, *USP 29* page 2976. It is proposed to revise the *Electronic Time—Temperature History Recorders* section to include a statement that acknowledges the existence of radio frequency devices used in monitoring pharmacopeial articles during storage and shipping.

(P&S: D. Hunt) RTS—C44226

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Change to read:

ELECTRONIC TIME–TEMPERATURE HISTORY RECORDERS

These devices, which may serve as an alternative to chemical-based TTIs, use one of the electronic temperature measurement technologies described above and create a record of the temperature history experienced by a device. Some are simple electronic devices that record and save temperature values representative of the cumulative temperature history over a period of time. These may be designated as electronic TTIs. They have the advantages of being able to calculate the Mean Kinetic Temperature (MKT) based on the measurements recorded and they can be calibrated.

Data Loggers—A more capable device records the temperature at very short intervals and is able to download the temperature history record to a peripheral system, such as a personal computer. Such devices may be termed electronic temperature data loggers. In addition, data loggers may record the humidity using sensors described below. ~~A data logger may be permanently fixed within a storage environment or it may be portable and travel with a product.~~

■Data loggers may be permanently fixed within a storage facility or they may be portable and travel with a product. Data loggers equipped with radio frequency capability can be used to remotely monitor temperature and humidity of a product while in transit, with the option of being able to download the recorded data when the data loggers arrive at a destination.■1S (*USP30*)

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Diisopropyl Ether, *USP 29* page 3126 and page 654 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to update the specifications for this reagent to reflect the materials available commercially.

(HDQ: M. Marques) RTS—C44419

Change to read:

Diisopropyl Ether *(Isopropyl Ether),* $[(CH_3)_2CH]_2O$—**102.17**

■[*108-20-3*]■1S (*USP30*)
—Colorless, mobile liquid. Slightly soluble in water. Miscible with alcohol and with ether. *[Caution—It is highly flammable. Do not use where it may be ignited. Do not evaporate to the point of near dryness, since it tends to form explosive peroxides.]*

~~*Specific gravity*— between 0.716 and 0.720.~~

~~*Distilling range, Method II* ⟨721⟩— Not less than 95% distills between 65° and 70°.~~

~~*Peroxides*— To 10 mL, contained in a clean, glass-stoppered cylinder previously rinsed with a portion of the ether under examination, add 1 mL of freshly prepared potassium iodide solution (1 in 10). Shake, and allow to stand for 1 minute: no yellow color is observed in either layer (about 0.001% as H_2O_2).~~

~~*Residue on evaporation*— [NOTE—*If peroxide is present, do not carry out this procedure.*] Evaporate 14 mL (10 g) from a tared shallow dish, and dry at 105° for 1 hour: the residue weighs not more than 1 mg (0.01%).~~

~~*Acidity*— Add 2 drops of bromothymol blue TS to 10 mL of water in a glass-stoppered, 50-mL flask, and titrate with 0.010 N sodium hydroxide until a blue color persists after vigorous shaking. Add 5 mL of diisopropyl ether, and titrate with 0.010 N sodium hydroxide: not more than 0.30 mL is required to restore the blue color (0.005% as CH_3COOH).~~

~~[NOTE—For spectrophotometric determinations, use diisopropyl ether that meets the following additional requirement.]~~

~~*Absorbance*— Its absorbance at 255 nm, in a 10-mm quartz cell, does not exceed 0.2, water being used as the blank.~~

■Use ACS reagent grade.■1S (*USP30*)

BRIEFING

2,4-Dinitrophenylhydrazine, *USP 29* page 3128. It is proposed to include the CAS number and some synonyms to facilitate the procurement of these reagents.

(HDQ: M. Marques) RTS—43402-18

Change to read:

2,4-Dinitrophenylhydrazine, $2,4\text{-}C_6H_3(NO_2)_2NHNH_2$—**198.14**

■[*119-26-6*]■1S (*USP30*)
—Orange-red crystals, which under the microscope appear individually to be lemon-yellow, lath-like needles. Very slightly soluble in water; slightly soluble in alcohol; moderately soluble in dilute inorganic acids.

Melting range ⟨741⟩: between 197° and 200°.

Solubility in sulfuric acid—Dissolve 500 mg in a mixture of 25 mL of sulfuric acid and 25 mL of water: the solution is clear or not more than slightly turbid.

Residue on ignition (Reagent test): negligible, from 500 mg.

BRIEFING

Dioxane, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43402-19

Change to read:

Dioxane *(Diethylene Dioxide; 1,4-Dioxane),* $C_4H_8O_2$—**88.11**

■[*123-91-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Diphenyl Ether, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43402-20

Change to read:

Diphenyl Ether *(Phenyl Ether),* $(C_6H_5)_2O$—**170.21**

■[*101-84-8*]■1S (*USP30*)
—A colorless liquid. Insoluble in water; soluble in glacial acetic acid and in most organic solvents. Boils at about 259°.

Melting range ⟨741⟩: between 26° and 28°.

BRIEFING

Diphenylamine, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-1

Change to read:

Diphenylamine, $(C_6H_5)_2NH$—**169.22**

■[*122-39-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Diphenylcarbazide, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-2

Change to read:

Diphenylcarbazide, $(C_6H_5NHNH)_2CO$—**242.28**

■[*140-22-7*]■1S (*USP30*)
—Use ACS reagent grade 1,5-Diphenylcarbohydrazide.

BRIEFING

Diphenylcarbazone, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-3

Change to read:

Diphenylcarbazone *[Diphenylcarbazone compd. with s-Diphenylcarbazide (1 : 1)],* $C_6H_5NHNHCON{:}\ NC_6H_5 \cdot C_6H_5NHNHCONHNHC_6H_5$—**482.54**

■[*538-62-5*]■1S (*USP30*)
—Use ACS reagent grade Diphenylcarbazone Compound with *s*-Diphenylcarbazide (1 : 1).

BRIEFING

2,2-Diphenylglycine, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-4

Change to read:

2,2-Diphenylglycine, $C_{14}H_{13}NO_2$—**227.26**

■[*3060-50-2*]■1S (*USP30*)
—Off-white powder. Melts at about 244°, with decomposition.

Assay—Dissolve about 115 mg, accurately weighed, in 30 mL of methanol. Slowly add about 20 mL of water, heating slightly if necessary for complete solution. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 22.73 mg of $C_{14}H_{13}NO_2$. Not less than 98.0% is found.

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BRIEFING

Dipropyl Phthalate, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-5

Change to read:

Dipropyl Phthalate, $C_{14}H_{18}O_4$—**250.29**

■[*131-16-8*]■1S (*USP30*)
—Viscous, colorless liquid.

Assay—

MOBILE PHASE—Prepare a mixture of acetonitrile and water (52 : 48).

PROCEDURE—Inject about 20 µL into a suitable liquid chromatograph (see *Chromatography* ⟨621⟩) equipped with a 230-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 2.0 mL per minute. The area of the $C_{14}H_{18}O_4$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.495 and 1.499 at 20°.

BRIEFING

4,4′-Dipyridyl Dihydrochloride, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-6

Change to read:

4,4′-Dipyridyl Dihydrochloride, $C_{10}H_8N_2 \cdot 2HCl$—**229.11**

■[*27926-72-3*]■1S (*USP30*)
—White to off-white crystals.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 230°; the detector temperature is maintained at 300°; and the column temperature is maintained at 160° and programmed to rise 10° per minute to 260°. The area of the $C_{10}H_8N_2 \cdot 2HCl$ peak is not less than 98.5% of the total peak area.

BRIEFING

5,5′-Dithiobis(2-nitrobenzoic Acid), *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-7

Change to read:

5,5′-Dithiobis(2-nitrobenzoic Acid) *(3-Carboxy-4-nitrophenyl disulfide; Ellman's reagent),* $C_{14}H_8N_2O_8S_2$—**396.35**

■[*69-78-3*]■1S (*USP30*)
—Yellow powder, melting at about 242°. Sparingly soluble in alcohol.

BRIEFING

Dithiothreitol, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-8

Change to read:

Dithiothreitol *(Cleland's Reagent; Threo-1,4-dimercapto-2,3-butanediol; DTT),* $HSCH_2CH(OH)CH(OH)CH_2SH$—**154.25**

■[*3483-12-3*]■1S (*USP30*)
—Slightly hygroscopic needles from ether. Freely soluble in water, in alcohol, in acetone, in ethyl acetate, and in ether.

Melting range ⟨741⟩: between 42° and 44°.

BRIEFING

Dithizone, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-9

Change to read:

Dithizone *(Diphenylthiocarbazone; Phenylazothioformic Acid 2-Phenylhydrazide),* $C_6H_5N{:}\ NCSNHNHC_6H_5$—**256.33**

■[*60-10-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

1-Dodecanol, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-10

Change to read:

1-Dodecanol *(Dodecyl Alcohol),* $CH_3(CH_2)_{11}OH$—**186.33**

■[*112-53-8*]■1S (*USP30*)
—A clear, colorless liquid. Crystallizes as leaflets from dilute alcohol solution. Use ACS reagent grade.

In-Process Revision

BRIEFING

***n*-Eicosane,** *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-11

Change to read:

***n*-Eicosane,** $C_{20}H_{42}$—**282.55**

■[*112-95-8*]■1S (*USP30*)
—White, crystalline solid.

Melting range ⟨741⟩: between 37° and 39°.

BRIEFING

Eicosanol, *USP 29* page 3128—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-12

Change to read:

Eicosanol—

■[*629-96-9*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Eosin Y (Eosin Yellowish Y), *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-13

Change to read:

Eosin Y (Eosin Yellowish Y) *(Certified Biological Eosin Y; Sodium Tetrabromofluorescein),* $C_{20}H_6Br_4Na_2O_5$—**691.85**

■[*17372-87-1*]■1S (*USP30*)
—Red to brownish-red pieces or powder. Use ACS reagent grade.

BRIEFING

Epiandrosterone, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-14

Change to read:

Epiandrosterone, $C_{19}H_{30}O_2$—**290.44**

■[*481-29-8*]■1S (*USP30*)
—White, crystalline powder.

Assay—When tested by thin-layer chromatography (see *Chromatography* ⟨621⟩) with the use of plates coated with chromatographic silica gel mixture and a developing system consisting of a mixture of toluene and ethanol (9 : 1), examined under short-wavelength UV light, a single spot is exhibited, with trace impurities.

Melting range ⟨741⟩: between 172° and 177°.

BRIEFING

Equilenin, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-15

Change to read:

Equilenin, $C_{18}H_{18}O_2$—**266.33**

■[*517-09-9*]■1S (*USP30*)
—Colorless or white crystals or crystalline powder. Insoluble in water; soluble in chloroform and in dioxane; moderately soluble in alcohol.

Melting range, Class II ⟨741⟩: between 256° and 260°.

Specific rotation ⟨781⟩: between +85° and +88°, determined in a solution in dioxane containing 75 mg of equilenin in each 10 mL.

Absorption maxima—An alcohol solution exhibits absorption maxima at 231, 282, 325, and 340 nm.

BRIEFING

Eriochrome Cyanine R, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-16

Change to read:

Eriochrome Cyanine R, $C_{23}H_{15}Na_3O_9S$—**536.40**

■[*3564-18-9*]■1S (*USP30*)
—Dark, red-brown powder. Freely soluble in water; insoluble in alcohol.

In-Process Revision

Solubility—200 mg in 100 mL of water yields a solution that remains clear and free from undissolved matter for 30 minutes.

Loss on drying ⟨731⟩—Dry it in vacuum over silica gel to constant weight: it loses not more than 2% of its weight.

Residue on ignition (Reagent test)—0.5 g, treated with 1 mL of sulfuric acid and 2 mL of nitric acid, yields between 42.0% and 44.0% of the dry weight (theoretical yield is 42.9% of Na_2SO_4).

Sensitiveness—Add 2 mL of a solution (1 in 1000) to 1 mL of aluminum sulfate solution (1 in 10,000), heat at 37 ± 3° for 5 minutes, cool, and add 1 mL of sodium acetate TS: a strong red to red-violet color is produced in not more than 5 minutes.

BRIEFING

Ethanesulfonic Acid, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-18

Change to read:

Ethanesulfonic Acid, $C_2H_5SO_3H$—**110.13**

■[*594-45-6*]■1S (*USP30*)
—Colorless to light yellow liquid. Soluble in water.

Assay—Accurately weigh about 300 mg, dissolve in 30 mL of water, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Each mL of 0.1 N sodium hydroxide is equivalent to 11.013 mg of $C_2H_5SO_3H$: between 94.0% and 106.0% is found.

Refractive index ⟨831⟩: between 1.432 and 1.436 at 20°.

BRIEFING

2-Ethoxyethanol, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-19

Change to read:

2-Ethoxyethanol *(Ethylene Glycol Monoethyl Ether),* $C_4H_{10}O_2$—**90.12**

■[*110-80-5*]■1S (*USP30*)
—Clear, colorless liquid. ~~having a slight, characteristic odor.~~

■■1S (*USP30*)
Miscible with water, with alcohol, with ether, and with acetone.

Specific gravity ⟨841⟩: about 0.93.

Boiling range (Reagent test)—Not less than 95% distills between 133° and 135°.

BRIEFING

Ethyl Acetate, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43403-20

Change to read:

Ethyl Acetate, $CH_3COOC_2H_5$—**88.11**

■[*141-78-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ethyl Acrylate, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-1

Change to read:

Ethyl Acrylate—

■[*140-88-5*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Ethyl Benzoate, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-2

Change to read:

Ethyl Benzoate, $C_9H_{10}O_2$—**150.17**

■[*93-89-0*]■1S (*USP30*)
—Clear, colorless liquid. Has an aromatic odor. Practically insoluble in water; miscible with alcohol, with chloroform, and with ether.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩), helium being used as the carrier gas. The following conditions have been found suitable: a 3-mm × 2.4-m stainless steel column containing 20% phase G16 on support S1A; the injection port, column, and detector temperatures are maintained at 180°, 195°, and 250°, respectively. The area of the ethyl benzoate peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: between 1.5048 and 1.5058 at 20°.

BRIEFING

Ethyl Cyanoacetate, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-3

Change to read:

Ethyl Cyanoacetate, $CNCH_2COOC_2H_5$—**113.11**

■[*105-56-6*]■1S (*USP30*)
—Colorless to pale yellow liquid. ▲▲*USP29* Slightly soluble in water. Miscible with alcohol and with ether. At atmospheric pressure it boils between 205° and 209°, with decomposition. At a pressure of 10 mm of mercury it distills at about 90°.

Specific gravity ⟨841⟩: between 1.057 and 1.062.

Acidity—Dissolve 2 mL in 25 mL of neutralized alcohol, add phenolphthalein TS, and titrate with 0.10 N sodium hydroxide: not more than 1.5 mL is required to produce a pink color.

BRIEFING

Ethyl Ether, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-4

Change to read:

Ethyl Ether *(Diethyl Ether; Ether),* $(C_2H_5)_2O$—**74.12**

■[*60-29-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ethyl Ether, Anhydrous, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-5

Change to read:

Ethyl Ether, Anhydrous *(Diethyl Ether, Anhydrous; Ether, Absolute),* $(C_2H_5)_2O$—**74.12**

■[*60-29-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Ethyl Salicylate, *USP 29* page 3129—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-6

Change to read:

Ethyl Salicylate, $C_9H_{10}O_3$—**166.17**

■[*118-61-6*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 10-m capillary column coated with a 1-μm layer of methylsilicone; the injection port temperature is maintained at 240°; the detector temperature is maintained at 300°; the column temperature is maintained at 150° and programmed to rise 10° per minute to 250°. The area of the ethyl salicylate peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.5216 and 1.5236 at 20°.

BRIEFING

2-Ethylaminopropiophenone Hydrochloride, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-7

Change to read:

2-Ethylaminopropiophenone Hydrochloride, $C_6H_5COCH(CH_3)NHC_2H_5 \cdot HCl$—**213.70**

■[*51553-17-4*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

4-Ethylbenzaldehyde, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-8

Change to read:

4-Ethylbenzaldehyde, $C_2H_5C_6H_4CHO$—**134.18**

■[*4748-78-1*]■1S (*USP30*)
—Colorless to pale yellow liquid.

Assay—Dissolve about 600 mg, accurately weighed, in a mixture of 100 mL of alcohol and 25 mL of 1 M hydroxylamine hydrochloride in a beaker. Cover the beaker with a watch glass. Heat gently until condensate begins to form on the watch glass. Allow to cool for

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about 30 minutes. Titrate with 0.5 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 67.09 mg of $C_2H_5C_6H_4CHO$. Not less than 98% is found.

BRIEFING

Ethylbenzene, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-9

Change to read:

Ethylbenzene, C_8H_{10}—**106.17**

■[*100-41-4*]■1S *(USP30)*
—Not less than 99.5%.

BRIEFING

Ethylene Dichloride, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-10

Change to read:

Ethylene Dichloride *(1,2-Dichloroethane),* $C_2H_4Cl_2$—**98.96**

■[*107-06-2*]■1S *(USP30)*
—Use ACS reagent grade 1,2-Dichloroethane.

BRIEFING

Ethylene Glycol, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-11

Change to read:

Ethylene Glycol, $HOCH_2CH_2OH$—**62.07**

■[*107-21-1*]■1S *(USP30)*
—Clear, colorless, slightly viscous, hygroscopic ▲▲*USP29* liquid. Slightly soluble in ether; practically insoluble in benzene. Miscible with water and with alcohol.

Specific gravity ⟨841⟩: about 1.11.

Boiling range (Reagent test): between 194° and 200°.

Residue on ignition—Evaporate 100 mL (110 g) in a tared evaporating dish over a flame until the vapors continue to burn after the flame is removed. Allow the vapors to burn until the specimen is consumed. Ignite at 800 ± 25° for 1 hour, cool, and weigh: the residue weighs not more than 5.5 mg (0.005%).

Acidity—Add 0.2 mL of phenol red TS to 50 mL of water, and titrate with 0.1 N sodium hydroxide to a red endpoint. Add 50 mL (55 g) of ethylene glycol, and titrate with 0.1 N sodium hydroxide: not more than 1 mL is required to restore the red color (0.01% as CH_3COOH).

Chloride (Reagent test)—A 4.5-mL (5-g) portion shows not more than 0.025 mg of Cl (5 ppm).

Water, Method I ⟨921⟩: not more than 0.20%.

BRIEFING

1-Ethylquinaldinium Iodide, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-12

Change to read:

1-Ethylquinaldinium Iodide, $C_{12}H_{14}IN$—**299.15**

■[*606-55-3*]■1S *(USP30)*
—Yellow-green solid. Sparingly soluble in water.

Assay—Dissolve about 290 mg, accurately weighed, in 100 mL of water, and add 10 mL of glacial acetic acid. Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically, using a silver-ion selective electrode and a calomel reference electrode containing 1 M potassium nitrate. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N silver nitrate is equivalent to 29.92 mg of $C_{12}H_{14}IN$: not less than 97.0% is found.

BRIEFING

Fast Blue B Salt, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-14

Change to read:

Fast Blue B Salt, $C_{14}H_{12}N_4O_2 \cdot ZnCl_4$—**475.47**

■[*91-91-8*]■1S *(USP30)*
—Green powder.

Loss on drying ⟨731⟩—Dry it in vacuum at 110° for 1 hour: it loses not more than 5.0% of its weight.

Absorbance—Dissolve 50 mg in 100 mL of water. In a second container dissolve 100 mg of 2-naphthol in 100 mL of 2-methoxyethanol. Pipet 5 mL of the test solution and 10 mL of the 2-naphthol solution into a 100-mL volumetric flask, and dilute with acetone to volume. For the blank, pipet 5 mL of water and 10 mL of 2-naphthol solution into a second 100-mL volumetric flask, and dilute with acetone to volume. Determine the absorbance of the test solution in a 1-cm cell at the wavelength of maximum absorbance at about 545 nm, with a suitable spectrophotometer, using the blank to set the instrument: the absorbance is not less than 0.80.

BRIEFING

Fast Blue BB Salt, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-13

Change to read:

Fast Blue BB Salt, $(C_{17}H_{18}ClN_3O_3)_2 \cdot ZnCl_2$—**831.89**

■[*15710-69-7*]■1S *(USP30)*
—Yellow powder melting at about 162°, with decomposition. Sparingly soluble in water.

Chloride—Transfer about 80 mg, accurately weighed, to a suitable beaker. Add 25 mL of acetone, 25 mL of water, and 500 mg of sodium nitrate. Stir until solution is complete. Titrate with 0.01 N silver nitrate VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary correction. Not less than 15.0% of chloride is found.

BRIEFING

Ferric Chloride, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-15

Change to read:

Ferric Chloride, $FeCl_3 \cdot 6H_2O$—**270.29**

■[*7705-08-0*]■1S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Ferric Nitrate, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-16

Change to read:

Ferric Nitrate, $Fe(NO_3)_3 \cdot 9H_2O$—**404.00**

■[*10421-48-4*]■1S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Ferric Sulfate, *USP 29* page 3130—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-17

Change to read:

Ferric Sulfate, $Fe_2(SO_4)_3 \cdot xH_2O$—

■[*10028-22-5*]■1S *(USP30)*
—Grayish-white, hygroscopic powder, or fawn-colored pearls, slowly soluble in water.

Assay—Accurately weigh about 700 mg, and dissolve it in a mixture of 50 mL of water and 3 mL of hydrochloric acid in a glass-stoppered flask. Add 3 g of potassium iodide, and allow to stand in the dark for 30 minutes. Then dilute with 100 mL of water, and titrate with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Each mL of 0.1 N sodium thiosulfate is equivalent to 5.585 mg of Fe: not less than 21.0% and not more than 23.0% is found.

Insoluble matter (Reagent test)—A 10-g portion, dissolved in a mixture of 100 mL of water and 5 mL of sulfuric acid, shows not more than 2 mg of insoluble matter (0.02%).

Chloride—Dissolve 1 g by warming with a mixture of 10 mL of water and 1 mL of nitric acid, add 4 mL of additional nitric acid, and dilute with water to 50 mL. To 25 mL add 1 mL of phosphoric acid and 1 mL of silver nitrate TS. Any turbidity does not exceed that produced in a control containing 0.01 mg of chloride ion (Cl), 1 mL of nitric acid, 1 mL of phosphoric acid, and 1 mL of silver nitrate TS (0.002%).

Ferrous iron—Dissolve 4 g by warming with 50 mL of dilute sulfuric acid (1 in 10), cool, and titrate with 0.1 N potassium permanganate: not more than 0.16 mL is required to produce a permanent pink color (0.02% as Fe+2). [NOTE—Because the reagents used in the tests for *Copper* and *Zinc* may contain excessive amounts of copper and zinc, they should first be purified by extracting with *Dithizone Extraction Solution* (see *Lead* ⟨251⟩).]

Copper—Dissolve 1.2 g in 100 mL of water. To 10 mL add 50 mL of a solution containing 5 g of ammonium tartrate and 5 mL of ammonium hydroxide. Add 10 mL of *Standard Dithizone Solution* (see *Lead* ⟨251⟩), shake for 2 minutes, draw off the dithizone layer, and compare the pink color with that in a control containing 6 µg of copper ion (Cu) and treated exactly as the 10-mL portion of test solution. If the color in the test solution is less than that in the control, then the test specimen contains less than the limit of both *Copper* and *Zinc*. If the color in the test solution is more than that in the control, add 15 mL of dilute hydrochloric acid (1 in 250), and shake for 2 minutes. Draw off the dithizone solution, and shake with a second 15 mL of dilute hydrochloric acid (1 in 250) for 2 minutes. Draw off the dithizone, combine the two acid extracts, and reserve for the *Zinc* test. Any pink color in the dithizone solution is not darker than that in the control solution treated exactly as the test solution (0.005%).

Zinc—To the combined acid extracts saved from the *Copper* test, add 0.5 M sodium acetate to bring the pH between 5.0 and 5.5, and then add 1 mL of 0.1 N sodium thiosulfate. Add 10 mL of *Standard Dithizone Solution* (see *Lead* ⟨251⟩), shake for 2 minutes, and allow the layers to separate. Draw off the dithizone, and discard the water layer. Any pink color is not greater than that in a control prepared by adding 0.006 mg of zinc ion (Zn) to the combined acid extracts from the control used in the test for *Copper* (0.005%).

Nitrate—Dissolve 10 g in 100 mL of dilute sulfuric acid (1 in 100), heat to boiling, and pour, slowly, into a mixture of 140 mL of water and 50 mL of stronger ammonia TS. Filter through a folded filter while still hot, wash with hot water until the volume of the filtrate is 300 mL, mix, and cool. To 15 mL of this solution add 1 mL

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of sodium chloride solution (1 in 200), 0.10 mL of indigo carmine TS, and 15 mL of sulfuric acid. The blue color is not completely discharged at the end of 5 minutes (0.01%).

Substances not precipitated by ammonia—Evaporate to dryness 30 mL of the filtrate obtained in the test for *Nitrate*, and ignite gently: the weight of residue does not exceed 1 mg (0.10%).

BRIEFING

Ferrous Sulfate, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-18

Change to read:

Ferrous Sulfate, $FeSO_4 \cdot 7H_2O$—**278.02**

■[*7720-78-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Fluorene, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-19

Change to read:

Fluorene, $C_{13}H_{10}$—**166.22**

■[*86-73-7*]■1S (*USP30*)
—White to off-white crystals or powder. Soluble in benzene, in carbon disulfide, in ether, and in hot alcohol; freely soluble in glacial acetic acid.

Solubility test—One g dissolves in 10 mL of acetone to yield a clear and complete solution.

Melting range ⟨741⟩: between 113° and 117°, within a 2° range.

BRIEFING

9-Fluorenylmethyl Chloroformate, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43404-20

Change to read:

9-Fluorenylmethyl Chloroformate, $C_{15}H_{11}ClO_2$—**258.70**

■[*28920-43-6*]■1S (*USP30*)
—Clear, colorless solid. Melts at about 62°.

BRIEFING

Fluorescamine, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-1

Change to read:

Fluorescamine, $C_{17}H_{10}O_4$—**278.26**

■[*38183-12-9*]■1S (*USP30*)
—White to off-white powder. Very slightly soluble in water; freely soluble in methylene chloride; soluble in alcohol; slightly soluble in chloroform.

Assay—Dissolve about 600 mg in 75 mL of dimethylformamide, and titrate with 0.1 N lithium methoxide to a blue endpoint, using 1% thymol blue in dimethylformamide as the indicator. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N lithium methoxide is equivalent to 27.83 mg of $C_{17}H_{10}O_4$. Not less than 99% is found.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 0.5% of its weight.

BRIEFING

4′-Fluoroacetophenone, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-2

Change to read:

4′-Fluoroacetophenone, $FC_6H_4COCH_3$—**138.14**

■[*403-42-9*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 200°; the detector temperature is maintained at 250°; the column temperature is maintained at 100° and programmed to rise 10° per minute to 250°. The area of the $FC_6H_4COCH_3$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: 1.510 at 20°.

BRIEFING

Formamide, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-3

Change to read:

Formamide, $HCONH_2$—**45.04**

■[*75-12-7*]■1S (*USP30*)
—Use ACS reagent grade.

Preparation for Digitoxin Assay—To ensure freedom from ammonia, treat Formamide as follows. Shake a suitable quantity of formamide with about 10% of its weight of anhydrous potassium carbonate for 15 minutes, and filter. Distill the filtrate in an all-glass apparatus under vacuum at a pressure of about 25 mm of mercury or less. Reject the first portion of distillate containing water, and collect the fraction that boils at about 115° at a pressure of 25 mm of mercury or at 101° at a pressure of 12 mm of mercury. Store in tight containers, protected from light.

BRIEFING

Formic Acid, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-4

Change to read:

Formic Acid, HCOOH—**46.03**

■[*64-18-6*]■1S (*USP30*)
—Use ACS reagent grade Formic Acid, 88 Percent.

BRIEFING

Formic Acid, 96 Percent, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-5

Change to read:

Formic Acid, 96 Percent, HCOOH—**46.03**

■[*64-18-6*]■1S (*USP30*)
—Use ACS reagent grade Formic Acid, 96 Percent.

BRIEFING

Fuchsin, Basic, *USP 29* page 3131—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-8

Change to read:

Fuchsin, Basic—

■[*632-99-5*]■1S (*USP30*)
—A mixture of rosaniline and pararosaniline hydrochlorides. Crystals or crystalline fragments with a glossy, greenish-bronze luster. Soluble in water, in alcohol, and in amyl alcohol.

To 10 mL of a solution (1 in 500) add 10 mL of ammonia TS and 500 mg of zinc dust, and agitate the mixture: the solution becomes colorless. Place a few drops of the decolorized solution on filter paper and nearby, on the same paper, place a few drops of diluted hydrochloric acid: a red color develops at the zone of contact.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 5.0% of its weight.

Residue on ignition (Reagent test)—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 3 mg (0.3%).

BRIEFING

Gadolinium (Gd III) Acetate Hydrate, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-7

Change to read:

Gadolinium (Gd III) Acetate Hydrate, $(CH_3CO_2)_3Gd \cdot xH_2O$—**334.38**

■[*100587-93-7*]■1S (*USP30*)
—White, crystalline, hygroscopic powder. Irritant. Use a suitable grade.

BRIEFING

Gitoxin, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-10

Change to read:

Gitoxin, $C_{41}H_{64}O_{14}$—**780.94**

■[*4562-36-1*]■1S (*USP30*)
—White, crystalline powder. Practically insoluble in water, in chloroform, and in ether; slightly soluble in pyridine and in diluted alcohol. Melts at about 250°, with decomposition.

Specific rotation ⟨781⟩: between +3.8° and +4.8°, determined in a solution of pyridine containing 10 mg per mL, with the use of a mercury light at 546.1 nm; between +21° and +25°, determined in a solution of equal parts of chloroform and methanol containing 5 mg per mL, with the use of sodium light.

Suitability—Dissolve 10 mg each of USP Digitoxin RS, previously dried, USP Digoxin RS, previously dried, and gitoxin, respectively, in separate 5-mL portions of a mixture of 2 parts of chloroform and 1 part of methanol, and dilute each with additional

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solvent mixture to 10 mL. Then proceed as directed in the *Identification test* under *Digoxin*. The chromatogram of gitoxin shows one fluorescent spot, located between the digoxin and digitoxin spots.

BRIEFING

D-Gluconic Acid, 50 Percent in Water, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-11

Change to read:

D-Gluconic Acid, 50 Percent in Water, $C_6H_{12}O_7$—**196.16**

■[*526-95-4*]■1S (*USP30*)
—Pale yellow liquid.

Assay—Dilute about 200 mg of the solution, accurately weighed, with 30 mL of water. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 19.62 mg of $C_6H_{12}O_7$. Not less than 49.0% is found.

Refractive index ⟨831⟩ : between 1.4160 and 1.4180 at 20°.

Specific rotation ⟨781⟩ : between +9.9° and +11.9°, determined as is, at 20°.

BRIEFING

Glucose, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-12

Change to read:

Glucose, $C_6H_{12}O_6$—**180.2**

■[*50-99-7*]■1S (*USP30*)
—Use a suitable grade. A white, crystalline powder. ~~with a sweet taste.~~

■■1S (*USP30*)
Freely soluble in water; sparingly soluble in alcohol.

BRIEFING

D-Glucuronolactone, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-13

Change to read:

D-Glucuronolactone, $C_6H_8O_6$—**176.12**

■[*32449-92-6*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Glycerin, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-14

Change to read:

Glycerin *(Glycerol)*—

■[*56-81-5*]■1S (*USP30*)
—Use ACS reagent grade Glycerol.

BRIEFING

Glycolic Acid, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-15

Change to read:

Glycolic Acid, $C_2H_4O_3$—**76.05**

■[*79-14-1*]■1S (*USP30*)
—White crystalline powder or chunks.

Assay—Inject an appropriate volume (silanized) into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2. The injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; the column temperature is maintained at 100° and programmed to rise 10° per minute to 250°. The area of the $C_2H_4O_3$ peak is not less than 98.5% of the total peak area.

BRIEFING

Gold Chloride, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-16

Change to read:

Gold Chloride *(Chlorauric Acid),* $HAuCl_4 \cdot 3H_2O$—**393.83**

■[*16903-35-8*]■1S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Guaiacol, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-17

Change to read:

Guaiacol *(o-Methoxyphenol),* $C_7H_8O_2$—**124.14**

■[*95-05-1*]■1S *(USP30)*
—Colorless to yellowish, refractive liquid. ▲▲*USP29* Soluble in about 65 parts of water; soluble in sodium hydroxide solution; miscible with alcohol, with chloroform, with ether, and with glacial acetic acid.

Assay—When examined by gas–liquid chromatography, it shows a purity of not less than 98%. The following conditions have been found suitable for assaying it: a 3-mm × 1.8-m stainless steel column containing liquid phase G16 on 60- to 80-mesh support S1A. Helium is the carrier gas, the injection port temperature is maintained at 180°, the column temperature is maintained at 200°, and the flame-ionization detector is maintained at 280°. The retention time is about 8 minutes.

Refractive index ⟨831⟩: between 1.5430 and 1.5450, at 20°.

BRIEFING

Guanidine Hydrochloride, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-18

Change to read:

Guanidine Hydrochloride, $CH_5N_3 \cdot HCl$—**95.53**

■[*50-01-1*]■1S *(USP30)*
—White, crystalline powder. Freely soluble in water and in alcohol.

Melting range ⟨741⟩: between 178° and 189°.

Chloride content—Dissolve about 400 mg, accurately weighed, in 5 mL of water. Add 5 mL of glacial acetic acid, 50 mL of methanol, and 1 drop of eosin Y TS, and titrate with 0.1 N silver nitrate VS. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of Cl. Not less than 36.1% and not more than 37.1%, calculated on the anhydrous basis, is found.

BRIEFING

Guanine Hydrochloride, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-19

Change to read:

Guanine Hydrochloride, $C_5H_5N_5O \cdot HCl \cdot H_2O$—**205.60**

■[*635-39-2*]■1S *(USP30)*
—White, crystalline powder. Melts above 250°, with decomposition. Slightly soluble in water and in alcohol; soluble in acidulated water and in sodium hydroxide TS. Its solutions are not precipitated by iodine TS or by mercuric–potassium iodide TS, but form a precipitate with trinitrophenol TS.

Residue on ignition (Reagent test): negligible, from 100 mg.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 10.0% of its weight.

BRIEFING

Hematein, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43407-20

Change to read:

Hematein, $C_{16}H_{12}O_6$—**300.26**

■[*475-25-2*]■1S *(USP30)*
—Prepared from logwood extract or from hematoxylin by treatment with ammonia and exposure to air. Reddish-brown crystals with a yellowish-green metallic luster. Very slightly soluble in water (about 1 in 1700); slightly soluble in alcohol and in ether; insoluble in benzene and in chloroform; freely soluble in diluted ammonia solution to form a solution of dusky purplish-red color and in an aqueous solution of sodium hydroxide (1 in 50), to form a solution of bright red color, viewed in each case through a layer 1 cm in depth. Melts at a temperature above 200° and tends to decompose at 250°.

BRIEFING

Hematoxylin, *USP 29* page 3132—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-1

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Change to read:

Hematoxylin *(Hydroxybrasilin),* $C_{16}H_{14}O_6 \cdot 3H_2O$—**356.32**

■[*517-28-2*]■1S *(USP30)*
—A crystalline substance derived from the heartwood of *Haematoxylon campechianum* Linné (Fam. Leguminosae). Colorless to yellow prisms. Very slightly soluble in cold water and in ether; rapidly soluble in hot water and in hot alcohol. When exposed to light, it acquires a red color and yields a yellow solution. Dissolves in ammonia TS and in solutions of alkali hydroxides and carbonates. When dissolved in solutions of the following salts, it develops the colors indicated: in alum solution, a red color; in stannous chloride solution, a rose color; and in solutions of cupric salts, a greenish-gray color. It gradually turns black in potassium dichromate solution. Store hematoxylin and its solutions protected from light and air.

BRIEFING

Hexadecyl Hexadecanoate, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-2

Change to read:

Hexadecyl Hexadecanoate *(Hexadecyl Palmitate; Cetyl Palmitate),* $C_{32}H_{64}O_2$—**480.85**

■[*540-10-3*]■1S *(USP30)*
—Use a suitable grade.
[NOTE—Suitable grades are available commercially as Hexadecyl Palmitate and Palmitic Acid Palmityl Ester from Sigma-Aldrich, www.sigma-aldrich.com, and Cetyl Palmitate, Catalog number C1203, from Spectrum Chemical Mfg. Corp., www.spectrumchemical.com.]

BRIEFING

Hexamethyldisilazane, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-3

Change to read:

Hexamethyldisilazane, $C_6H_{19}NSi_2$—**161.39**

■[*999-97-3*]■1S *(USP30)*
—Clear, colorless liquid. ▲▲*USP29*

Assay—When examined by gas–liquid chromatography, it shows a purity of not less than 95%. The following conditions have been found suitable for assaying the article: A 2-mm × 1.8-m glass column packed with phase G3 on support S1. Helium, flowing at a rate of about 40 mL per minute, is the carrier gas; the detector temperature is about 310°; the injection port temperature is about 100°; and the column temperature is programmed to start at 35°, hold for 5 minutes, then rise at a rate of 8° per minute to 200°. A flame-ionization detector is employed.

Residue after evaporation—Transfer 200 g to a tared dish, and evaporate on a steam bath to dryness. Dry the residue at 105° for 1 hour, cool, and weigh: not more than 0.0025% of residue is found.

BRIEFING

Hexamethyleneimine, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-4

Change to read:

Hexamethyleneimine *(Homopiperidine),* $C_6H_{12}NH$—**99.17**

■[*111-49-9*]■1S *(USP30)*
— Colorless to nearly colorless liquid.
Refractive index ⟨831⟩: between 1.4640 and 1.4660 at 20°.

BRIEFING

***n*-Hexane,** *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-5

Change to read:

***n*-Hexane,** C_6H_{14}—**86.18**

■[*110-54-3*]■1S *(USP30)*
(for use in spectrophotometry)—Use *Hexanes*.

BRIEFING

Hexane, Solvent, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-6

Change to read:

Hexane, Solvent *(Petroleum Benzin; Petroleum Ether, Ligroin)*

■[*8032-32-4*]■1S *(USP30)*
—Clear, volatile liquid. ▲▲*USP29* Practically insoluble in water; soluble in absolute alcohol. Miscible with ether, with chloroform, with benzene, and with most fixed and volatile oils.
Caution—It is dangerously flammable. Keep it away from flames, and store in tight containers in a cool place.
Use ACS reagent grade Petroleum Ether.

In-Process Revision

BRIEFING

Hexanitrodiphenylamine, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-7

Change to read:

Hexanitrodiphenylamine *(Dipicrylamine),* $C_{12}H_5N_7O_{12}$—**439.21**

■[*131-73-7*]■1S *(USP30)*
—Yellow-gold powder or prisms. *[Caution—Explosive.]* Usually contains about 15% of water as a safety precaution. Insoluble in water, in alcohol, in acetone, and in ether; soluble in glacial acetic acid and in alkalies.

Water, *Method I* ⟨921⟩ : not more than 16%.

BRIEFING

Hexanophenone, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-8

Change to read:

Hexanophenone, $C_{12}H_{16}O$—**176.25**

■[*942-92-7*]■1S *(USP30)*
—Yellow liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G3; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_{12}H_{16}O$ peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: 1.511 ± 0.002 at 20°.

BRIEFING

Hydrazine Hydrate, 85% in Water, *USP 29* page 3133 and page 186 of *PF* 32(1) [Jan.–Feb. 2006]—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-9

Change to read:

Hydrazine Hydrate, 85% in Water, $(NH_2)_2 \cdot H_2O$—**50.06**

■[*7803-57-8*]■1S *(USP30)*
—Colorless liquid.

Assay—Transfer 600 mg, accurately weighed, to a 100-mL volumetric flask. Dilute with water to volume, and mix. Pipet 10 mL into a suitable beaker, and add 1.0 g of sodium bicarbonate and 50.0 mL of 0.1 N iodine VS. Titrate the excess iodine with 0.1 N sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N iodine is equivalent to ~~12.52 mg~~

▲1.252 mg▲*USP30*
of $(NH_2)_2 \cdot H_2O$. Not less than 83% is found.

BRIEFING

Hydrazine Dihydrochloride, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-10

Change to read:

Hydrazine Dihydrochloride, $(NH_2)_2 \cdot 2HCl$—**104.97**

■[*5341-61-7*]■1S *(USP30)*
—White powder.

Assay—Dissolve about 34 mg, accurately weighed, in 50 mL of water. Add carefully while stirring, 1 g of sodium bicarbonate. *[Caution—There may be a rapid evolution of carbon dioxide.]* Titrate with 0.1 N iodine solution, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 N iodine solution is equivalent to 2.63 mg of $(NH_2)_2 \cdot 2HCl$. Not less than 98% is found.

BRIEFING

Hydriodic Acid, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-11

Change to read:

Hydriodic Acid, HI—**127.91**

■[*10034-85-2*]■1S *(USP30)*
—Use ACS reagent grade (containing not less than 47.0% of HI).

[NOTE—For methoxy determination (see *Methoxy Determination* ⟨431⟩), use hydriodic acid ACS reagent grade 55%. Use this grade also for alkoxyl determinations in assays in the individual monographs.]

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BRIEFING

Hydrochloric Acid, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-12

Change to read:

Hydrochloric Acid, HCl—**36.46**

■[*7647-01-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Hydrochloric Acid, Diluted, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-12

Change to read:

Hydrochloric Acid, Diluted (10 percent)—

■[*7647-01-0*]■1S (*USP30*)
—Prepare by mixing 226 mL of hydrochloric acid with sufficient water to make 1000 mL.

BRIEFING

Hydrofluoric Acid, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-13

Change to read:

Hydrofluoric Acid, HF—**20.01**

■[*7664-39-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Hydrogen Peroxide, 30 Percent, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-14

Change to read:

Hydrogen Peroxide, 30 Percent, H_2O_2—**34.01**

■[*7722-84-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Hydrogen Sulfide, *USP 29* page 3133—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-15

Change to read:

Hydrogen Sulfide, H_2S—**34.08**

■[*7783-06-4*]■1S (*USP30*)
—Colorless, poisonous gas, heavier than air. Soluble in water. Is generated by treating ferrous sulfide with diluted sulfuric or diluted hydrochloric acid. Other sulfides yielding hydrogen sulfide with diluted acids may be used. Is also available in compressed form in cylinders.

BRIEFING

Hydroquinone, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-16

Change to read:

Hydroquinone, $C_6H_4(OH)_2$—**110.11**

■[*123-31-9*]■1S (*USP30*)
—Fine, colorless or white, needle crystals. Darkens on exposure to air and light. Soluble in water, in alcohol, and in ether.

Assay—Accurately weigh about 250 mg, and dissolve in a mixture of 100 mL of water and 10 mL of 0.1 N sulfuric acid in a 250-mL conical flask. Add 3 drops of a 1 in 100 solution of diphenylamine in sulfuric acid, and titrate with 0.1 N ceric sulfate VS until the solution is red-violet in color. Each mL of 0.1 N ceric sulfate is equivalent to 5.506 mg of $C_6H_4(OH)_2$. Not less than 99% is found.

Melting range ⟨741⟩: between 172° and 174°.

BRIEFING

3′-Hydroxyacetophenone, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-17

Change to read:

3′-Hydroxyacetophenone, $C_8H_8O_2$—**136.15**

■[*121-71-1*]■1S (*USP30*)
—Light brown powder chips and chunks. Melts at about 96°. Sparingly soluble in chloroform, yielding a clear, light yellow solution.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G1; the detector and the injection port temperatures are maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280° and held at that temperature for 10 minutes. The area of the main peak is not less than 97% of the total peak area.

BRIEFING

4′-Hydroxyacetophenone, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-18

Change to read:

4′-Hydroxyacetophenone, $HOC_6H_4COCH_3$—**136.15**

■[*99-93-4*]■1S (*USP30*)
—Gray powder, melting at about 109°.

BRIEFING

***p*-Hydroxybenzoic Acid,** *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-19

Change to read:

***p*-Hydroxybenzoic Acid,** $C_7H_6O_3$—**138.12**

■[*99-96-7*]■1S (*USP30*)
—White crystals.

Assay—Transfer about 700 mg, accurately weighed, to a suitable container, and dissolve in 50 mL of acetone. Add 100 mL of water, mix, and titrate with 0.5 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 69.06 mg of $C_7H_6O_3$: not less than 97% is found.

Melting range ⟨741⟩: over a range of 2° that includes 216°.

BRIEFING

4-Hydroxybenzoic Acid Isopropyl Ester, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43408-20

Change to read:

4-Hydroxybenzoic Acid Isopropyl Ester, $HOC_6H_4COOCH(CH_2)_2$—**180.18**

■[*4191-73-5*]■1S (*USP30*)
—Use a suitable grade.

Melting range ⟨741⟩: between 84° and 87°.

[NOTE—A suitable grade is available from TCI America, www.tciamerica.com.]

BRIEFING

1-Hydroxybenzotriazole Hydrate, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-1

Change to read:

1-Hydroxybenzotriazole Hydrate, $C_6H_5N_3O \cdot xH_2O$—**135.13** (anhydrous)

■[*123333-53-9*]■1S (*USP30*)
—White, crystalline powder. Sparingly soluble in alcohol yielding a clear, pale yellow solution.

BRIEFING

2-Hydroxybenzyl Alcohol, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-2

Change to read:

2-Hydroxybenzyl Alcohol, $C_7H_8O_2$—**124.14**

■[*90-01-7*]■1S (*USP30*)
—Off-white flakes. Very soluble in alcohol, in chloroform, and in ether; soluble in 15 parts water and in benzene.

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Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩), equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the $C_7H_8O_2$ peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 83° and 85°.

BRIEFING

4-Hydroxyisophthalic Acid, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-3

Change to read:

4-Hydroxyisophthalic Acid, $C_8H_6O_4$—**182.13**

■[*636-46-4*]■1S (*USP30*)
—Colorless branched needles. Freely soluble in alcohol and in ether.

Melting range ⟨741⟩: between 308° and 310°, with decomposition at 314° to 315°.

BRIEFING

Hydroxylamine Hydrochloride, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-4

Change to read:

Hydroxylamine Hydrochloride, $NH_2OH \cdot HCl$—**69.49**

■[*5470-11-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Hydroxy Naphthol Blue, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-5

Change to read:

Hydroxy Naphthol Blue *(1-(2-Naphtholazo-3,6-disulfonic Acid)-2-naphthol-4-sulfonic Acid, Disodium Salt),* $C_{20}H_{12}N_2O_{11}S_3Na_2$—**598.50**

■[*165660-27-5*]■1S (*USP30*)
—Deposited on crystals of sodium chloride in the concentration of about 1%. Use ACS reagent grade.

BRIEFING

D-α-4-Hydroxyphenylglycine, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-6

Change to read:

D-α-4-Hydroxyphenylglycine, $C_8H_9NO_3$—**167.16**

■[*22818-40-2*]■1S (*USP30*)
—Shiny leaflets. Sparingly soluble in water, in alcohol, in acetone, in ether, in chloroform, in ethyl acetate, in benzene, and in glacial acetic acid; soluble in alkalies and in mineral acids; freely soluble in warm 20% v/v hydrochloric acid.

Melting range ⟨741⟩: between 220° and 247°, with decomposition.

BRIEFING

4-(4-Hydroxyphenyl)-2-butanone, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-7

Change to read:

4-(4-Hydroxyphenyl)-2-butanone, $C_{10}H_{12}O_2$—**164.20**

■[*5471-51-2*]■1S (*USP30*)
—White powder.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G43; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_{10}H_{12}O_2$ peak is not less than 98.5% of the total peak area.

Melting range ⟨741⟩: between 81° and 87°.

BRIEFING

8-Hydroxyquinoline, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-8

Change to read:

8-Hydroxyquinoline *(Oxine),* C_9H_7NO—**145.16**

■[*148-24-3*]■1S *(USP30)*
—Use ACS reagent grade 8-Quinolinol.

BRIEFING

Hypophosphorous Acid, 50 Percent, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-9

Change to read:

Hypophosphorous Acid, 50 Percent *(Hypophosphorous Acid),* HPH_2O_2—**66.00**

■[*6303-21-5*]■1S *(USP30)*
—A colorless to faintly yellow liquid. Miscible with water and with alcohol.

Assay—Accurately weigh about 4 mL, dilute with 25 mL of water, add methyl red TS, and titrate with 1 N sodium hydroxide VS: each mL of 1 N sodium hydroxide is equivalent to 66.00 mg of HPH_2O_2. Not less than 48% is found.

Chloride—Add 0.2 mL to a mixture of 10 mL of silver nitrate TS and 5 mL of nitric acid, and heat until brown fumes are no longer evolved: any white, insoluble residue remaining is negligible.

Phosphate—Dilute 1 mL with water to 50 mL, render alkaline with ammonia TS, filter if a precipitate is formed, and add to the filtrate 5 mL of magnesia mixture TS: not more than a slight precipitate is formed within 5 minutes.

Sulfate (Reagent test, *Method I*)—Dilute 1 mL with water to 50 mL: 20 mL of the solution shows not more than 0.2 mg of SO_4.

BRIEFING

Imidazole, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-10

Change to read:

Imidazole, $C_3H_4N_2$—**68.08**

■[*288-32-4*]■1S *(USP30)*
—White to light yellow crystals. Freely soluble in water. Use ACS reagent grade.

BRIEFING

Indene, *USP 29* page 3134—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-12

Change to read:

Indene, C_9H_8—**116.16**

■[*95-13-6*]■1S *(USP30)*
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 10-m capillary column coated with a 1-μm layer of methylsilicone; the injection port temperature is maintained at 200°; the detector temperature is maintained at 300°; the column temperature is maintained at 100° and programmed to rise 10° per minute to 250°. The area of the indene peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.5749 and 1.5769 at 20°.

BRIEFING

Inosine, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-13

Change to read:

Inosine, $C_{10}H_{12}N_4O_5$—**268.23**

■[*58-63-9*]■1S *(USP30)*
—White, crystalline powder.

Melting point ⟨741⟩: about 90°.

BRIEFING

Inositol, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-14

Change to read:

Inositol *(Hexahydroxycyclohexane),* $C_6H_6(OH)_6$—**180.16**

■[*87-89-8*]■1S *(USP30)*
—Fine, white crystals or a white, crystalline powder; ▲▲*USP29* stable in air. Its solutions are neutral to litmus. Optically inactive. One g dissolves in 5.7 mL of water. Slightly soluble in alcohol; insoluble in ether and in chloroform. Store in well-closed containers.

Melting range ⟨741⟩: between 223° and 226°.

In-Process Revision

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition (Reagent test): not more than 0.1%.

BRIEFING

Iodic Acid, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-15

Change to read:

Iodic Acid, HIO_3—**175.91**

■[*7782-68-5*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Iodine, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-16

Change to read:

Iodine, I_2—**253.81**

■[*7553-56-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Iodine Monobromide, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-17

Change to read:

Iodine Monobromide, IBr—**206.81**

■[*7789-35-5*]■1S (*USP30*)
—Black, gray, or blue-purple crystals, crystalline needles, or crystalline chunks.

Assay—Place about 100 mL of acetic acid in a 150-mL beaker. Separately dissolve 2 g of potassium iodide in a minimum volume of water, add this solution to the acetic acid, and mix. Transfer about 200 mg of Iodine Monobromide, accurately weighed, to the beaker containing the potassium iodide and acetic acid mixture, and stir to dissolve. Titrate immediately with 0.1 N sodium thiosulfate VS, determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium thiosulfate is equivalent to 20.681 mg of IBr. Not less than 97.5% is found.

BRIEFING

Iodine Monochloride, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-18

Change to read:

Iodine Monochloride, ICl—**162.36**

■[*7790-99-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Isobutyl Acetate, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-19

Change to read:

Isobutyl Acetate, $C_6H_{12}O_2$—**116.16**

■[*110-19-0*]■1S (*USP30*)
—Clear, colorless liquid. Slightly soluble in water. Miscible with alcohol.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G2. The injection port temperature is maintained at 130°; the column temperature is maintained at 30° and programmed to rise 10° per minute to 180° and held there for 10 minutes. The detector temperature is maintained at 300°. The area of the main peak is not less than 99% of the total peak area.

Specific gravity ⟨841⟩: between 0.863 and 0.868.

Refractive index ⟨831⟩: between 1.3900 and 1.3920 at 20°.

BRIEFING

Isobutyl Alcohol, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43417-20

In-Process Revision

Change to read:

Isobutyl Alcohol (*2-Methyl-1-propanol*), $(CH_3)_2CHCH_2OH$—**74.12**

■[*78-83-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Isonicotinic Acid, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-1

Change to read:

Isonicotinic Acid, $C_6H_5NO_2$—**123.11**

■[*52-22-1*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Isopropyl Alcohol, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-2

Change to read:

Isopropyl Alcohol *(2-Propanol),* $(CH_3)_2CHOH$—**60.10**

■[*67-63-0*]■1S (*USP30*)
—Use ACS reagent grade.
[NOTE—For use in assays and tests involving UV spectrophotometry, use ACS reagent grade Isopropyl Alcohol Suitable for Use in UV Spectrophotometry.]

BRIEFING

Isopropyl Alcohol, Dehydrated, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-3

Change to read:

Isopropyl Alcohol, Dehydrated—

■[*67-63-0*]■1S (*USP30*)
—Use Isopropyl Alcohol that previously has been dried by being shaken with a suitable molecular sieve capable of adsorbing water, and filtered.

BRIEFING

Isopropyl Myristate, *USP 29* page 3135—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-5

Change to read:

Isopropyl Myristate, $C_{17}H_{34}O_2$—**270.45**

■[*110-27-0*]■1S (*USP30*)
—Use *Isopropyl Myristate* (NF monograph). For use as a solvent in sterility test procedures, Isopropyl Myristate conforms to the following additional specification:

pH of water extract—Transfer 100 mL to a 250-mL centrifuge bottle, add 10 mL of twice-distilled water, close the bottle with a suitable closure, and shake vigorously for 60 minutes. Centrifuge the mixture at 1800 rpm for 20 minutes, aspirate the upper (isopropyl myristate) layer, and determine the pH of the residual water layer: the pH is not less than 6.5.

Isopropyl Myristate not conforming to the test for *pH of water extract* may be rendered suitable for use in sterility test procedures as follows:

Using a 20-mm × 20-cm glass column, add activated alumina, and tamp down to a height of 15 cm. Pass 500 mL of the isopropyl myristate through the column, using a slight positive pressure to maintain an even flow, and use the eluate collected directly in the sterility test procedure.

BRIEFING

Isopropylamine, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-6

Change to read:

Isopropylamine *(2-Aminopropane),* $C_3H_7NH_2$—**59.11**

■[*75-31-0*]■1S (*USP30*)
—Clear, colorless, flammable liquid. ▲▲*USP29* Miscible with water, with alcohol, and with ether.

Assay—Transfer about 0.2 g, accurately weighed, to a suitable container, add 50 mL of water, and mix. Titrate with 0.1 N hydrochloric acid VS, using a mixture of bromocresol green TS and methyl red TS (5 : 1) as indicator. Each mL of 0.1 N hydrochloric acid is equivalent to 59.11 mg of C_3H_9N. Not less than 98% is found.

Boiling range (Reagent test)—Not less than 95% distills between 31° and 33°.

Refractive index ⟨831⟩: between 1.3743 and 1.3753, at 20°.

In-Process Revision

BRIEFING

Kerosene, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-7

Change to read:

Kerosene—

■[*8008-20-6*]■1S (*USP30*)
—A mixture of hydrocarbons, chiefly of the methane series. A clear, colorless liquid. ~~possessing a characteristic, but not disagreeable, odor.~~

■■1S (*USP30*)
Specific gravity: about 0.80. Distills between 180° and 300°.

BRIEFING

Lactose, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-8

Change to read:

Lactose, $C_{12}H_{22}O_{11} \cdot H_2O$—**342.30**

■[*64-42-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Lanthanum Chloride, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-9

Change to read:

Lanthanum Chloride, $LaCl_3 \cdot (6–7)H_2O$—

■[*10025-84-0*]■1S (*USP30*)
—This reagent is available in degrees of hydration ranging from 6 to 7 molecules of water. Use ACS reagent grade.

BRIEFING

Lead Acetate, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-10

Change to read:

Lead Acetate, $Pb(C_2H_3O_2)_2 \cdot 3H_2O$—**379.33**

■[*301-04-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Lead Monoxide, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-11

Change to read:

Lead Monoxide *(Litharge),* PbO—**223.20**

■[*1317-36-8*]■1S (*USP30*)
—Heavy, yellowish or reddish-yellow powder. Insoluble in water and in alcohol; soluble in acetic acid, in diluted nitric acid, and in warm solutions of the fixed alkali hydroxides.

Assay—Accurately weigh about 300 mg, freshly ignited in a muffle furnace at 600 ± 50°, and dissolve it by warming with 10 mL of water and 1 mL of glacial acetic acid. Dilute with 75 mL of water, heat to boiling, add 50.0 mL of 0.1 N potassium dichromate VS, and boil for 2 to 3 minutes. Cool, transfer to a 200-mL volumetric flask with the aid of water, dilute with water to volume, mix, and allow to settle. Withdraw 100.0 mL of the clear liquid, and transfer to a glass-stoppered flask. Add 10 mL of diluted sulfuric acid and 1 g of potassium iodide, insert the stopper, mix gently, and allow to stand for 10 minutes. Then titrate the liberated iodine, representing the excess of dichromate, with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached: each mL of 0.1 N potassium dichromate is equivalent to 7.440 mg of PbO. Not less than 98% is found.

Insoluble in acetic acid—Dissolve 2 g in 30 mL of dilute glacial acetic acid (1 in 2), boil gently for 5 minutes, filter, wash the residue with diluted acetic acid, and dry at 105° for 2 hours: the residue weighs not more than 10 mg (0.5%).

Substances not precipitated by hydrogen sulfide—Completely precipitate the lead from the filtrate obtained in the test for *Insoluble in acetic acid* by passing hydrogen sulfide into it, filter, and wash the precipitate with 20 mL of water. To one-half of the mixed filtrate and washings add 5 drops of sulfuric acid, evaporate to dryness, and ignite at 800 ± 25° for 15 minutes: the residue weighs not more than 5 mg (0.5%).

Volatile substances—Accurately weigh about 5 g, and heat strongly in a covered porcelain crucible: it loses not more than 2.0% of its weight.

BRIEFING

Lead Nitrate, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-12

Change to read:

Lead Nitrate, $Pb(NO_3)_2$—**331.21**

■[*10099-74-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Lithium Chloride, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-13

Change to read:

Lithium Chloride, LiCl—**42.39**

■[*7447-41-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Lithium Hydroxide, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-13

Change to read:

Lithium Hydroxide, $LiOH \cdot H_2O$—**41.96**

■[*1310-65-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Lithium Metaborate, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-14

Change to read:

Lithium Metaborate, $LiBO_2$—**49.75**

■[*13453-69-5*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Lithium Nitrate, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-14

Change to read:

Lithium Nitrate, $LiNO_3$—**68.95**

■[*7790-69-4*]■1S (*USP30*)
—Colorless crystals. Use a suitable grade labeled to contain not less than 97.0%.

BRIEFING

Lithium Perchlorate, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-15

Change to read:

Lithium Perchlorate, $LiClO_4$—**106.39**

■[*7791-03-9*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Lithium Sulfate, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-16

Change to read:

Lithium Sulfate, $Li_2SO_4 \cdot H_2O$—**127.96**

■[*10377-48-7*]■1S (*USP30*)
—Use ACS reagent grade.

In-Process Revision

BRIEFING

Lithocholic Acid, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-17

Change to read:

Lithocholic Acid, $C_{24}H_{40}O_3$—**376.57**

■[*434-13-9*]■1S (*USP30*)
—White powder.

Assay—When tested by thin-layer chromatography, with the use of plates coated with chromatographic silica gel mixture, a developing system consisting of a mixture of toluene, 1,4-dioxane, and acetic acid (15.2 : 4.2 : 0.6), and sprayed with a mixture of sulfuric acid and methanol (1 : 1), heated at 110° for 20 minutes, and examined visually and under long-wavelength UV light, a single spot is exhibited.

Melting range ⟨741⟩: between 184° and 186°.

BRIEFING

Litmus, *USP 29* page 3136—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-18

Change to read:

Litmus

■—[*1393-92-6*]■1S (*USP30*)
—A blue pigment prepared from various species of *Rocella* DeCandolle, *Lecanora* Acharius, or other lichens (Fam. Parmeliaceae).

Description—Cubes, masses, fragments, or granules, of an indigo blue or deep violet color. Has the combined odor of indigo and violets, and tinges the saliva a deep blue. The indicator substances it contains are soluble in water and less soluble or insoluble in alcohol.

Ash—It yields not more than 60.0% of ash.

BRIEFING

L-Lysine, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-19

Change to read:

L-Lysine *(2,6-Diaminohexanoic Acid),* $C_6H_{14}N_2O_2$—**146.19**

■[*56-87-1*]■1S (*USP30*)
—Crystalline needles or hexagonal plates. Soluble in water; very slightly soluble in alcohol; insoluble in ether.

Specific rotation ⟨781⟩: between +25.5° and +26.0°.

Test solution: 20 mg per mL, in dilute hydrochloric acid (1 in 2).

Nitrogen content, Method I ⟨461⟩: between 18.88% and 19.44% of N is found, corresponding to not less than 98.5% of $C_6H_{14}N_2O_2$, the test specimen previously having been dried at 105° for 2 hours.

BRIEFING

Magnesium, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-20

Change to read:

Magnesium, Mg—**24.305**

■[*7439-95-4*]■1S (*USP30*)
—Silvery metal in ribbon form. Reacts slowly with water at room temperature. Dissolves readily in dilute acids with the liberation of hydrogen.

Assay—Transfer 1 g, accurately weighed, to a 250-mL volumetric flask, and dissolve in a mixture of 15 mL of hydrochloric acid and 85 mL of water. When solution is complete, dilute with water to volume, and mix. Pipet 25 mL of the dilution into a 400-mL beaker, dilute with water to 250 mL, add 20 mL of ammonia–ammonium chloride TS and a few mg of eriochrome black T trituration, and titrate with 0.1 M edetate disodium VS to a blue endpoint. Each mL of 0.1 M edetate disodium VS is equivalent to 2.430 mg of Mg. Not less than 99% is found.

BRIEFING

Magnesium Acetate, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43418-21

Change to read:

Magnesium Acetate, $Mg(C_2H_3O_2)_2 \cdot 4H_2O$—**214.45**

■[*142-72-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Magnesium Chloride, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-1

Change to read:

Magnesium Chloride, $MgCl_2 \cdot 6H_2O$—**203.30**

■[*7786-30-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Magnesium Nitrate, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-2

Change to read:

Magnesium Nitrate, $Mg(NO_3)_2 \cdot 6H_2O$—**256.41**

■[*10377-60-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Magnesium Oxide, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-3

Change to read:

Magnesium Oxide, MgO—**40.30**

■[*1309-48-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Magnesium Perchlorate, Anhydrous, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-4

Change to read:

Magnesium Perchlorate, Anhydrous, $Mg(ClO_4)_2$—**223.21**

■[*10034-81-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Magnesium Sulfate, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-5

Change to read:

Magnesium Sulfate, $MgSO_4 \cdot 7H_2O$—**246.48**

■[*10034-99-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Magnesium Sulfate, Anhydrous, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-6

Change to read:

Magnesium Sulfate, Anhydrous, $MgSO_4$—**120.37**

■[*7487-88-9*]■1S (*USP30*)
—Anhydrous Magnesium Sulfate may be prepared as follows. Place a suitable quantity of magnesium sulfate (see above), preferably powdered, in a shallow vessel, and expose to a temperature of about 80° for several hours with occasional stirring. Then heat at 275° to 300° until the weight is practically constant. Transfer the product while still warm to tight containers, as the anhydrous salt is very hygroscopic.

BRIEFING

Maleic Acid, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-7

Change to read:

Maleic Acid, $C_4H_4O_4$—**116.07**

■[*110-16-7*]■1S (*USP30*)
—White, ▲*USP29* crystalline powder. Soluble in 1.5 parts of water, in 2 parts of alcohol, and in 12 parts of ether.

Assay—Dissolve about 2 g, accurately weighed, in 100 mL of water and titrate with 1 N sodium hydroxide VS, using phenolphthalein TS as the indicator. Each mL of 1 N sodium hydroxide is equivalent to 58.04 mg of $C_4H_4O_4$: not less than 99% of $C_4H_4O_4$, calculated on the dried basis, is found.

Loss on drying—Dry it in vacuum over phosphorus pentoxide for 2 hours: it loses not more than 1.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

In-Process Revision

BRIEFING

Manganese Dioxide, Activated, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-8

Change to read:

Manganese Dioxide, Activated *(Manganese (IV) Oxide, Activated),* MnO_2—**86.94**

■[*1313-13-9*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Mercuric Acetate, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-9

Change to read:

Mercuric Acetate, $Hg(C_2H_3O_2)_2$—**318.68**

■[*1600-27-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Mercuric Bromide, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-10

Change to read:

Mercuric Bromide, $HgBr_2$—**360.40**

■[*7789-47-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Mercuric Chloride, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-11

Change to read:

Mercuric Chloride, $HgCl_2$—**271.50**

■[*7487-94-7*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Mercuric Iodide, Red, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-12

Change to read:

Mercuric Iodide, Red, HgI_2—**454.40**

■[*7774-29-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Mercuric Nitrate, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-14

Change to read:

Mercuric Nitrate, $Hg(NO_3)_2 \cdot xH_2O$—**342.62**

■[*10045-94-0*]■1S (*USP30*)
—Use ACS reagent grade. This reagent is available as either the mono- or dihydrate.

BRIEFING

Mercuric Oxide, Yellow, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-15

Change to read:

Mercuric Oxide, Yellow, HgO—**216.59**

■[*21908-53-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Mercuric Sulfate, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-16

Change to read:

Mercuric Sulfate, $HgSO_4$—**296.65**

■[*7783-35-9*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Mercuric Thiocyanate, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-17

Change to read:

Mercuric Thiocyanate, $Hg(SCN)_2$—**316.76**

■[*592-85-8*]■1S (*USP30*)
—White, crystalline powder. Very slightly soluble in water; soluble in solutions of sodium chloride; slightly soluble in alcohol and in ether.

BRIEFING

Mercury, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-18

Change to read:

Mercury, Hg—**At. Wt. 200.59**

■[*7439-97-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Mesityl Oxide, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-19

Change to read:

Mesityl Oxide, $C_6H_{10}O$—**98.14**

■[*141-79-7*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 150°; the detector temperature is maintained at 300°; the column temperature is maintained at 50° and programmed to rise 10° per minute to 200°. The area of the $C_6H_{10}O$ peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: between 1.443 and 1.447 at 20°.

BRIEFING

Metaphosphoric Acid, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43419-20

Change to read:

Metaphosphoric Acid *(Vitreous Sodium Acid Metaphosphate),* HPO_3—**79.98**

■[*37267-86-0*]■1S (*USP30*)
—Use ACS reagent grade.

In-Process Revision

BRIEFING

Methacrylic Acid, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-1

Change to read:

Methacrylic Acid—

■[*79-41-4*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Methanesulfonic Acid, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-2

Change to read:

Methanesulfonic Acid, CH_4O_3S—**96.11**

■[*75-75-2*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Methanol, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-3

Change to read:

Methanol *(Methyl Alcohol),* CH_3OH—**32.04**

■[*67-56-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Methoxyethanol, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-4

Change to read:

Methoxyethanol *(Ethylene Glycol Monomethyl Ether; 2-Methoxyethanol),* $CH_3OCH_2CH_2OH$—**76.09**

■[*109-86-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

2-Methoxyethanol, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-5

Change to read:

2-Methoxyethanol *(Ethylene Glycol Monomethyl Ether; Methoxyethanol),* $CH_3OCH_2CH_2OH$—**76.09**

■[*109-86-4*]■1S (*USP30*)
—See *Methoxyethanol.*

BRIEFING

5-Methoxy-2-methyl-3-indoleacetic Acid, *USP 29* page 3137—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-18

Change to read:

5-Methoxy-2-methyl-3-indoleacetic Acid, $C_{12}H_{13}NO_3$—**219.24**

■[*2882-15-7*]■1S (*USP30*)
—Off-white powder.

Assay—Transfer about 110 mg, accurately weighed, to a 100-mL beaker. Add 30 mL of methanol and dissolve by stirring. Add 40 mL of water, and mix. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 21.92 mg of $C_{12}H_{13}NO_3$. Not less than 98% is found.

Melting range ⟨741⟩: between 161° and 168°, but the range between beginning and end of melting does not exceed 3°.

BRIEFING

Methyl Acetate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-19

Change to read:

Methyl Acetate, $C_3H_6O_2$—**74.08**

■[*74-20-9*]■1S (*USP30*)
—Colorless liquid. ▲▲*USP29* Soluble in water. Miscible with alcohol and with ether.

Specific gravity ⟨841⟩: about 0.933.

Refractive index ⟨831⟩: between 1.3615 and 1.3625 at 20°.

Boiling range (Reagent test)—Not less than 95% distills between 57° and 58°.

BRIEFING

Methyl 4-Aminobenzoate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43420-20

Change to read:

Methyl 4-Aminobenzoate, $C_8H_9NO_2$—**151.16**

■[*619-45-4*]■1S (*USP30*)
—Off-white powder.

Assay—Dissolve about 38 mg, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 15.12 mg of $C_8H_9NO_2$. Not less than 99.0% is found.

Melting range ⟨741⟩: between 108° and 110°.

BRIEFING

Methyl Arachidate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-1

Change to read:

Methyl Arachidate

■*(Eicosanoic acid, methyl ester),*■1S (*USP30*)
$C_{21}H_{42}O_2$—**326.56**

■[*1120-28-1*]■1S (*USP30*)
—Off-white flakes.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal-conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: a 2.0-mm × 1.8-m glass column packed with 5% G2 phase on support S1A; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; the column temperature is maintained at 230° and programmed to rise 3° per minute to 280°. The area of the $C_2H_{42}O_2$ peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 46° and 51°.

BRIEFING

Methyl Behenate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-2

Change to read:

Methyl Behenate, $C_{23}H_{46}O_2$—**354.61**

■[*929-77-1*]■1S (*USP30*)
—White powder.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: a 2.0-mm × 1.8-m glass column packed with 5% G3 phase on support S1A; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; the initial temperature of the oven is 220°, which is held for 2 minutes, and then programmed to rise 3° per minute to attain a final temperature of 270°, which is held for 10 minutes. The area of the $C_{23}H_{46}O_2$ peak is not less than 98% of the total peak area.

Melting range ⟨741⟩: between 54° and 56°.

BRIEFING

Methyl Caprate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-3

Change to read:

Methyl Caprate, $C_{11}H_{22}O_2$—**186.29**

■[*110-42-9*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the $C_{11}H_{22}O_2$ peak is not less than 98.5% of the total peak area.

BRIEFING

Methyl Caprylate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-4

In-Process Revision

Change to read:

Methyl Caprylate, $C_9H_{18}O_2$—**158.24**

■[*111-11-5*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 230°; the detector temperature is maintained at 300°; the column temperature is maintained at 130° and programmed to rise 10° per minute to 280°. The area of the $C_9H_{18}O_2$ peak is not less than 98.5% of the total peak area.

BRIEFING

Methyl Carbamate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-5

Change to read:

Methyl Carbamate, $C_2H_5NO_2$—**75.07**

■[*598-55-0*]■1S (*USP30*)
—White crystals. Freely soluble in water.
Melting range ⟨741⟩: between 54° and 56°.

BRIEFING

Methyl Chloroform, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-6

Change to read:

Methyl Chloroform *(Methylchloroform; 1,1,1-Trichloroethane),* CH_3CCl_3—**133.40**

■[*71-55-6*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Methyl Erucate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-8

Change to read:

Methyl Erucate, $C_{23}H_{44}O_2$—**352.59**

■[*1120-34-9*]■1S (*USP30*)
—Colorless liquid.

BRIEFING

Methyl Ethyl Ketone, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-9

Change to read:

Methyl Ethyl Ketone, $CH_3COC_2H_5$—**72.11**

■[*78-93-3*]■1S (*USP30*)
—Use ACS reagent grade 2-butanone.

BRIEFING

Methyl Heptadecanoate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-10

Change to read:

Methyl Heptadecanoate, $C_{18}H_{36}O_2$—**284.48**

■[*1731-92-6*]■1S (*USP30*)
—White, crystalline flakes.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G8; the injection port temperature is maintained at 220°; the detector temperature is maintained at 220°; the column temperature is maintained at 180° and programmed to rise 4° per minute to 220°. The area of the $C_{18}H_{36}O_2$ peak is not less than 99% of the total peak area.
Melting range ⟨741⟩: between 31° and 32°.

BRIEFING

Methyl Iodide, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-11

Change to read:

Methyl Iodide, CH_3I—**141.94**

■[*74-88-4*]■1S *(USP30)*
—Colorless, heavy, transparent liquid. Slightly soluble in water. Miscible with alcohol, with ether, and with solvent hexane. Turns brown on exposure to light as a result of liberation of iodine.

Assay—Add 1 mL to a 100-mL volumetric flask tared with 10 mL of alcohol. Weigh again, add alcohol to volume, and mix. Pipet 20 mL into a glass-stoppered flask, and add 50.0 mL of 0.1 N silver nitrate VS and 2 mL of nitric acid. Insert the stopper immediately, shake frequently during 2 hours, and allow to stand in the dark overnight. Shake again for 2 hours, then add 50 mL of water and 3 mL of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Each mL of 0.1 N silver nitrate is equivalent to 14.19 mg of CH_3I: not less than 98.5% is found.

Boiling range (Reagent test)—Distill 50 mL into a chilled, partly closed receiver: not less than 48 mL distills between 41.5° and 43°.

Density: between 2.270 and 2.285.

Residue on evaporation—Evaporate 4 mL (10 g) on a steam bath, and dry the residue at 105° for 1 hour: the residue weighs not more than 1 mg (0.01%).

Acidity—Shake 3 mL with 5 mL of water for 30 seconds, and immediately draw off the lower layer: the aqueous layer is neutral to litmus, and when 1 mL of silver nitrate TS is added, it shows not more than a slight opalescence.

BRIEFING

Methyl Laurate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-12

Change to read:

Methyl Laurate, $C_{13}H_{26}O_2$—**214.34**

■[*110-82-0*]■1S *(USP30)*
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_{13}H_{26}O_2$ peak is not less than 99.45% of the total peak area.

BRIEFING

Methyl Lignocerate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-13

Change to read:

Methyl Lignocerate, $C_{25}H_{50}O_2$—**382.66**

■[*2442-49-1*]■1S *(USP30)*
—White crystals.

BRIEFING

Methyl Linoleate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-14

Change to read:

Methyl Linoleate, $C_{19}H_{34}O_2$—**294.47**

■[*112-63-0*]■1S *(USP30)*
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; the column temperature is maintained at 200° and programmed to rise 10° per minute to 300°. The area of the $C_{19}H_{34}O_2$ peak is not less than 99% of the total peak area.

BRIEFING

Methyl Linolenate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-15

Change to read:

Methyl Linolenate, $C_{19}H_{32}O_2$—**292.46**

■[*301-00-8*]■1S *(USP30)*
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase 14% cyanopropylphenyl-86% dimethylpolysiloxane; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_{19}H_{32}O_2$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.469 and 1.473 at 20°.

In-Process Revision

BRIEFING

Methyl Methacrylate, *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-16

Change to read:

Methyl Methacrylate—

■[*80-62-6*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Methyl Myristate, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-17

Change to read:

Methyl Myristate, $C_{15}H_{30}O_2$—**242.40**

■[*124-10-7*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; the column temperature is maintained at 200° and programmed to rise 10° per minute to 300°. The area of the $C_{15}H_{30}O_2$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.434 and 1.438 at 20°.

BRIEFING

Methyl Oleate, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-18

Change to read:

Methyl Oleate, $C_{19}H_{36}O_2$—**296.49**

■[*112-62-9*]■1S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; the column temperature is maintained at 230° and programmed to rise 10° per minute to 280°. The area of the $C_{19}H_{36}O_2$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: 1.452 at 20°.

BRIEFING

Methyl Palmitate, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-19

Change to read:

Methyl Palmitate, $C_{17}H_{34}O_2$—**270.45**

■[*112-39-0*]■1S (*USP30*)
—White solid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; the column temperature is maintained at 200° and programmed to rise 10° per minute to 300°. The area of the $C_{17}H_{34}O_2$ peak is not less than 96.5% of the total peak area.

BRIEFING

Methyl Stearate, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-20

Change to read:

Methyl Stearate, $C_{19}H_{38}O_2$—**298.50**

■[*112-61-8*]■1S (*USP30*)
—Off-white, crystalline solid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; the column temperature is maintained at 200° and programmed to rise 10° per minute to 300°. The area of the $C_{19}H_{38}O_2$ peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 40° and 42°.

BRIEFING

Methyl Sulfoxide, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-1

Change to read:

Methyl Sulfoxide—

■[*67-68-5*]■1S (*USP30*)
—See *Dimethyl Sulfoxide*.

BRIEFING

Methylamine, 40 Percent in Water, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-2

Change to read:

Methylamine, 40 Percent in Water, CH_5N—**31.06**

■[*74-89-5*]■1S (*USP30*)
—Colorless liquid.

Assay—Using a syringe, transfer about 0.5 mL of a well-shaken specimen to 100 mL of water at a point below the surface of the water. Determine the weight of the specimen by weighing the syringe before and after the transfer. Mix, and titrate with 0.5 N hydrochloric acid VS, determining the endpoint potentiometrically, using a silver-silver chloride pH electrode and a calomel reference electrode. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N hydrochloric acid is equivalent to 15.53 mg of CH_5N: between 39.0% and 41.0% is found.

Refractive index ⟨831⟩: between 1.3680 and 1.3710, at 20°.

BRIEFING

***p*-Methylaminophenol Sulfate,** *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-3

Change to read:

***p*-Methylaminophenol Sulfate,** $(p\text{-}CH_3NHC_6H_4OH)_2 \cdot H_2SO_4$—**344.38**

■[*55-55-0*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Methylene Blue, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-4

Change to read:

Methylene Blue, $C_{16}H_{18}ClN_3S \cdot 3H_2O$—**373.90**

■[*61-73-4*]■1S (*USP30*)
—Dark green crystals or a crystalline powder, having a bronze-like luster. One g dissolves in about 25 mL of water and in about 65 mL of alcohol. Soluble in chloroform. Use a suitable grade with a dye content of not less than 85%.

BRIEFING

Methylene Chloride, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-5

Change to read:

Methylene Chloride (*Dichloromethane*), CH_2Cl_2—**84.93**

■[*75-09-2*]■1S (*USP30*)
—Use ACS reagent grade Dichloromethane.

BRIEFING

5,5′-Methylenedisalicylic Acid *USP 29* page 3138—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43421-7

Change to read:

5,5′-Methylenedisalicylic Acid *(3,3′-Methylene-bis[6-hydroxybenzoic Acid]),* $C_{15}H_{12}O_6$—**288.25**

■[*122-25-8*]■1S (*USP30*)
—Use a suitable grade.

In-Process Revision

BRIEFING

4-Methyl-2-pentanone, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-6

Change to read:

4-Methyl-2-pentanone *(Methyl Isobutyl Ketone),* $(CH_3)_2CHCH_2COCH_3$—**100.16**

■[*108-10-1*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

2-Methyl-2-propyl-1,3-propanediol, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-7

Change to read:

2-Methyl-2-propyl-1,3-propanediol, $C_7H_{16}O_2$—**132.20**

■[*78-26-2*]■1S (*USP30*)
—White crystals, melting at about 58°.

BRIEFING

Molybdic Acid, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-8

Change to read:

Molybdic Acid *(85 Percent Molybdic Acid)*—

■[*7782-91-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Monochloroacetic Acid, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-9

Change to read:

Monochloroacetic Acid *(Chloroacetic Acid, Chloroethanoic Acid),* $CH_2ClCOOH$—**94.50**

■[*79-11-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Morpholine, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-10

Change to read:

Morpholine *(Tetrahydro-1,4-oxazine),* C_4H_9NO—**87.12**

■[*110-91-8*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Naphthalene, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-11

Change to read:

Naphthalene, $C_{10}H_8$—**128.17**

■[*91-20-3*]■1S (*USP30*)
—Monoclinic prismatic plates, or white scales or powder. A solution in solvent hexane shows a purple fluorescence under light from a mercury-arc lamp. Insoluble in water; very soluble in ether and in fixed and volatile oils; freely soluble in benzene, in carbon disulfide, in carbon tetrachloride, in chloroform, in olive oil, and in toluene; soluble in alcohol and in methanol. Sublimes at temperatures above the melting temperature.

Melting range ⟨741⟩: between 80° and 81°.

Boiling range (Reagent test): between 217° and 219°.

BRIEFING

1,3-Naphthalenediol, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-12

Change to read:

1,3-Naphthalenediol *(Naphthoresorcinol),* $C_{10}H_6(OH)_2$—**160.17**

■[*132-86-5*]■1S *(USP30)*
—Grayish-white to tan crystals or powder. Freely soluble in methanol; sparingly soluble in water, in alcohol, and in ether.

Melting range ⟨741⟩: between 122° and 127°.

Solubility in methanol—Dissolve 500 mg in 50 mL of methanol: the solution is clear and complete.

BRIEFING

2,7-Naphthalenediol, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-13

Change to read:

2,7-Naphthalenediol *(2,7-Dihydroxynaphthalene),* $C_{10}H_8O_2$—**160.17**

■[*582-17-2*]■1S *(USP30)*
—Off-white to yellow, crystalline solid or powder. Dissolves in acetone.

Melting range ⟨741⟩: between 187° and 191°.

BRIEFING

2-Naphthalenesulfonic Acid, *USP 29* page 3139—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-14

Change to read:

2-Naphthalenesulfonic Acid, $C_{10}H_8O_3S \cdot H_2O$—**226.25**

■[*120-18-3*]■1S *(USP30)*
—Off-white to light gray crystals. Soluble in water.

Assay—Dissolve about 1 g, accurately weighed, in 100 mL of water, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 22.63 mg of $C_{10}H_8O_3S \cdot H_2O$. Not less than 98.0% is found.

Melting range ⟨741⟩: between 122° and 126°, but the range between beginning and end of melting does not exceed 2°.

BRIEFING

1-Naphthol, *USP 29* page 3140 and page 186 of *PF* 32(1) [Jan.–Feb. 2006]—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-15

Change to read:

1-Naphthol *(Alphanaphthol),* $C_{10}H_7OH$—**144.17**

■[*90-15-3*]■1S *(USP30)*
—Colorless or slightly pinkish crystals or crystalline powder. ▲▲*USP29* ~~Insoluble in water; soluble in alcohol, in benzene, and in ether.~~

~~*Melting range* ⟨741⟩: between 95° and 97°.~~

~~*Solubility*—Separate 1-g portions dissolve in alcohol and in benzene to yield solutions that are clear and colorless or nearly colorless.~~

~~*Acidity*—Shake 1 g with 50 mL of water occasionally during 15 minutes, and filter: the filtrate is neutral to litmus.~~

~~*Residue on ignition* (Reagent test): not more than 0.05%.~~

▲Use a suitable grade with a content of not less than 99%.▲*USP30*

BRIEFING

2-Naphthol, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-16

Change to read:

2-Naphthol *(Betanaphthol),* $C_{10}H_7OH$—**144.17**

■[*135-19-3*]■1S *(USP30)*
—White leaflets or crystalline powder. ▲▲*USP29* Discolors on exposure to light. Very slightly soluble in water; soluble in alcohol, in ether, in chloroform, and in solutions of alkali hydroxides.

Melting range ⟨741⟩: between 121° and 123°.

Solubility in alcohol—A solution of 1 g in 10 mL of alcohol is complete and colorless or practically so.

Residue on ignition (Reagent test): not more than 0.05%.

Acidity—Shake 1 g with 50 mL of water occasionally during 15 minutes, and filter: the filtrate is neutral to litmus.

1-Naphthol—Boil 100 mg with 10 mL of water until dissolved, cool, and filter. Add to the filtrate 0.3 mL of 1 N sodium hydroxide and 0.3 mL of 0.1 N iodine: no violet color is produced.

Insoluble in ammonia (naphthalene, etc.)—Shake 500 mg with 30 mL of ammonia TS: the 2-naphthol dissolves completely and the solution is not darker than pale yellow.

In-Process Revision

BRIEFING

***p*-Naphtholbenzein,** *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-17

Change to read:

***p*-Naphtholbenzein,** $C_{27}H_{18}O_2$—**374.43**

■[*6948-88-5*]■1S (*USP30*)
—Red-brown powder. Use a suitable grade.

BRIEFING

Naphthoresorcinol, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-18

Change to read:

Naphthoresorcinol (*1,3-Dihydroresorcinol*), $C_{10}H_8O_2$—**160.17**

■[*132-86-5*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

1-Naphthylamine Hydrochloride, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-19

Change to read:

1-Naphthylamine Hydrochloride, $C_{10}H_7NH_2 \cdot HCl$—**179.65**

■[*552-46-5*]■1S (*USP30*)
—White, crystalline powder that turns bluish upon exposure to light and air. Soluble in water, in alcohol, and in ether.

A 1 in 100 solution, made slightly acid with acetic acid, gives a violet color with 5 drops of ferric chloride TS. A 1 in 40 solution in diluted acetic acid is colorless and not more than slightly opalescent.

Residue on ignition (Reagent test)—Ignite 200 mg with a few drops of sulfuric acid: the weight of the residue is negligible.

BRIEFING

2-Naphthyl Chloroformate, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43548-20

Change to read:

2-Naphthyl Chloroformate *(Chloroformic Acid 2-Naphthyl Ester),* $ClCOOC_{10}H_7$—**206.62**

■[*7693-50-7*]■1S (*USP30*)
—Use a suitable grade.

[NOTE—A suitable grade is available from TCI America, www.tciamerica.com.]

BRIEFING

***N*-(1-Naphthyl)ethylenediamine Dihydrochloride,** *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-1

Change to read:

***N*-(1-Naphthyl)ethylenediamine Dihydrochloride,** $C_{10}H_7NH(CH_2)_2NH_2 \cdot 2HCl$—**259.17**

■[*1465-25-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Nickel, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-2

Change to read:

Nickel, Ni—**58.6934**

■[*7440-02-0*]■1S (*USP30*)
—Use a suitable grade.

BRIEFING

Nickel Sulfate, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-3

Change to read:

Nickel Sulfate, $NiSO_4 \cdot 6H_2O$—**262.85**

■[*7786-81-4*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

***β*-Nicotinamide Adenine Dinucleotide,** *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-4

Change to read:

***β*-Nicotinamide Adenine Dinucleotide,** $C_{21}H_{27}N_7O_{14}P_2$—**663.4**

■[*53-84-9*]■1S (*USP30*)
—White, very hygroscopic powder. Freely soluble in water.

Assay—Dissolve 17.9 g of anhydrous dibasic sodium phosphate in water to make 500 mL (*Solution A*). Dissolve 6.8 g of monobasic potassium phosphate in water to make 500 mL (*Solution B*). To a volume of *Solution A*, add *Solution B* until the mixture is adjusted to a pH of 7.0 (about 2 : 1 by volume of *Solutions A* and *B*) to obtain a *pH 7.0 Buffer*. Transfer about 25 mg of *β*-nicotinamide adenine dinucleotide, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 0.2 mL of this solution to a 10-mL volumetric flask, dilute with *pH 7.0 Buffer* to volume, and mix. Use this solution as the *Assay preparation*. Determine the absorbances of the *Assay preparation* and the *pH 7.0 Buffer* in 1-cm cells at a wavelength of 260 nm, using water as the reference. Calculate the quantity, in mg, of $C_{21}H_{27}N_7O_{14}P_2$ in the portion of *β*-nicotinamide adenine dinucleotide taken by the formula:

$$(0.6634/17.6)(10/0.2)(25)(A_A - A_B)$$

in which A_A and A_B are the absorbances of the *Assay preparation* and the *pH 7.0 Buffer,* respectively. Not less than 94.5% is found.

BRIEFING

Ninhydrin, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-5

Change to read:

Ninhydrin—$C_9H_4O_3 \cdot H_2O$—**178.14**

■[*485-47-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Nitric Acid, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-6

Change to read:

Nitric Acid, HNO_3—**63.01**

■[*7697-37-2*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Nitric Acid, Diluted, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-7

Change to read:

Nitric Acid, Diluted (10 percent HNO_3)—

■[*7697-37-2*]■1S (*USP30*)
—Dilute 105 mL of nitric acid with water to 1000 mL.

BRIEFING

Nitric Acid, Fuming, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-8

Change to read:

Nitric Acid, Fuming (*90 Percent Nitric Acid*), HNO_3—**63.01**

■[*7697-37-2*]■1S (*USP30*)
—Use ACS reagent grade Nitric Acid, 90 Percent.

In-Process Revision

BRIEFING

Nitrilotriacetic Acid, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-9

Change to read:

Nitrilotriacetic Acid, $N(CH_2COOH)_3$—**191.14**

■[*139-13-9*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

4′-Nitroacetophenone, *USP 29* page 3140—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-10

Change to read:

4′-Nitroacetophenone (*p′-Nitroacetophenone*), $C_8H_7NO_3$—**165.15**

■[*100-19-6*]■1S (*USP30*)
—Yellow crystals.

Assay—Inject an appropriate ether solution of the specimen (about 0.5 µL) into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: a 4-mm × 1.8-m stainless steel column containing 10% phase G1 on support S1A; the injection port and detector are maintained at 200° and 300°, respectively; the column temperature is maintained at 170° and programmed to rise 3° per minute to 220°. The area of the 4′-nitroacetophenone peak is not less than 97% of the total peak area.

Melting range ⟨741⟩: between 78° and 80°.

BRIEFING

***o*-Nitroaniline,** *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-11

Change to read:

***o*-Nitroaniline,** $NO_2C_6H_4NH_2$—**138.12**

■[*88-74-4*]■1S (*USP30*)
—Orange-yellow crystals. Slightly soluble in cold water; soluble in hot water; freely soluble in alcohol and in chloroform. It forms water-soluble salts with mineral acids.

Melting range ⟨741⟩: between 71° and 72°.

BRIEFING

***p*-Nitroaniline,** *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-12

Change to read:

***p*-Nitroaniline,** $NO_2C_6H_4NH_2$—**138.12**

■[*100-01-6*]■1S (*USP30*)
—Bright yellow, crystalline powder. Insoluble in water; soluble in alcohol and in ether.

Melting range ⟨741⟩: between 146° and 148°.

Solubility—Separate 1-g portions dissolve in 30 mL of alcohol and in 40 mL of ether, respectively, to yield solutions that are clear or practically so.

Residue on ignition (Reagent test): not more than 0.2%.

BRIEFING

Nitrobenzene, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-13

Change to read:

Nitrobenzene, $C_6H_5NO_2$—**123.11**

■[*98-95-3*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

***p*-Nitrobenzenediazonium Tetrafluoroborate,** *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-14

Change to read:

***p*-Nitrobenzenediazonium Tetrafluoroborate,** $NO_2C_6H_4N_2BF_4$ **—236.92**

■[*456-27-9*]■1S (*USP30*)
—Yellow-gold crystals. Soluble in acetonitrile. *[Caution—Shock-sensitive; keep refrigerated.]*

Assay—Transfer about 30 mg, accurately weighed, to a low-actinic, 100-mL volumetric flask. Dissolve in 0.01 N hydrochloric acid, dilute with 0.01 N hydrochloric acid to volume, and mix. Using low-actinic glassware, dilute 2.0 mL of the resulting solution with spectrophotometric grade methanol to 50.0 mL. Measure the absorbance of this solution in a 1-cm cell at about 255 nm, using methanol as the blank. Calculate the absorptivity of the solution by dividing the measured absorbance by the concentration in g per mL. Calculate the assay value by the formula:

$$100a / 59.4$$

in which a is the absorptivity of the solution: not less than 95.0% is found.

BRIEFING

4-(*p*-Nitrobenzyl)pyridine, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-15

Change to read:

4-(*p*-Nitrobenzyl)pyridine, $C_{12}H_{10}N_2O_2$**—214.22**

■[*1083-48-3*]■1S (*USP30*)
—Yellow crystals. Soluble in acetone.

Insoluble matter—Dissolve 1 g in 10 mL of acetone: the solution is clear and complete.

Melting range ⟨741⟩: between 71° and 74°.

BRIEFING

Nitromethane, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-16

Change to read:

Nitromethane, CH_3NO_2**—61.04**

■[*75-52-5*]■1S (*USP30*)
—Use ACS reagent grade.

BRIEFING

5-Nitro-1,10-phenanthroline, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-17

Change to read:

5-Nitro-1,10-phenanthroline, $C_{12}H_7N_3O_2$**—225.20**

■[*4199-88-6*]■1S (*USP30*)
—White ▲▲*USP29* powder. Soluble in water.

Melting range ⟨741⟩**:** between 198° and 200°.

Suitability as redox indicator—Dissolve 25 mg in a minimum volume of diluted sulfuric acid, add 10 mg of ferrous sulfate, and dilute with water to 100 mL: the solution is deep red in color and exhibits an absorption maximum at 510 nm. To 1.0 mL of the solution add 1.0 mL of 0.01 M ceric sulfate: the red color is discharged.

BRIEFING

1-Nitroso-2-naphthol, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-17

Change to read:

1-Nitroso-2-naphthol, $C_{10}H_7NO_2$**—173.17**

■[*131-91-9*]■1S (*USP30*)
—Brown to yellowish-brown powder. Insoluble in water; soluble in alcohol, in benzene, in ether, in carbon tetrachloride, and in acetic acid.

Assay—Transfer about 250 mg, previously dried over silica gel to constant weight and accurately weighed, to a glass-stoppered flask, and dissolve in 10 mL of sodium hydroxide solution (1 in 10). Cool the solution in an ice bath, add dilute sulfuric acid (1 in 6) until a slight, permanent precipitate is formed and the solution is slightly acid, then add 3 g of potassium iodide, shake to dissolve, add 20 mL of dilute sulfuric acid (1 in 6), immediately insert the stopper in the flask, and allow to stand in the dark for 2 hours. Titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Perform a complete blank determination, and make any necessary correction. Each mL of 0.1 N sodium thiosulfate is equivalent to 8.66 mg of $C_{10}H_7NO_2$: not less than 95.0% is found.

Melting range ⟨741⟩: between 109° and 111°.

Residue on ignition (Reagent test): not more than 0.2%.

BRIEFING

Nitroso R Salt, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-18

Change to read:

Nitroso R Salt *(1-Nitroso-2-naphthol-3,6-disodium Disulfonate),* $NOC_{10}H_4OH(SO_3Na)_2$—**377.26**

■[*525-05-3*]■1S (*USP30*)
—Yellow crystals or crystalline powder. One g dissolves in about 40 mL of water; insoluble in alcohol.

Sensitiveness—Dissolve 500 mg of sodium acetate in a solution of 0.4 mg of cobaltous chloride (0.1 mg of cobalt) in 5 mL of water. Add 1 mL of diluted acetic acid, and follow with 1 mL of a solution of the nitroso R salt (1 in 500): a red color, which is produced at once, persists when the solution is boiled with 1 mL of hydrochloric acid for 1 minute.

BRIEFING

Nitrous Oxide Certified Standard, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-19

Change to read:

Nitrous Oxide Certified Standard—

■[*10024-97-2*]■1S (*USP30*)
—A container of 99.9% nitrous oxide. It is available from most suppliers of specialty gases.

BRIEFING

Nonadecane, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43556-20

Change to read:

Nonadecane, $C_{19}H_{40}$—**268.52**

■[*629-92-5*]■1S (*USP30*)
—White solid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: 3-mm × 1.8-m stainless steel column containing 5% phase G2 on support S1AB; the injection port temperature is maintained at 330°; the detector temperature is maintained at 300°; and the oven temperature is held initially at 190° and allowed to rise gradually to 250°. The area of the nonadecane peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 31.5° and 33.5°.

BRIEFING

Nonanoic Acid, *USP 29* page 3141—See briefing under *2,4-Dinitrophenylhydrazine.*

(HDQ: M. Marques) RTS—43576-1

Change to read:

Nonanoic Acid, $C_9H_{18}O_2$—**158.24**

■[*112-05-0*]■1S (*USP30*)
—Clear, colorless to faint yellow liquid. Miscible with water and with methanol.

Assay—Accurately weigh about 500 mg, transfer to a suitable container, add 30 mL of water, and mix. Add 40 mL of water, and mix. Add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Each mL of 0.1 N sodium hydroxide is equivalent to 15.82 mg of $C_9H_{18}O_2$: not less than 96.0% of $C_9H_{18}O_2$ is found.

Refractive index ⟨831⟩: about 1.432 at 20°.

Volumetric Solutions

BRIEFING

Volumetric Solutions, *USP 29* page 3175 and page 660 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to correct the equivalent for *Sodium Hydroxide, Normal (1 N)* and to update the instructions for drying the primary standard used to standardize *Sodium Thiosulfate, Tenth-Normal (0.1 N)*.

(HDQ: M. Marques) RTS—C44418; C44427

Change to read:

Potassium Hydroxide, Normal (1 N)
KOH, **56.11**

56.11 g in 1000 mL

Dissolve 68 g of potassium hydroxide in about 950 mL of water. Add a freshly prepared saturated solution of barium hydroxide until no more precipitate forms. Shake the mixture thoroughly, and allow it to stand overnight in a stoppered bottle. Decant the clear liquid, or filter the solution in a tight, polyolefin bottle, and standardize by the procedure set forth for *Sodium Hydroxide, Normal (1 N)*.

~~$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH}}$$~~

$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL KOH}}$$ ■1S (*USP30*)

Change to read:

Sodium Hydroxide, Normal (1 N)
NaOH, **40.00**

40.00 g in 1000 mL

Dissolve 162 g of sodium hydroxide in 150 mL of carbon dioxide-free water, cool the solution to room temperature, and filter through hardened filter paper. Transfer 54.5 mL of the clear filtrate to a tight, polyolefin container, and dilute with carbon dioxide-free water to 1000 mL.

Accurately weigh about 5 g of potassium biphthalate, previously crushed lightly and dried at 120° for 2 hours, and dissolve in 75 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS, and titrate with the sodium hydroxide solution to the production of a permanent pink color. Each ~~204.2 mg~~

■204.23 mg■1S (*USP30*)
of potassium biphthalate is equivalent to 1 mL of 1 N sodium hydroxide.

$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH solution}}$$

NOTES—(1) Solutions of alkali hydroxides absorb carbon dioxide when exposed to air. They should be preserved in bottles having well-fitted, suitable stoppers, provided with a tube filled with a mixture of sodium hydroxide and lime (soda-lime tubes) so that air entering the container must pass through this tube, which will absorb the carbon dioxide. (2) Prepare solutions of lower concentration (e.g., 0.1 N, 0.01 N) by quantitatively diluting accurately measured volumes of the 1 N solution with sufficient carbon dioxide-free water to yield the desired concentration.

Restandardize the solution frequently.

Change to read:

Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)
NaOH, **40.00**

To 250 mL of alcohol add 2 mL of a 50% ~~(w/w)~~

■(w/v)■2S (*USP29*)
solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced.

$$N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL sodium hydroxide}}$$

Change to read:

Sodium Thiosulfate, Tenth-Normal (0.1 N)
$Na_2S_2O_3 \cdot 5H_2O$, **248.19**

24.82 g in 1000 mL

Dissolve about 26 g of sodium thiosulfate and 200 mg of sodium carbonate in 1000 mL of recently boiled and cooled water. Standardize the solution as follows.

Accurately weigh about 210 mg of primary standard potassium dichromate, previously pulverized and dried ~~at 120° for 4 hours,~~

■according to the instructions on its label, if necessary, ■1S (*USP30*)
and dissolve in 100 mL of water in a glass-stoppered, 500-mL flask. Swirl to dissolve the solid, remove the stopper, and quickly add 3 g of potassium iodide, 2 g of sodium bicarbonate, and 5 mL of hydrochloric acid. Insert the stopper gently in the flask, swirl to mix, and allow to stand in the dark for exactly 10 minutes. Rinse the stopper and the inner walls of the flask with water, and titrate the liberated iodine with the sodium thiosulfate solution until the solution is yellowish green in color. Add 3 mL of starch TS, and continue the titration until the blue color is discharged. Perform a blank determination.

Restandardize the solution as frequently as supported by laboratory stability data. In the absence of such data, restandardize the solution weekly.

$$N = \frac{\text{mg } K_2Cr_2O_7}{49.04 \times \text{mL } Na_2S_2O_3}$$

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 29* page 3184, page 3625 of the *First Supplement,* and page 661 of *PF* 32(2) [Mar.–Apr. 2006].

(HDQ) RTS—C42828; C42839; C43516; C44099

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Add the following:	
▲Benazepril Hydrochloride Tablets	W ▲*USP30*
Add the following:	
■Citalopram Tablets	W ■2S (*USP29*)
Add the following:	
■Black Cohosh Tablets	T, LR ■2S (*USP29*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W ■2S (*USP29*)
Add the following:	
■Diclofenac Potassium Tablets	T, LR ■2S (*USP29*)
Add the following:	
■Didanosine Tablets	T ■2S (*USP29*)
Add the following:	
▲Estradiol Vaginal Tablets	T ▲*USP30*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W ■2S (*USP29*)
Add the following:	
■Fexofenadine Hydrochloride Tablets	W ■2S (*USP29*)
Add the following:	
■Fosinopril Sodium Tablets	T ■2S (*USP29*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T ■2S (*USP29*)
Add the following:	
■Ginkgo Capsules	T, LR ■2S (*USP29*)
Add the following:	
■Ginkgo Tablets	T, LR ■2S (*USP29*)
Change to read:	
Asian Ginseng Capsules	~~T, LR~~ ■LR ■2S (*USP29*)
Add the following:	
▲Glipizide and Metformin Hydrochloride Tablets	W ▲*USP30*
Add the following:	
■Irbesartan Tablets	W ■2S (*USP29*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W ■2S (*USP29*)
Add the following:	
■Isosorbide Mononitrate Tablets	T ■2S (*USP29*)
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T ■2S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Ketoprofen Capsules, Extended-Release	T■2S (*USP29*)
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■2S (*USP29*)
Add the following:	
■Methylsulfonylmethane Tablets	T, LR■1S (*USP30*)
Add the following:	
■Modafinil Tablets	T■2S (*USP29*)
Add the following:	
■Nefazodone Hydrochloride Tablets	T■2S (*USP29*)
Add the following:	
■Nevirapine Tablets	W■1S (*USP30*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■2S (*USP29*)
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	T, LR■2S (*USP29*)
Add the following:	
■Pravastatin Sodium Tablets	T■1S (*USP30*)
Add the following:	
■Quinapril Tablets	W■2S (*USP29*)
Add the following:	
■Tizanidine Tablets	T■2S (*USP29*)
Add the following:	
■Valerian Capsules	T, LR■2S (*USP29*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Valganciclovir Tablets	T■1S (*USP30*)
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	~~W~~ T■2S (*USP29*)

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 29* page 3191, page 3625 of the *First Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 812 of *PF* 29(3) [May–June 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 2183 of *PF* 30(6) [Nov.–Dec. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], page 1193 of *PF* 31(4) [July–Aug. 2005], page 1491 of *PF* 31(5) [Sept.–Oct. 2005], page 1703 of *PF* 31(6) [Nov.–Dec. 2005], page 188 of *PF* 32(1) [Jan.–Feb. 2006], and page 662 of *PF* 32(2) [Mar.–Apr. 2006].

(HDQ) RTS—C43054; C44099; C44144

Add the following:

■**Amlodipine Besylate:** A white or almost white powder. Freely soluble in methanol; sparingly soluble in alcohol; slightly soluble in 2-propanol and in water.■1S (*USP30*)

Add the following:

■**Methylsulfonylmethane:** White powder or flake crystal. Melts at about 109°. Freely soluble in water, in methanol, in alcohol, and in acetone. Sparingly soluble in ether.■1S (*USP30*)

Change to read:

Milrinone: White to tan, crystalline solid. Is hygroscopic. Freely soluble in dimethyl sulfoxide; ~~practically insoluble in water, in chloroform, and in methanol.~~

■very slightly soluble in methanol; practically insoluble in water and in chloroform.■1S (*USP30*)

In-Process Revision

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 32(1) through 32(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF.*

	***PF* Volume, Issue, and Page Numbers of Pending Proposals**		
Title and Proposal	***Vol.***	***No.***	***Page(s)***
General Notices—*Tests and Assays—Foreign Substances and Impurities; Preservation, Packaging, Storage, and Labeling—Storage Temperature and Humidity; Repackaging Instructions; Guidelines for Packaging and Storage Statements in USP–NF Monographs* (*Controlled Cold Temperature*-added)	31	3	718
<u>*USP Monographs*</u>			
Acetaminophen—*Packaging and storage*	31	4	1024
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetazolamide Oral Solution (new)	32	1	43
Acetazolamide Oral Suspension (new)	32	1	44
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Medical Air—*Definition, Packaging and storage*	31	4	1024
Albendazole Oral Suspension—*Labeling*	32	1	46
Alprazolam Oral Suspension (new)	32	1	46
Albumin Human—*Definition, Packaging and storage, Expiration date, Labeling, USP Reference standards* (add), *Identification A, B* (add), *Bacterial endotoxins* (add), *Safety* (add), *Sterility* (add), *pH* (add), *Molecular size distribution* (add), *Heat stability* (add), *Incubation* (add) *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add)	31	5	1338
Albuterol Tablets—*Assay*	31	3	726
Alendronate Sodium—*Packaging and storage*	31	5	1344
Allopurinol—*Definition, Packaging and storage, USP Reference standards, Chromatographic purity (delete), Related compounds,* (add), *Assay*	32	2	302
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Amantadine Hydrochloride—*Chromatographic purity*	31	5	1344
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—*Dissolution*	31	4	1025
Amitriptyline Hydrochloride—*USP Reference standards, Identification, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	31	6	1606

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Amoxicillin Capsules—*Labeling* (add), *Dissolution*	32	1	47
Amoxicillin Tablets—*Dissolution*	32	2	305
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water* (delete)	31	4	1026
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Aspartic Acid—*Chloride*	31	5	1345
Aspirin Boluses—*Dissolution*	31	4	1026
Atenolol—*Assay*	31	5	1345
Atracurium Besylate—*Chromatographic purity, Assay*	32	2	305
Azathioprine Oral Suspension (new)	32	1	48
Azithromycin—*Labeling, USP Reference standards, Limit of related substances*	32	2	306
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Oral Solution (new)	32	1	49
Baclofen Oral Suspension (new)	32	1	51
Benazepril Hydrochloride (new)	31	4	1027
Benazepril Hydrochloride Tablets (new)	32	1	52
Benzonatate Capsules—*Dissolution* (add)	32	1	55
Betamethasone Oral Solution—*Thin-layer chromatographic identification test*	31	4	1032
Bethanechol Chloride Oral Solution (new)	32	1	55
Bethanechol Chloride Oral Suspension (new)	32	1	57
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	31	3	741
Bisoctrizole (new)	32	2	309
Bromocriptine Mesylate—*Chromatographic purity*	31	5	1346
Bromocriptine Mesylate Capsules—*Dissolution*	32	1	58
Budesonide (new)	30	6	1978
Bupropion Hydrochloride Extended-Release Tablets—*Drug release, Dissolution*	32	2	312
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butorphanol Tartrate Nasal Solution (new)	31	5	1346
Calcitonin Salmon (new)	31	4	1036
Calcitonin Salmon Nasal Solution (new)	30	4	1178
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	32	1	58
Calcitriol Injection (new)	32	1	61
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate—*USP Reference standards* (add), *Identification*	31	6	1608
Calcium Lactate Tablets—*Identification*	31	6	1609
Calcium Pantothenate—*USP Reference standards, Ordinary impurities*	32	1	62
Camphor—*Water*	31	3	742
Captopril Oral Solution (new)	32	1	63
Captopril Oral Suspension (new)	32	1	64
Carbamazepine—*USP Reference standards, Chromatographic purity (Related compounds), Assay*	32	1	65
Carbamazepine Tablets—*Dissolution*	31	4	1044
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium—*Heavy metals*	31	5	1349
Carboxymethylcellulose Sodium Paste—*Heavy metals*	31	5	1349
Cefaclor Tablets (new)	32	2	314
Cefadroxil for Oral Suspension—*Dissolution* (add), *Water*	32	2	315
Cefepime Hydrochloride—*Limit of N-methylpyrrolidine, Related compounds*	32	2	316

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Cefonicid for Injection—*Assay*	32	1	67
Ceftazidime—*USP Reference standards, Assay*	32	1	67
Ceftazidime Injection—*USP Reference standards*	32	1	68
Ceftazidime for Injection—*USP Reference standards*	32	1	68
Cetirizine Hydrochloride (new)	32	2	317
Chlorthalidone—*USP Reference standards, Limit of 4'-chloro-3'-sulfamoyl-2-benzophenone carboxylic acid (CCA) (Limit of chlorthalidone related compound A), Assay*	32	1	68
Cholestyramine Resin—*Dialyzable quaternary amines*	32	2	320
Cilostazol (new)	32	1	69
Cimetidine Tablets—*Dissolution*	32	1	72
Ciprofloxacin—*Chromatographic purity, Assay*	32	2	320
Ciprofloxacin and Dexamethasone Otic Suspension (new)	32	2	321
Ciprofloxacin Hydrochloride—*Chromatographic purity, Assay*	32	2	325
Ciprofloxacin Injection—*Limit of ciprofloxacin ethylenediamine analog, Assay*	32	2	326
Citalopram Hydrobromide (new)	31	3	742
Citalopram Tablets (new)	31	4	1046
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid (delayed implementation to January 1, 2009)*	31	2	394
Cladribine (new)	31	2	395
Cladribine—*Specific rotation, Related compounds, Limit of residual solvents*	31	6	1609
Clindamycin Hydrochloride Oral Solution—*pH*	31	5	1350
Clonazepam Oral Suspension (new)	32	1	73
Clopidogrel Bisulfate—*Related compounds, Assay*	32	1	74
Clopidogrel Tablets—*Related compounds, Assay*	32	1	76
Clotrimazole Lozenges—*Dissolution*	32	1	78
Cloxacillin Benzathine—*Assay*	31	4	1050
Cloxacillin Benzathine Intramammary Infusion—*Assay*	31	4	1051
Cyanocobalamin—*Pseudo cyanocobalamin*	31	5	1350
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dantrolene Sodium (new)	32	2	327
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Diazepam Extended-Release Capsules—*USP Reference standards, Assay*	32	2	330
Diclofenac Potassium (new)	31	5	1350
Diclofenac Potassium Tablets (new)	31	5	1352
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Didanosine (new)	31	5	1355
Didanosine for Oral Solution (new)	31	5	1357
Didanosine Tablets (new)	31	5	1359
Digoxin Oral Solution—*Assay*	31	5	1361
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diltiazem Hydrochloride Oral Solution (new)	32	1	79
Diltiazem Hydrochloride Oral Suspension (new)	32	1	80
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1612

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

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Diphenoxylate Hydrochloride and Atropine Sulfate Tablets—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1614
Diphtheria Toxin for Schick Test (delete)	31	6	1616
Dipyridamole Oral Suspension (new)	32	1	81
Divalproex Sodium (new)	31	5	1362
Docusate Calcium—*Limit of bis(2-ethylhexyl)maleate*	31	3	752
Docusate Potassium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Docusate Sodium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Dolasetron Mesylate Oral Solution (new)	32	1	83
Dolasetron Mesylate Oral Suspension (new)	32	1	84
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Doxepin Hydrochloride—*USP Reference standards, Identification, Melting range* (delete), *Chloride content* (delete), *Related compounds* (add)	32	2	330
Dronabinol—*USP Reference standards, Identification, Limit of* Δ^8*-tetrahydrocannabinol* (delete), *Related compounds* (add), *Assay*	32	1	86
Drospirenone (new)	31	3	754
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Ensulizole—*USP Reference standards, Assay*	31	6	1617
Estradiol and Norethindrone Acetate Tablets (new)	31	5	1364
Estradiol Transdermal System (new)	31	4	1063
Estradiol Vaginal Tablets (new)	31	6	1617
Conjugated Estrogens—*Definition*	30	3	840
Synthetic Conjugated Estrogens (new)	31	6	1620
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add), *Related compounds*	31	4	1067
Ethotoin Tablets—*USP Reference standards, Assay*	32	2	332
Ethyl Chloride—*Alcohol* (delete)	31	5	1368
Etidronate Disodium—*Limit of phosphite*	31	6	1625
Famotidine Injection (new)	32	2	333
Felodipine Extended-Release Tablets—*Labeling* (add), *Dissolution*	32	1	89
Fenofibrate (new)	31	3	763
Fentanyl (new)	31	6	1626
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Fluconazole—*Melting range* (delete), *Related compounds*	32	2	335
Flucytozine Oral Suspension (new)	32	1	92
Flumazenil—*USP Reference standards, Related compounds, Assay*	32	1	94
Fluorometholone Acetate (new)	31	5	1371
Fluoxetine Delayed-Release Capsules—*Chromatographic purity*	32	2	337
Flurazepam Hydrochloride—*Identification*	31	3	766
Flurbiprofen—*Identification*	31	4	1069
Fluticasone Propionate—*Chemical information, Definition, Bromofluoromethane content* (delete), *Content of acetone, Assay*	32	2	337
Fluticasone Propionate Nasal Spray (new)	32	2	339
Fluvastatin Sodium—*Packaging and storage, USP Reference standards, Identification, Loss on drying* (add), *Water* (delete), *Chromatographic purity*	32	1	103
Fluvastatin Capsules—*USP Reference standards, Identification, Chromatographic purity*	32	1	105
Fluvoxamine Maleate—*Maleic acid* (delete), *Assay*	32	2	344
Fluvoxamine Maleate Tablets (new)	30	5	1622
Formoterol Fumarate (new)	32	1	106
Fosinopril Sodium (new)	32	1	110
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Ganciclovir Oral Suspension (new)	32	1	113

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

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Gemcitabine for Injection—*USP Reference standards, Chromatographic purity*	31	6	1630
Gemcitabine Hydrochloride—*USP Reference standards*	32	1	114
Glipizide and Metformin Hydrochloride Tablets (new)	31	6	1631
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Dissolution*	29	2	418
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Glycopyrrolate Tablets—*Identification*	31	4	1077
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	31	6	1637
Helium—*Definition, Packaging and storage*	31	4	1077
Hepatitis B Virus Vaccine Inactivated (delete)	31	6	1641
Hydrocodone Bitartrate—*USP Reference standards* *Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hydroxyzine Hydrochloride—*USP Reference standards, Chromatographic purity*	32	1	114
Hyoscyamine Sulfate—*USP Reference standards, Identification, Melting temperature* (delete), *Loss on drying* (delete), *Water* (add), *Residue on ignition, Other alkaloids* (delete), *Readily carbonizable substances* (delete), *Chromatographic purity* (add), *Assay*	31	4	1078
Hyoscyamine Sulfate Elixir—*Identification*	31	5	1372
Hyoscyamine Sulfate Injection—*Identification*	31	5	1373
Hyoscyamine Sulfate Oral Solution—*Identification*	31	5	1373
Hyoscyamine Sulfate Tablets—*Identification*	31	5	1374
Hypromellose Ophthalmic Solution—*Identification*	31	3	771
Ibuprofen—*Assay*	31	5	1374
Indinavir Sulfate—*Heavy metals, Method I,* (delete), *Heavy metals* (add), *Chromatographic purity, Assay*	32	2	345
Insulin—*USP Reference standards*	31	5	1375
Insulin Human—*USP Reference standards*	31	5	1375
Sodium Iodide I 123 Capsules—*Definition*	31	6	1642
Sodium Iodide I 123 Solution—*Definition, Radionuclidic purity, Bacterial endotoxins, pH*	31	6	1642
Sodium Iodide I 131 Solution—*pH*	31	6	1643
Iodoform—*Molecular weight*	32	1	115
Irbesartan—*Limit of azide*	32	1	115
Irbesartan Tablets (new)	31	4	1080
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isopropyl Alcohol—*USP Reference standards* (add), *Identification*	31	5	1375
Isosorbide Dinitrate Tablets—*Dissolution, Assay*	31	5	1375
Isosorbide Dinitrate Chewable Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Extended-Release Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Sublingual Tablets—*Assay*	31	5	1377
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082
Ivermectin—*Specific rotation, Limit of alcohol and formamide*	31	6	1645
Ketoprofen—*Assay*	31	3	772
Ketoprofen Extended-Release Capsules (new)	31	5	1378
Labetalol Hydrochloride Oral Solution (new)	32	1	116
Labetalol Hydrochloride Oral Suspension (new)	32	1	117
Lamivudine—*Assay*	32	2	346
Leflunomide (new)	31	5	1380
Leflunomide Tablets (new)	31	5	1383
Leuprolide Acetate (new)	30	3	882
Levocabastine Hydrochloride (new)	31	6	1647
Levofloxacin (new)	32	2	347
Lidocaine and Prilocaine Cream (new)	31	4	1087
Lindane—*Definition, Assay*	31	6	1648
Lipid Injectable Emulsion (new)	32	2	350
Lisinopril Tablets—*Dissolution*	31	4	1090
Loperamide Hydrochloride Oral Solution—*Assay*	32	2	353
Lovastatin—*Assay*	32	1	118
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Milk of Magnesia—*Limit of calcium* (delete)	32	2	353
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	419
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	31	5	1386
Magnesium Chloride—*Identification*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	421
Magnesium Oxide—*Labeling, Bulk density* (add)	31	4	1091
Mangafodipir Trisodium—*Limit of residual solvents*	31	6	1650
Mannitol Injection—*Labeling*	32	2	263
Mebendazole Oral Suspension—*Labeling*	32	1	119
Megestrol Acetate Oral Suspension—*Dissolution*	31	5	1387
Meloxicam (new)	31	1	57
Metformin Hydrochloride—*Related compounds*	31	4	1092
Metformin Hydrochloride Tablets—*Identification, Related compounds*	31	4	1093
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
Methoxyflurane—*Foreign odor* (delete)	31	5	1388
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Methyldopa Oral Suspension—*USP Reference standards, Limit of methyldopa-glucose reaction product* (delete)	32	2	354
Methylprednisolone—*Chromatographic purity*	32	2	354
Metolazone Oral Suspension (new)	32	1	119
Metoprolol Tartrate Oral Solution (new)	32	1	121
Metoprolol Tartrate Oral Suspension (new)	32	1	122
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Miconazole Nitrate Cream—*Identification*	32	1	123
Miconazole Nitrate Vaginal Suppositories—*Assay*	31	5	1389
Mirtazapine—*Heavy metals*	31	6	1650
Mitoxantrone Injection—*Packaging and storage*	32	2	355
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Morantel Tartrate—*pH*	32	2	355
Morphine Sulfate Extended-Release Capsules—*Packaging and storage* (add)	32	1	124
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage* (add)	32	1	124
Narasin Granular—*Molecular weight, Assay*	32	1	124
Narasin Premix—*Assay*	32	1	126
Nefazodone Hydrochloride (new)	31	4	1094
Nefazodone Hydrochloride Tablets (new)	31	4	1096
Nifedipine Extended-Release Tablets—*Drug release, Dissolution*	32	2	355
Nimodipine—*Identification, Related compounds*	32	2	360
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate—*USP Reference standards, Limit of residual solvents, Chromatographic purity, Assay*	31	5	1390
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole—*Chromatographic purity*	31	4	1100
Omeprazole Delayed-Release Capsules—*Identification, Chromatographic purity*	31	5	1392
Ondansetron Hydrochloride—*Limit of ondansetron related compound D, Assay*	32	1	126
Ondansetron Hydrochloride Oral Suspension (new)	32	1	127

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Ondansetron Injection—*Chromatographic purity*	31	6	1651
Ondansetron Oral Solution—*Packaging and storage* (add), *Limit of ondansetron related compound D, Related compounds*	32	1	128
Ondansetron Orally Disintegrating Tablets (new)	31	4	1101
Orphenadrine Citrate Injection—*Assay*	31	6	1651
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete), *Related compounds* (add), *Assay*	31	1	64
Oxaprozin—*Packaging and storage* (add)	32	1	130
Oxaprozin Tablets—*Packaging and storage* (add)	32	1	130
Oxybutynin Chloride Extended-Release Tablets (new)	31	6	1652
Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxygen—*Definition, Packaging and storage*	31	4	1107
Oxygen 93 Percent—*Definition, Packaging and storage*	31	4	1107
Paclitaxel—*USP Reference standards, Related compounds*	32	2	361
Pamidronate Disodium (new)	31	4	1108
Pamidronate Disodium for Injection (new)	31	4	1111
Pancuronium Bromide (new)	32	1	130
Paricalcitol—*Identification, Chromatographic purity, Assay*	32	1	132
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital Sodium—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Pentobarbital Sodium Injection—*Identification, Assay*	32	2	364
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piroxicam Cream (new)	32	1	134
PEG 3350 and Electrolytes for Oral Solution—*Title* (name change—*delayed implementation to February 1, 2009*), *Definition, Assay for potassium and sodium*	31	5	1393
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay (delayed implementation to January 1, 2009)*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Perchlorate—*USP Reference standards* (delete), *Assay*	32	2	364
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Pravastatin Sodium (new)	31	5	1394
Prednicarbate (new)	31	5	1398
Prednicarbate Cream (new)	31	6	1655
Prednicarbate Ointment (new)	31	6	1657
Prednisolone Sodium Phosphate—*USP Reference standards, Identification*	32	2	365
Promethazine Hydrochloride—*USP Reference standards, Related substances*	32	2	365
Promethazine Hydrochloride Tablets—*USP Reference standards, Related compounds, Assay*	32	2	367
Pseudoephedrine Sulfate—*Ordinary impurities*	32	1	135
Pyridoxine Hydrochloride Injection—*Assay*	32	2	369
Quazepam Tablets—*USP Reference standards, Assay*	32	2	370
Quinapril Tablets—*Packaging and storage*	29	4	1071
Quinidine Sulfate Oral Suspension (new)	32	1	136
Ramipril—*Definition, Assay*	31	3	787
Ranitidine Hydrochloride—*USP Reference standards, Chromatographic purity, Assay*	30	6	2033

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Oral Rehydration Salts—*USP Reference standards* (add), *Identification F* (delete), *Assay for citrate (delayed implementation to January 1, 2009)*	31	5	1399
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Risperidone (new)	31	6	1659
Ritonavir (new)	32	2	370
Ropivacaine Hydrochloride Injection (new)	32	2	374
Rubella and Mumps Virus Vaccine Live (delete)	31	6	1662
Saccharin Calcium (new)—*Harmonization*	31	2	607
Saccharin Sodium (new)—*Harmonization*	31	4	1225
Saquinavir Mesylate—*Identification*	31	5	1400
Schick Test Control (delete)	31	6	1662
Senna—*Title, Definition, Packaging and storage, Labeling* (add), *USP Reference standards* (add), *Botanic characteristics, Identification, Microbial enumeration* (add) *Loss on drying* (add), *Total ash* (add), *Assay* (add)	32	1	137
Senna Pods (new)	32	1	140
Sennosides—*Definition, Packaging and storage, Residue on ignition*	32	1	141
Sevoflurane (new)	30	1	178
Simvastatin—*Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	32	1	141
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	31	3	795
Sodium Bicarbonate Injection—*Packaging and storage*	31	5	1401
Sodium Chloride—*Limit of phosphates*	31	5	1401
Sodium Chloride—*Identification, Loss on drying, Limit of potassium (postponed indefinitely)*	32	2	264
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate (delayed implementation to April 1, 2009)*	31	3	797
Sodium Lactate Injection—*Identification B* (delete)	31	5	1402
Sodium Phosphates Rectal Solution—*Assay*	31	5	1403
Sodium Salicylate Tablets—*USP Reference standards* (add)	31	4	1116
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Spironolactone and Hydrochlorothiazide Tablets—*Dissolution*	32	2	376
Stavudine Capsules—*Assay*	31	5	1403
Succinylcholine Chloride—*Limit of ammonium salts* (delete), *Chromatographic purity*	31	5	1404
Sulfamethazine Granulated—*Assay*	31	3	797
Sumatriptan Succinate Oral Suspension (new)	32	1	144
Talc—*Packaging and storage* (add), *Limit of iron, Limit of calcium, Limit of aluminum*	31	6	1662
Tazobactam (new)	31	4	1116
Technetium Tc 99m Fanolesomab Injection (new)—*Packaging and storage* (add)	31	5	1405
Temazepam—*Identification*	32	1	145
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Thalidomide—*Microbial limits, Chromatographic purity*	32	1	146
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thimerosal—*Identification*	32	1	147
Thioridazine Hydrochloride—*Identification*	31	3	798
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Titanium Dioxide—*Definition, Packaging and storage, Labeling, Loss on ignition, Water-soluble substances, Acid-soluble substances, Limit of lead* (add), *Limit of antimony* (add), *Limit of mercury* (add), *Organic volatile impurities* (delete), *Assay*	30	4	1301
Tizanidine Tablets (new)	32	1	147
Tolazamide—*Chromatographic purity*	31	4	1118
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Travoprost (new)	31	4	1119
Travoprost Ophthalmic Solution (new)	31	4	1121
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800

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Tricitrates Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	465
Triclosan—*Assay*	32	2	377
Trimethoprim—*Packaging and storage*	31	5	1409
Tryptophan—*Chloride, Sulfate*	31	5	1410
Tylosin Tartrate (new)	31	5	1410
Ursodiol Capsules—*Dissolution*	31	3	800
Valganciclovir Hydrochloride (new)	32	2	379
Valganciclovir Tablets (new)	32	2	384
Valsartan (new)	32	1	150
Valsartan and Hydrochlorothiazide Tablets (new)	31	4	1123
Valproic Acid Injection (new)—*Title (delayed implementation to October 1, 2008)*	32	2	387
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add)	30	6	2055
Vasopressin—*Identification*	31	4	1127
Verapamil Hydrochloride—*USP Reference standards Identification, Chromatographic purity*	32	2	389
Verapamil Hydrochloride Injection—*USP Reference standards, Related compounds*	32	1	154
Verapamil Hydrochloride Oral Solution (new)	32	1	155
Verapamil Hydrochloride Oral Suspension (new)	32	1	156
Verapamil Hydrochloride Tablets—*USP Reference standards, Related compounds*	32	1	158
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins*	31	2	468
Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Sterile Purified Water—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
Zidovudine Tablets—*USP Reference standards, Related compounds, Assay*	32	1	158
<u>*Dietary Supplements Monographs*</u>			
Ademetionine Disulfate Tosylate (new)	31	2	469
Acesulfame Potassium—*Packaging and storage* (add), *Limit of fluoride*	31	3	811
Black Cohosh (new)	28	5	1455
Powdered Black Cohosh (new)	28	5	1460
Powdered Black Cohosh Extract (new)	28	5	1461
Black Cohosh Tablets (new)	28	5	1462
Ethylcellulose Aqueous Dispersion—*Identification*	31	3	811
Ethylparaben—*Identification*	31	3	812
Gamma Cyclodextrin (new)	31	3	812
Ginger—*Packaging and storage, Labeling, USP Reference standards, Identification, Microbial enumeration, Alcohol-soluble extractives, Limit of shogaols, Content of gingerols and gingerdiones*	32	1	160
Powdered Ginger—*Packaging and storage, USP Reference standards*	32	1	162
Ginger Capsules—*USP Reference standards, Content of gingerols, gingerdiones, and shogaols*	32	1	163
Ginger Tincture—*USP Reference standards, Thin-layer chromatographic identification test, Microbial enumeration, Content of gingerols*	32	1	163
Ginkgo—*Definition, Packaging and storage, USP Reference standards, Thin-layer chromatographic identification test, Microbial enumeration, Content of terpene lactones*	32	1	164
Powdered Ginkgo Extract (new)	32	1	166

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Ginkgo Capsules (new)	32	1	172
Ginkgo Tablets (new)	32	1	174
Lutein—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1133
Lutein Preparation—*Definition, Packaging and storage, Identification, Zeaxanthin and other related compounds, Content of lutein, Content of total carotenoids*	31	4	1134
Tomato Extract Containing Lycopene—*Microbial enumeration, Limit of aflatoxins*	30	2	578
Maleic Acid—*Identification*	31	3	815
Maltose—*Water*	31	3	815
Fish Oil Containing Omega-3 Acids (new)	31	2	474
Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481
Olive Oil—*Definition, Labeling* (add), *Teaseed oil*	31	3	815
Phenoxyethanol—*Chromatographic purity, Assay*	31	3	816
Polyethylene Glycol (new)—*Harmonization*	31	3	897
Polyoxyl 10 Oleyl Ether—*Free ethylene oxide*	31	3	816
Polyoxyl 20 Oleyl Cetostearyl Ether—*Free ethylene oxide*	31	3	817
Pygeum Extract—*Packaging and storage*	30	3	956
Sodium Benzoate—*USP Reference standards* (add), *Identification*	31	3	818
Sucrose (new)—*Harmonization*	31	3	902
Sugar Spheres—*Identification, Specific rotation*	31	3	819
Tagatose (new)	31	3	819
Thymol—*USP Reference standards* (add), *Identification*	31	3	821
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Valerian—*Packaging and storage, Extractable matter, Microbial enumeration*	32	2	394
Powdered Valerian—*Packaging and storage, Labeling, Botanic characteristics*	32	2	395
Valerian Tablets—*Packaging and storage, USP Reference standards*	32	2	395
Xanthan Gum—*Assay*	31	3	821
USP General Test Chapters			
⟨1⟩ Injections—*Labels and Labeling, Packaging*	32	2	402
⟨1⟩ Injections—*Packaging—Printing on Ferrules and Cap Overseals (delayed implementation to February 1, 2009)*	32	2	406
⟨1⟩ Injections *(Harmonization)—Packaging*	31	1	192
⟨11⟩ USP Reference Standards—	26	4	1101
	27	1	1832
	27	6	3348
	28	2	433
	28	3	839
	28	5	1468
	29	3	710
	29	5	1601
	29	6	2022
	30	2	613
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
	31	3	822
	31	4	1154
	31	5	1433
	31	6	1680
	32	1	181
	32	2	407
⟨41⟩ Weights and Balances—*Introduction*	32	2	514
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨61⟩ Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests *(Harmonization)—Title, Introduction, General Procedures, Enumeration Methods, Growth Promotion Test and Suitability of the Counting Method, Testing of Products*	29	5	1714

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⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) *(Harmonization)—Title, Introduction, General Procedures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
⟨121⟩ Insulin Assays—*Appendix* (add)	30	5	1675
⟨231⟩ Heavy Metals—*Method II*	32	1	182
⟨267⟩ Porosimetry by Mercury Intrusion (new)—*Harmonization*	31	3	905
⟨281⟩ Residue on Ignition—*Harmonization*	31	5	1526
⟨311⟩ Alginates Assay—*System Suitability*	32	2	516
⟨345⟩ Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514
⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures (delayed implementation to January 1, 2006)*	30	1	220
⟨401⟩ Fats and Fixed Oils—*Acid Value (Free Fatty Acids)*	31	4	1157
⟨429⟩ Light Diffraction Measure of Particle Size (new)—*Harmonization*	31	4	1234
⟨616⟩ Bulk Density and Tapped Density—*Harmonization*	31	3	909
⟨621⟩ Chromatography—*Chromatographic Reagents*	31	6	1681
⟨621⟩ Chromatography—*System Suitability (postponed indefinitely)*	32	2	265
⟨644⟩ Conductivity (new)	31	3	841
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨699⟩ Density of Solids (new)—*Harmonization*	31	3	912
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	31	5	1448
⟨730⟩ Inductively-Coupled Plasma—*References* (add)	30	3	1022
⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	31	3	845
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *(Harmonization)*	31	1	228
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
⟨941⟩ X-Ray Diffraction (new)—*Harmonization*	31	4	1241
General Information Chapters			
⟨1047⟩ Biotechnology-Derived Articles—Tests (delete)	32	2	516
⟨1052⟩ Biotechnology-Derived Articles—Amino Acid Analysis (new)	32	2	542
⟨1053⟩ Biotechnology-Derived Articles—Capillary Electrophoresis (new)	32	2	559
⟨1054⟩ Biotechnology-Derived Articles—Isoelectric Focusing (new)	32	2	568
⟨1055⟩ Biotechnology-Derived Articles—Peptide Mapping (new)	32	2	571
⟨1056⟩ Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis (new)	32	2	580
⟨1057⟩ Biotechnology-Derived Articles—Total Protein Assay (new)	32	2	589
⟨1058⟩ Analytical Instrument Qualification (new)	32	2	595
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	32	2	605
⟨1072⟩ Disinfectants and Antiseptics (new)	30	6	2108
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients—*Background* (delete), *General Guidance* (delete), *Excipient Quality Systems* (delete), *Appendix 1* (delete), *Appendix* (delete), *Background* (add), *General Guidance* (add), *Quality Management System—Excipient Quality Systems* (add), *Management Responsibility* (add), *Resource Management* (add), *Product Realization* (add), *Measurement, Analysis, and Improvement* (add), *Appendix 1* (add), *Appendix 2* (add)	28	5	1504
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	31	4	1167
⟨1082⟩ Genotoxicity Testing (new)	30	1	264

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⟨1092⟩ The Dissolution Procedure: Development and Validation (new)	31	5	1463
⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products—*Introduction (Tables 1 and 2)*	29	5	1733
⟨1112⟩ Application of Water Activity Determination to Nonsterile Pharmaceutical Products (new)	30	5	1709
⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add),*Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding—*Basic Pharmaceutical Calculations*	31	3	847
⟨1184⟩ Sensitization Testing (new)	30	1	289
⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)	31	4	1180
⟨1208⟩ Sterility Testing—Validation of Isolator Systems—*Introduction, Isolator Design and Construction, Validation of the Isolator System, Package Integrity Verification, Maintenance of Asepsis Within the Isolator Environment, Interpretation of Sterility Test Results, Training and Safety*	30	6	2162
⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1217⟩ Tablet Breaking Force (new)	31	6	1695
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1223⟩ Validation of Alternative Microbiological Methods (new)	31	5	1475
⟨1225⟩ Validation of Compendial Methods—*Title, Introduction, Submissions to the Compendia, Validation*	31	2	549
⟨1226⟩ Verification of Compendial Procedures (new)	31	2	555
⟨1230⟩ Water for Health Applications—*Microbial Considerations*	31	5	1486
⟨1232⟩ Instrumentation for Analysis of High Purity Pharmaceutical Waters (new)	30	5	1806
⟨2030⟩ Supplemental Information for Articles of Botanical Origin (new)	31	2	555
⟨2040⟩ Disintegration and Dissolution of Dietary *Supplements—Disintegration, Rupture Test for Soft Gelatin Capsules* (add)	32	1	184

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Polacrilin Potassium—*CAS number, Chemical name*	31	6	1671
Polyethylene Glycol—*Harmonization*	31	3	897
Polyethylene Oxide—*Packaging and storage, USP Reference standards, Identification, Heavy metals, Method II* (delete), *Heavy metals* (add), *Limit of free ethylene oxide, Organic volatile impurities, Method I* (delete), *Residual solvents* (delete)	32	2	398
Polyoxyl 35 Castor Oil—*Viscosity*	31	6	1671
Polyvinyl Acetate (new)	32	2	400
Potassium Alginate (new)	31	5	1426
Saccharin	31	2	616
Saccharin (new)—*Harmonization*	31	2	618
Sesame Oil—*USP Reference standards* (add), *Triglyceride composition*	30	5	1668
Silicon Dioxide (new)—*Harmonization*	31	4	1229

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals*		
	Vol.	*No.*	*Page(s)*
Colloidal Silicon Dioxide (new)—*Harmonization*	31	4	1233
Sodium Starch Glycolate—*Harmonization*	31	5	1523
Tribasic Sodium Phosphate—*Loss on ignition*	32	2	402
Sodium Sulfite—*Identification*	31	4	1146
Rice Starch (new)—*Harmonization*	30	2	721
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706
Sucralose—*Limit of hydrolysis products*	31	4	1146
Sucrose—*Harmonization*	31	3	902
Compressible Sugar—*Loss on drying*	31	4	1147
Confectioner's Sugar—*Identification*	31	4	1147
Strawberry Syrup (new)	32	1	179
Tagatose (new)	30	5	1672
Tetrafluoroethane (new)	31	6	1672
Tributyl Citrate—*Assay*	32	1	179
Triethyl Citrate—*Assay*	32	1	180
Trolamine—*USP Reference standards* (add), *Identification*	31	5	1427
Xylitol—*USP Reference standards, Limit of other polyols, Assay*	31	4	1147

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
<u>*USP Monographs*</u>			
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albuterol Tablets—			
Dissolution	30	1	50
Dissolution	31	1	40
Allopurinol—*Chromatographic purity, Related compounds*	28	5	1386
Alprazolam Tablets—*Dissolution*	30	5	1582
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Baclofen Tablets—*Dissolution*	30	1	61
Betamethasone Tablets—*Dissolution*	30	1	62
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Carboxymethylcellulose Sodium Suspension (entire submission)	30	3	812
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Colchicine Tablets—*Dissolution*	30	1	91
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add)	29	6	1870
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Estradiol Transdermal System (new)—*Drug release*	30	4	1201
Ethinyl Estradiol Tablets—*Related compounds*	31	2	402
Ethosuximide Capsules—*Dissolution*	30	1	102
Fluticasone Propionate—*Content of acetone (Procedure)*	31	4	1070
Gabapentin Capsules (new) (entire submission)	28	2	298
Glycopyrrolate Tablets—*Dissolution*	30	1	105
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Indocyanine Green—*Definition, Assay*	29	6	1905

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Irbesartan Tablets (new)—*Dissolution*	29	4	1035
Isosorbide Dinitrate Sublingual Tablets—*Dissolution*	30	1	113
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Levothyroxine Sodium Oral Solution (new)—*Preview*	31	3	938
Lisinopril Tablets—*Dissolution*	30	1	121
Loperamide Hydrochloride Tablets—*Dissolution*	30	5	1633
Magnesium Oxide—*Bulk density* (add)	29	4	1047
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Meprobamate Tablets—*Dissolution*	30	1	129
Methenamine Tablets—*Dissolution*	30	1	130
Methocarbamol Tablets—*Dissolution*	30	1	130
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Ondansetron Orally Disintegrating Tablets (new)—*Disintegration, Dissolution*	30	6	2024
Oxybutynin Chloride Extended-Release Tablets (new) (entire submission)	30	4	1276
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
Penicillamine Capsules—*Dissolution*	30	1	153
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036
Spironolactone Oral Suspension (new) (entire submission)	30	3	929
Spironolactone and Hydrochlorothiazide Oral Suspension (new) (entire submission)	30	3	930
Terbutaline Sulfate Tablets—*Dissolution*	31	1	76
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Timolol Maleate Tablets—*Dissolution*	30	1	191
Titanium Dioxide (new) (entire submission)	30	4	1304
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Vecuronium Bromide for Injection (new)—*Preview*	25	4	8449
Dietary Supplements Monographs			
Ginkgo Capsules (new)—*Disintegration and dissolution*	27	2	2238
Ginkgo Tablets (new)—*Disintegration and dissolution*	27	2	2240
Asian Ginseng Capsules (new)—*Dissolution*	30	2	571
American Ginseng Capsules (new)—*Dissolution*	30	2	565
American Ginseng Tablets—*Dissolution*	30	2	567
Valerian Capsules (new)—*Disintegration and dissolution*	27	1	1825
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
USP Fluvastatin for System Suitability RS (add)	31	1	99
USP Polyoxyl 35 Castor Oil RS	30	5	1674
⟨41⟩ Weights and Balances (entire submission)	31	2	508

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
⟨386⟩ Environmentally Sensitive Preparations (new) (entire submission)	30	5	1680
⟨429⟩ Light Diffraction Measure of Particle Size (new) (entire submission)	28	3	895
⟨621⟩ Chromatography—*System Suitability (All revisions after the first two paragraphs, through the end up to Glossary)*	30	6	2094
⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets* (delete), *Interpretation*	30	1	234
USP General Information Chapters			
⟨1089⟩ In Vitro, Absorption-Indicating Cell Culture System (new)—*Preview*	25	5	8733
Reagents, Indicators, and Solutions			
1,4-Butanediol (add)—*Preview*	25	5	8747
1-Vinyl-2-pyrrolidone	31	1	108
Reference Tables			
Container Specifications			
Citalopram Hydrobromide Tablets (add)	31	3	859
Description and Relative Solubility			
Magnesium Oxide	29	4	1262
Titanium Dioxide (add)	30	4	1405
NF Monographs			
Alfadex—*Packaging and storage*	30	1	202
Sodium Caprylate—*Packaging and storage*	30	3	990

†New cancellations in *PF* 32(3).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

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

BRIEFING

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

(DSN: L. Evans) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

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Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in the *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

All manuscripts are subject to review by USP headquarters staff, Committee members, or qualified outside referees, and if accepted for publication will be subject to editing by USP staff. Accepted manuscripts become the property of the USP Convention (USPC) and may not be published elsewhere without written permission from the USPC. Authors are also responsible for obtaining permission for reprinting any illustrations that have been published elsewhere.

Abstract—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

References—Consult a current copy of the *Pharmacopeial Forum* and the *ACS Style Guide* for assistance with reference style.

Copyright—Copyright transfer documents will be sent to authors after manuscripts have been accepted for publication.

Contact Person—When submitting a manuscript, designate one author of the article as correspondent and include that author's full address, telephone number, fax number, and e-mail address.

Submission Instructions—Manuscripts must be submitted both as an electronic file and as a printed copy of the electronic file. Submit the text in Microsoft® Word or another current word-processing application. The preferred format for graphics submitted electronically is tagged image file format (TIFF). Graphics that cannot be submitted electronically must be camera-ready, of easily reproducible quality and size, and clearly labeled. Photocopies are not acceptable. Manuscripts submitted for publication should be addressed to:

Pharmacopeial Forum
Executive Secretariat, USP
12601 Twinbrook Pkwy.
Rockville, MD 20852

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

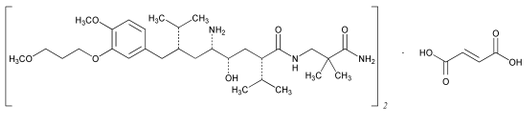
USP Dictionary of USAN and International Drug Names
2006 USP DICTIONARY SUPPLEMENT 1

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2006 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2006) edition will be included in the next complete edition of the Dictionary.

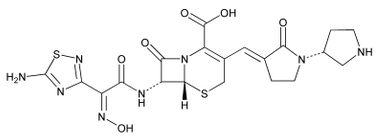
Newly Approved United States Adopted Names (USAN), Released for Publication

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

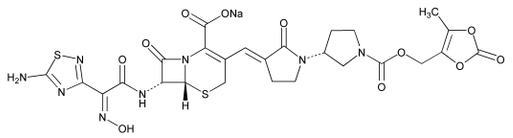
Aliskiren Fumarate [*2006*] (a lis kye′ ren fue′ ma rate). $(C_{30}H_{53}N_3O_6)_2 \cdot C_4H_4O_4$. 1219.60. (1) Benzeneoctanamide, δ-amino-*N*-(3-amino-2,2-dimethyl-3-oxopropyl)-γ-hydroxy-4-methoxy-3-(3-methoxypropoxy)-α,ζ-bis(1-methylethyl)-, (α*S*, γ*S*, δ*S*, ζ*S*)-, (2*E*)-2-butenedioate (2:1) (salt); (2) Bis(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(3-amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methyl-2-(1-methylethyl)nonanamide] (2*E*)-but-2-enedioate. *CAS-173334-58-2*. *Treatment of essential hypertension (renin inhibitor).* (Novartis Pharma AG, Switzerland) ✧*SPP100*



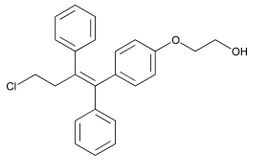
Ceftobiprole [*2006*] (sef toe′ bye prole). $C_{20}H_{22}N_8O_6S_2$. 534.60. (1) 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2*Z*)-(5-amino-1,2,4-thiadiazol-3-yl)(hydroxyimino)acetyl]-amino]-8-oxo-3-[(*E*)-[(3′*R*)-2-oxo[1,3′-bipyrrolidin]-3-ylidene]-methyl]-, (6*R*,7*R*)-; (2) (6*R*,7*R*)-7-[(2*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetamido]-8-oxo-3-[(*E*){(3′*R*)-2-oxo-[1,3′-bipyrrolidin]-3-ylidene}methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. *CAS-209467-52-7*. INN. *Broad spectrum antibiotic.* (Antibioticos S.p.A.); (Johnson & Johnson) ✧*BAL9141-000; Ro 63-9141*



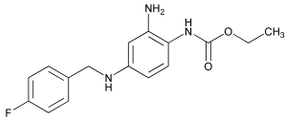
Ceftobiprole Medocaril [*2006*] (sef toe′ bi prole me dok′ a ril). $C_{26}H_{25}N_8NaO_{11}S_2$. 712.64. (1) 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2*Z*)-(5-amino-1,2,4-thiadiazol-3-yl)(hydroxyimino)acetyl]amino]-3-[(*E*)-[(3′*R*)-1′-[[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxy]carbonyl]-2-oxo[1,3′-bipyrrolidin]-3-ylidene]methyl]-8-oxo-, monosodium salt, (6*R*,7*R*)-; (2) (6*R*,7*R*)-7-[(2*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetamido]-3-[(*E*)[(3′*R*)-1′-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]-2-oxo-[1,3′-bipyrrolidin]-3-ylidene]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monosodium salt. *CAS-252188-71-9; CAS-376653-43-9*. INN. *Broad spectrum antibiotic.* (Antibioticos S.p.A.); (Johnson & Johnson) ✧*BAL5788; BAL5788-001; Ro 65-5788*



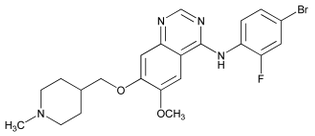
Ospemifene [*2006*] (os pem′ i feen). $C_{24}H_{23}ClO_2$. 378.89. (1) Ethanol, 2-[4-[(1*Z*)-4-chloro-1,2-diphenyl-1-butenyl]phenoxy]-; (2) 2-[*p*-[(*Z*)-4-Chloro-1,2-diphenyl-1-butenyl]phenoxy]ethanol. *CAS-128607-22-7*. INN; BAN. *Treatment of vaginal atrophy, osteoporosis, and vasomotor symptoms.* (Quatrx) ✧*FC-1271a; Fc-1271*



Retigabine [*2006*] (re tig′ a been). $C_{16}H_{18}FN_3O_2$. 303.33. (1) Carbamic acid, [2-amino-4-[[(4-fluoro-phenyl)methyl]amino]phenyl]-ethyl ester; (2) *N*-[2-Amino-4-(4-fluorobenzylamino)-phenyl]-carbamic acid ethyl ester. *CAS-150812-12-7*. INN. *Antiepileptic, adjunctive therapy for partial onset seizures.* (Valeant) ✧*D-23129*



Vandetanib [*2006*] (van det′ a nib). $C_{22}H_{24}BrFN_4O_2$. 475.40. (1) 4-Quinazolinamine, *N*-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]-; (2) *N*-(4-Bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine.*CAS-443913-73-3; CAS-338992-00-0* [replaced]. INN; BAN. *Treatment of nonsmall cell lung cancer and other solid tumors.* Zactima (AstraZeneca) ✧*ZD6474*

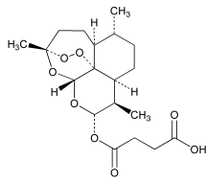


Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

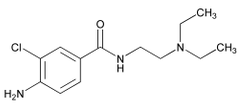
Artesunate

Change the chemical structure to read:



Declopramide

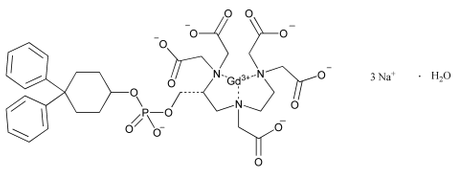
Add the chemical structure to read:



Gadofosveset Trisodium

Change the chemical information and structure to read:

[*1999*] (gad″ oh fos′ ve set). $C_{33}H_{40}GdN_3Na_3O_{15}P$. 975.87. [Gadofosveset is INN.] (1) Gadolinate(3-), aqua [[4-[bis[(carboxy-κ*O*)methyl]amino-κ*N*]-6,9-bis[(carboxy-κ*O*)methyl]-1-[(4,4-diphenylcyclohexyl)oxy]-1-hydroxy-2-oxa-6,9-diaza-1-phosphaundecan-11-oic acid- κ*N*6, κ*N*9, κ*O*11] 1-oxidato(6-)]-, trisodium; (2) Trisodium [*N*-[2-[bis(carboxymethyl)amino]ethyl]-*N*-[(*R*)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl]glycine 4,4-diphenylcyclohexyl hydrogen phosphato (6-)]gadolinate(3-). *CAS-211570-55-7; CAS-193901-90-5* [anhydrous]. *Diagnostic contrast agent for vascular enhancement of MRI scans.* (Mallinckrodt) ✧*MS 32520*



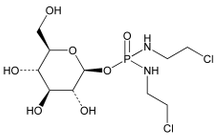
Gallium Nitrate

Delete the chemical structure.

Glufosfamide

Change the chemical information and add structure to read:

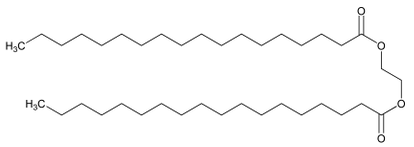
β-D-Glucopyranose 1-[*N,N*′-bis(2-chloroethyl)]phosphorodiamidate.



Glycol Distearate

Add the CAS number and structure to read:

CAS-627-83-8



Guaiacol

Add a chemical name and structure to read:

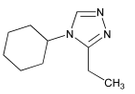
2-methoxyphenol.

Hemoglobin

Delete the chemical structure.

Hexazole

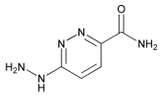
Add the chemical structure to read:



Nomenclature

Hydracarbazine

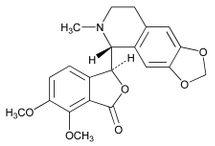
Change the chemical structure to read:



Hydrastine

Add the chemical information and structure to read:

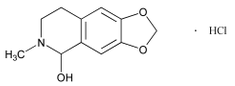
$C_{21}H_{21}NO_6$. 383.39. (1) Phthalide (*S*)-6,7-dimethoxy-3-(*R*)-(5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo(4,5-*g*)isoquinolin-5-yl)-; (2) (*S*)-6,7-Dimethoxy-3-(*R*)-(6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl)isobenzofuran-1(3*H*)-one. *CAS-118-08-1.* USP IX; MI.



Hydrastinine Hydrochloride

Add the chemical information and structure to read:

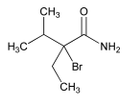
$C_{11}H_{13}NO_3 \cdot HCl$. 207.23. (1) 1,3-Dioxolo(4,5-*g*)isoquinolin-5-ol, hydrochloride; (2) 5,6,7,8-Tetrahydro-6-methyl-5,6,7,8-Tetrahydro-6-methyl-1,3-dioxolo(4,5-*g*)isoquinolin-5-ol, hydrochloride.



Ibrotamide

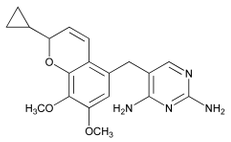
Change the chemical information and structure to read:

(1) Butanamide, 2-bromo-2-ethyl-3-methyl-; (2) 2-Bromo-2-ethyl-isovaleramide. *CAS-466-14-8.* INN; DCF; MI.



Iclaprim

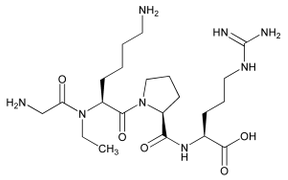
Add the chemical structure to read:



Icrocaptide

Add the molecular weight and chemical structure to read:

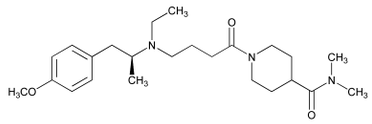
484.59.



Idaverine

Change the chemical information and structure to read:

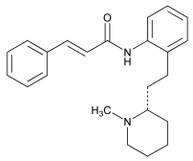
(+)-1-(4-{Ethyl[(*S*)-*p*-methoxy-α-methylphenethyl]amino}butyryl)-*N,N*-dimethylisonipecotamide.



Iferanserin

Add the molecular weight and chemical structure to read:

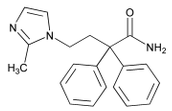
348.48.



Imidafenacin

Add the molecular weight and chemical structure to read:

319.40.



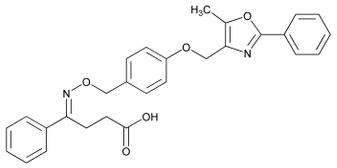
Imiglitazar

Add the molecular weight to read:

470.52.

Change the chemical information and structure to read:

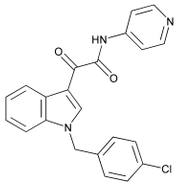
(*E*)-4-[({4-[(5-Methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]phenyl}-methoxy)imino]-4-phenylbutanoic acid.



Indibulin

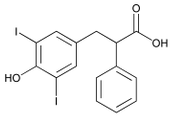
Add the molecular weight and chemical structure to read:

389.83.



Iodoalphionic Acid

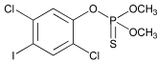
Add the chemical structure to read:



Iodofenphos

Change the chemical formula, molecular weight, and structure to read:

$C_8H_8Cl_2IO_3PS$. 413.00.



Iodol

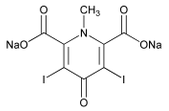
Add the chemical formula, molecular weight, and structure to read:

C_4HI_4N. 570.68.

Iodomethamate

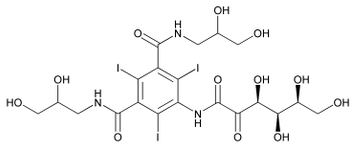
Add the chemical information and structure to read:

$C_8H_3I_2NNa_2O_5$. 492.90. 1,4-Dihydro-3,5-diiodo-1-methyl-4-oxo-2,6-pyridinedicarboxylic acid, disodium salt.



Iogulamide

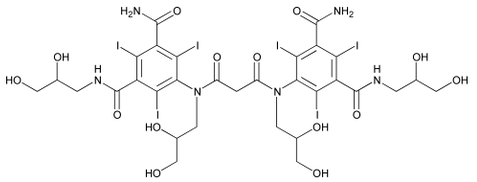
Change the chemical structure to read:



Iosimenol

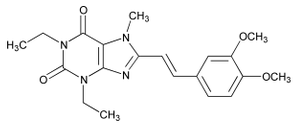
Change the chemical name and add the structure to read:

5,5′-[Propanedioylbis[(2,3-dihydroxypropyl)imino]]bis[*N*-(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide].



Istradefylline

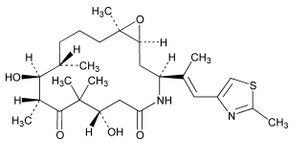
Add the chemical structure to read:



Ixabepilone

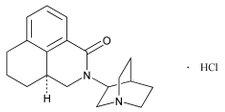
Change the chemical information and add the structure to read:

(2) (1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[(1*E*)-1-methyl-2-(2-methylthiazol-4-yl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione.



Palonosetron

Change the chemical structure to read:



Proposed International Nonproprietary Names

The following 73 names have been selected by the World Health Organization (WHO) as Proposed International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information,* Vol. 19, No. 4, 2005.

Any comments or formal objections to the proposed names should be addressed to Helene Biernacki, Research Associate, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Proposed INN	Therapeutic Indication
Alcaftadine	*Tricyclic histamine-H_1 receptor antagonist*
Amibegron	*β_3-adrenoreceptor agonist*
Apadenoson	*Adenosine A receptor agonist*
Aplaviroc	*Antiviral*
Axitinib	*Antineoplastic*
Bosutinib	*Antineoplastic*
Brecanavir	*Antiviral*
Capeserod	*Serotonin partial agonist*
Casopitant	*Neurokinin NK1 receptor antagonist*
Celivarone	*Anti-arrhythmic*
Cevoglitazar	*Antidiabetic*
Darapladib	*Phospholipase A_2 inhibitor*
Dasatinib	*Antineoplastic*
Denagliptin	*Antidiabetic*
Denosumab	*Immunological agent*
Dexamethasone Cipecilate	*Steroidal anti-inflammatory*
Diaplasinin	*Inhibitor of plasminogen activator inhibitor-type 1 (PAI-1)*
Dilopetine	*Antidepressant*
Disomotide	*Immunological agent for active immunization*
Dutacatib	*Cathepsin K inhibitor*
Eltrombopag	*Thrombopoietin receptor agonist*
Eprodisate	*Inhibition of amyloid A fibril formation and deposition*
Fimasartan	*Angiotensin II receptor antagonist*
Fosaprepitant	*Neurokinin NK1 receptor antagonist*
Fospropofol	*General anesthetic*
Gabapentin Enacarbil	*Gabamimetic agent*
Goxalapladib	*Phospholipase A_2 inhibitor*
Incyclinide	*Anti-inflammatory agent*
Indantadol	*Analgesic*
Ipilimumab	*Immunomodulator*
Iratumumab	*Antineoplastic*
Larotaxel	*Antineoplastic*
Lisdexamfetamine	*Central stimulant*
Lodenafil Carbonate	*Vasodilator*
Masilukast	*Leukotriene receptor antagonist*
Mavacoxib	*Selective cyclo-oxygenase inhibitor (veterinary drug)*
Nilotinib	*Antineoplastic*
Nimotuzumab	*Antineoplastic*
Obatoclax	*Antineoplastic*
Ocrelizumab	*Immunomodulator, Antirheumatic*
Oglemilast	*Anti-asthmatic, Anti-allergic*
Olaparib	*Antineoplastic*
Orvepitant	*Neurokinin NK1 receptor antagonist*
Ovemotide	*Immunological agent for active immunization*
Ozarelix	*GnRH antagonist*
Paquinimod	*Immunomodulator*
Parogrelil	*Inhibition of PDE-II, PDE-IV, and TxA_2 synthetase*
Pazopanib	*Antineoplastic*
Relacatib	*Cathepsin K inhibitor*
Rilapladib	*Phospholipase A_2 inhibitor*
Rolipoltide	*Immunomodulator*
Romidepsin	*Antineoplastic*
Rotigaptide	*Anti-arrythmic*
Sapacitabine	*Antineoplastic*
Simotaxel	*Antineoplastic*
Sitagliptin	*Antidiabetic*
Sontuzumab	*Antineoplastic*
Sotirimod	*Immunomodulator*
Stamulumab	*Immunological agent*
Tadocizumab	*Antithrombotic*
Talotrexin	*Antineoplastic*
Telaprevir	*Antiviral*
Ticilimumab	*Antineoplastic*
Tiplasinin	*Inhibitor of plasminogen activator inhibitor-type 1 (PAI-1)*
Tramiprosate	*Inhibition of amyloid A fibril formation and deposition*
Transferrin Aldifitox	*Antineoplastic*
Tucotuzumab Celmoleukin	*Antineoplastic*
Velafermin	*Induction of epithelial and mesenchymal cell growth*
Verpasep Caltespen	*Immunological agent*
Vicriviroc	*Antiviral*
Vorinostat	*Antineoplastic*
Zibotentan	*Endothelin receptor antagonist*
Zotarolimus	*Immunosuppressant*

Nomenclature

INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

[*NOTE—THIS INDEX COVERS VOL. 32 NO. 1, PP. 1–224, VOL. 32 NO. 3, PP. 705–988*]

MONOGRAPHS

EXCIPIENTS

GENERAL CHAPTERS

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

REFERENCE TABLES

GENERAL SUBJECTS

USP CATALOG

The complete USP Catalog may be downloaded from USP's website at www.usp.org.

If you wish to receive your own free printed copy of the complete USP Catalog call Maureen Rawson at 1-800-227-8772 ext.8237 or 301.816.8237. You may also email your request to marketing@usp.org.

New Items at a Glance

See what's new in USP Reference Standards. For your convenient and quick reference, here's a list of Reference Standards released by USP over the past year.

This list is continuously updated with the newest Reference Standards released within the past 12 months.

Cat. No.	Description	Curr. Lot	Price
1006801	Acetone (1.5 mL/ampule; 3 ampules)	F0D028	$168
1011007	Acitretin (200 mg)	F0E266	$394
1011018	Acitretin Related Compound A (20 mg)	F0E264	$536
1011029	Acitretin Related Compound B (20 mg)	F0E265	$536
1019712	Amiloride Related Compound A (30 mg) (AS)	F0E287	$526
1034909	Anecortave Acetate (200 mg)	F0E298	$168
1034910	Anecortave Acetate Related Compound A (20 mg)	F0E299	$526
1042102	L-Arabinitol (500 mg)	F0E311	$168
1065210	Berberine Chloride (50 mg)	F0E185	$281
1071202	Bicalutamide (200 mg)	F0E321	$168
1071213	Bicalutamide Related Compound A (25 mg)	F0E322	$526
1078201	Budesonide (200 mg)	F0E302	$168
1086301	Calcitriol (10 mg)	F0E062	$1,352
1086312	Calcitriol Solution (5 mL)	F0D330	$208
1086888	Calcium Lactate (1 g)	F0D227	$168
1086935	Calcium Levulinate (1 g) (AS)	F0E142	$168
1091040	Caprylic Acid (300 mg)	F0D378	$168
1496802	Parachlorophenol (500 mg)	F0E061	$168
1134346	Ciprofloxacin Related Compound A (25 mg) (AS)	F0E333	$526
1134390	Clarithromycin Identity (100 mg)	F0E141	$526
1140430	Clopidogrel Bisulfate (125 mg)	F0E115	$753
1140586	Clopidogrel Related Compound A (20 mg)	F0E117	$640
1140597	Clopidogrel Related Compound B (20 mg)	F0E119	$640
1140600	Clopidogrel Related Compound C (20 mg)	F0E118	$640
1145207	Cod Liver Oil (1 g)	F0D400	$168
1162148	Cytosine (100 mg)	F0E284	$168
1046089	N-Demethylazithromycin (15 mg)	F0E068	$526
1187954	2,4-Dichlorophenol (100 mg)	F0E113	$168
1241903	Erythritol (200 mg)	F0E313	$168
1268513	Etidronate Disodium Related Compound A (300 mg)	F0E227	$526
1270446	Fexofenadine Related Compound C (15 mg) (AS)	F0E291	$526
1273819	Flumazenil Related Compound A (20 mg)	F0E147	$675
1273820	Flumazenil Related Compound B (20 mg)	F0E148	$675
1285873	Fluticasone Propionate (100 mg)	F0F036	$832
1285884	Fluticasone Propionate Resolution Mixture (25 mg)	F0E123	$675
1285895	Fluticasone Propionate System Suitability Mixture (25 mg)	F0E122	$675
1285964	Fluvastatin Related Compound B (25 mg)	F0F017	$526
1285942	Fluvastatin for System Suitability (25 mg)	F0F016	$526
1287369	Gabapentin Related Compound E (25 mg)	F0E190	$526
1292303	Glimepiride (200 mg)	F0E228	$250
1292314	Glimepiride Related Compound A (20 mg)	F0E232	$526
1292325	Glimepiride Related Compound B (20 mg)	F0E233	$526
1292336	Glimepiride Related Compound C (20 mg)	F0E234	$526
1292347	Glimepiride Related Compound D (20 mg)	F0E235	$526
1295516	Glyburide Related Compound A (25 mg)	F0E224	$526
1313210	Hydrastine (10 mg)	F0E204	$281
1335010	Hyoscyamine Related Compound A (10 mg)	F0E250	$526
1342321	Insulin Lispro (5.97 mg)	F0E140	$168
1349626	Isomalt (200 mg)	F0E263	$168
1374292	Magnesium Phosphate (2 g) (AS)	F0E107	$168
1379059	Mefloquine Hydrochloride (100 mg)	F0E165	$168
1379060	Mefloquine Related Compound A (20 mg)	F0E166	$526
1380105	Melatonin (100 mg) (AS)	F0E027	$179
1379401	Meloxicam (400 mg)	F0E158	$281
1379412	Meloxicam Related Compound A (25 mg)	F0E167	$526
1379423	Meloxicam Related Compound B (25 mg)	F0E168	$526
1379434	Meloxicam Related Compound C (30 mg)	F0E159	$526
1379445	Meloxicam Related Compound D (30 mg)	F0E160	$526
1396331	Metformin Related Compound B (25 mg)	F0F019	$526
1396342	Metformin Related Compound C (25 mg)	F0E343	$526
1424109	Methyl Alcohol (3 x 1.5 mL)	F0D015	$168
1445404	Modafinil **CIV** (200 mg)	F0D351	$270
1448990	Myristic Acid (200 mg)	F0E120	$168
1460204	Neotame (200 mg)	F0F044	$168
1460215	Neotame Related Compound A (15 mg)	F0F045	$526
1473206	Norphenylephrine Hydrochloride (25 mg)	F0E205	$526
1478119	Ofloxacin Related Compound A (25 mg)	F0E276	$526
1478571	Ondansetron (300 mg)	F0E281	$225
1491015	Oxytetracycline Hydrochloride (200 mg) (AS)	F0E258	$168
1500353	Paroxetine System Suitability Mixture A (50 mg)	F0E150	$526
1534402	Phenyltoloxamine Citrate (100 mg)	F0E127	$168
1534413	Phenyltoloxamine Related Compound A (50 mg)	F0E128	$526
1546401	Polyethylene Glycol 200 (1 g)	F0E316	$168
1546423	Polyethylene Glycol 300 (1 g)	F0E336	$168
1546445	Polyethylene Glycol 400 (1 g)	F0E344	$168
1546525	Polyethylene Glycol 3000 (1 g)	F0F013	$168
1546547	Polyethylene Glycol 3350 (1 g)	F0F012	$168
1546966	Polyisobutylene (1 g)	F0E108	$168
1547200	Polyoxyl 35 Castor Oil (1 g)	F0E116	$168

New Items at a Glance *(Continued)*

Cat. No.	Description	Curr. Lot	Price
1547801	Polyoxyl 20 Cetostearyl Ether (100 mg)	F0C292	$168
1372402	Polyoxyl Lauryl Ether (500 mg)	F0E253	$168
1547346	Polyoxyl 2 Stearyl Ether (1 g) (AS)	F0D353	$168
1372606	Polyoxyl 10 Stearyl Ether (1 g)	F0D354	$168
1547368	Polyoxyl 20 Stearyl Ether (1 g) (AS)	F0D355	$168
1557000	Prednisolone Sodium Phosphate (100 mg)	F0E300	$168
1578554	Prostaglandin B1 (25 mg)	F0E022	$1,352
1598338	Ramipril Related Compound C (20 mg)	F0E157	$526
1598450	Ranitidine Resolution Mixture (20 mg)	F0E323	$1,052
1605500	Ropivacaine Hydrochloride (200 mg)	F0E334	$168
1605512	Ropivacaine Related Compound A (25 mg)	F0E315	$526
1605523	Ropivacaine Related Compound B (50 mg)	F0E318	$526
1612404	Sesame Oil (1 mL/ampule; 2 ampules) (AS)	F0E134	$168
1612415	Sesame Oil Related Compound A (6 mg/vial; 3 vials)	F0E131	$526
1612426	Sesame Oil Related Compound B (6 mg/vial; 3 vials)	F0E132	$526
1614363	Sodium Lauryl Sulfate (1 g) (AS)	F0D381	$168
1614670	Sodium Starch Glycolate Type B (400 mg)	F0E222	$168
1615708	Somatropin (8.63 USP Somatropin Units/vial)	F0E191	$182
1619017	Spironolactone Related Compound A (100 mg) (AS)	F0E184	$526
1642019	Sulindac Related Compound A (20 mg)	F0E314	$526
1667280	Tiagabine Hydrochloride (300 mg)	F0E178	$260
1667235	Racemic Tiagabine Hydrochloride Mixture (25 mg)	F0E179	$526
1667224	Tiagabine Related Compound A (15 mg)	F0E177	$526
1667355	Tiamulin (100 mg)	F0E219	$168
1667541	Tinidazole Related Compound B (20 mg)	F0E274	$526
1672010	o-Toluenesulfonamide (200 mg)	F0E163	$263
1672020	p-Toluenesulfonamide (200 mg)	F0E162	$263
1682217	Triclosan Related Compounds Mixture A (1.2 mL/ampule; 3 ampules)	F0E292	$526
1705323	Ubidecarenone Related Compound A (15 mg)	F0E210	$526
1708718	Valproic Acid Related Compound B (50 mg) (AS)	F0E201	$526
1711428	Verapamil Related Compound D (50 mg)	F0E342	$526

New Lots in Distribution

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1042102	L-Arabinitol (500 mg)	F0E311	1.00 mg/mg (an)	1		[7643-75-6]	$168
1071202	Bicalutamide (200 mg)	F0E321	0.999 mg/mg (ai)	1		[90357-06-5]	$168
1071213	Bicalutamide Related Compound A (25 mg) (N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluoro-phenyl)sulfinyl]-2-hydroxy-2-methyl-propanamide)	F0E322		1		n/f	$526
1134346	Ciprofloxacin Related Compound A (25 mg) (AS) (7-Chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride salt)	F0E333		1		n/f	$526
1285873	Fluticasone Propionate (100 mg)	F0F036	0.989 mg/mg (ai)	1		[80474-14-2]	$832
1285964	Fluvastatin Related Compound B (15 mg) ([R*,S*-E]-(+/-)-7-[3-(4-fluorophenyl)-1-methylethyl-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1, dimethylethyl ester)	F0F017		1		[129332-29-2]	$526
1285942	Fluvastatin for System Suitability (25 mg) (Fluvastatin sodium and fluvastatin sodium anti-isomer ([R*,R*-E]-(+/-)-7-[3-(4-Fluorophenyl)-1-(methyl-ethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt))	F0F016		1		n/f	$526
1396331	Metformin Related Compound B (25 mg) (1-Methylbiguanide hydrochloride)	F0F019		1		[1674-62-0]	$526
1396342	Metformin Related Compound C (25 mg) (N,N-Dimethyl-[1,3,5]triazine-2,4,6-triamine)	F0E343		1		[1985-46-2]	$526
1460204	Neotame (200 mg)	F0F044	0.954 mg/mg (ai)	1		[165450-17-9]	$168
1460215	Neotame Related Compound A (15 mg) (N-[N-(3,3-dimethylbutyl)-L-alpha-aspartyl]-L-phenylalanine)	F0F045	1.00 mg/mg (ai)	1		n/f	$526
1546401	Polyethylene Glycol 200 (1 g)	F0E316		1		[25322-68-3]	$168
1546423	Polyethylene Glycol 300 (1 g)	F0E336		1		[25322-68-3]	$168
1546445	Polyethylene Glycol 400 (1 g)	F0E344		1		[25322-68-3]	$168
1546525	Polyethylene Glycol 3000 (1 g)	F0F013		1		[25322-68-3]	$168
1546547	Polyethylene Glycol 3350 (1 g)	F0F012		1		[25322-68-3]	$168
1546966	Polyisobutylene (1 g)	F0E108		1		[9003-27-4]	$168
1598450	Ranitidine Resolution Mixture (20 mg)	F0E323		1		n/f	$1,052
1605500	Ropivacaine Hydrochloride (200 mg)	F0E334	0.943 mg/mg (ai)	1		[132112-35-7]	$168
1605512	Ropivacaine Related Compound A (25 mg) (2,6-dimethylaniline hydrochloride)	F0E315	1.00 mg/mg (ai)	1		[21436-98-6]	$526
1605523	Ropivacaine Related Compound B (50 mg) ((R)-(+)-1-Propylpiperidine-2-carboxylic acid (2,6-dimethylphenyl)-amide hydrochloride monohydrate)	F0E318		1		[112773-90-7]	$526
1614363	Sodium Lauryl Sulfate (1 g) (AS)	F0D381		1		[151-21-3]	$168
1642019	Sulindac Related Compound A (20 mg) (trans-sulindac)	F0E314		1		[53933-60-1]	$526
1708718	Valproic Acid Related Compound B (50 mg) ((2RS)-2-(1-methylethyl)pentanoic acid) (AS)	F0E201		1		[62391-99-5]	$526
1711428	Verapamil Related Compound D (50 mg) (5,5'-[[2-(3,4)dimethoxyphenyl)ethyl]imino]bis[2-(3,4-dimethoxyphenyl)-2-(1-methylethyl)pentanenitrile] hydrochloride)	F0E342		1		[190850-50-1]	$526
1009923	Acetyltriethyl Citrate (500 mg)	G0E085		2	F-1 (01/07) F (05/02)	[77-89-4]	$168
1055002	Benzoic Acid (300 mg)	G0D223	1.000 mg/mg (dr)	2	F6B173 (02/07) F-5 (03/04) F-4 (07/01)	[65-85-0]	$168

New Lots in Distribution

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1176506	Dexamethasone Acetate (200 mg)	H0E339	0.996 mg/mg (dr)	2	G (12/06) F-1 (06/99)	[1177-87-3]	$168
1177000	Dexamethasone Phosphate (200 mg)	K0E275	0.996 mg/mg (dr)	2	J1B070 (01/07) J (08/03) I (03/00)	[312-93-6]	$168
1242000	Erythromycin (250 mg)	M1E251	96.7% Erythromycin A 978 ug/mg (ai) (microbial)	2	M (02/07) L (08/99)	[114-07-8]	$168
1270377	Fexofenadine Hydrochloride (200 mg)	F1E289	0.996 mg/mg (ai)	2	F0D244 (02/07)	[138452-21-8]	$168
1354207	Isradipine (200 mg)	H0E252	0.995 mg/mg (dr)	2	G0B054 (01/07) F (05/03)	[75695-93-1]	$168
1365000	Levothyroxine (500 mg)	L0D226	0.994 mg/mg (dr)	2	K (12/06) J (10/00)	[51-48-9]	$168
1431603	Methyl Palmitate (300 mg)	G0E329	1.00 mg/mg (ai)	2	F(02/07)	[112-39-0]	$168
1438001	Methyltestosterone **CIII** (200 mg)	J1E324	0.996 mg/mg (dr)	2	J (02/07) I (11/01)	[58-18-4]	$224
1440003	Methysergide Maleate (350 mg)	H1F038	0.997 mg/mg (dr)	2,3	H (12/06)	[129-49-7]	$260
1445470	Mometasone Furoate (200 mg)	H0E009	0.998 mg/mg (dr)	2	G0B073 (01/07) F-1 (04/03) F (02/01)	[83919-23-7]	$168
1457006	Naphazoline Hydrochloride (200 mg)	L0E207	0.989 mg/mg (dr)	2	K (02/07)	[550-99-2]	$168
1458009	Neomycin Sulfate (200 mg)	L3E135	782 ug/mg (dr)	2	L-2 (01/07) L-1 (09/01) L (02/99)	[1405-10-3]	$168
1461003	Niacin (200 mg)	I0E295	0.998 mg/mg (ai)	2	H2C121 (02/07) H-1 (01/05)	[59-67-6]	$168
1494079	Pancreatin Lipase (2 g)	I1E327	21.2 USP Units of Lipase Activity/mg (ai)	2	I (12/06) H-1 (03/01)	[8049-47-6]	$168
1500251	Paroxetine Related Compound D (10 mg) (AS) (cis-Paroxetine hydrochloride)	G0E096		2,3	F0C228 (12/06)	n/f	$526
1500262	Paroxetine Related Compound E Mixture (25 mg) (1-Methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydro-pyridine in Paroxetine Hydrochloride Matrix)	F1F028	0.86 ng/mg (ai)	2	F0D225 (11/06)	n/f	$526
1500284	Paroxetine Related Compound G (0.4 mg) ((+/-)-trans-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4''-fluorophenyl-4'-phenyl)piperidine hydrochloride)	G0E121	0.4 mg in ~1.5 mg povidone	2,3	F0D110 (12/06)	n/f	$526
1535507	Phenytoin Sodium (200 mg)	H1E335	1.000 mg/mg (dr) (UV)	2	H (02/07) G (05/99)	[630-93-3]	$168
1623502	Succinylcholine Chloride (500 mg)	H1E325	0.995 mg/mg (an)	2	H (12/06)	[71-27-2]	$168
1636005	Sulfasalazine (125 mg)	G3F035	1.000 mg/mg (dr)	2	G-2 (02/07) G-1 (06/99)	[599-79-1]	$134
1699005	Tropicamide (200 mg)	H0E307	0.99 mg/mg (ai)	2,3	G-1 (01/07) G (02/99)	[1508-75-4]	$134
1719102	Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one)	H0E268		2	G1B111 (02/07) G (01/04)	[37209-23-7]	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1000601	Acebutolol Hydrochloride (125 mg)	F-1				[34381-68-5]	$168
1001003	Acenocoumarol (200 mg)	G0D300			F (10/05)	[152-72-7]	$168
1001502	Acepromazine Maleate (250 mg)	F-2			F-1 (05/02)	[3598-37-6]	$168
1002505	Acesulfame Potassium (200 mg)	F0C136				[55589-62-3]	$281
1003009	Acetaminophen (400 mg)	J2C423	0.996 mg/mg (dr)		J-1 (04/06) J (05/02) I (05/99)	[103-90-2]	$134
1004001	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)	M0A029			L (06/04) K (02/00)	[103-84-4]	$81
1005004	Acetazolamide (2 g)	J1E041	0.997 mg/mg (dr)		J (02/06)	[59-66-5]	$168
1005706	Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D002	99.9% (ai)			[64-19-7]	$168
1006007	Acetohexamide (250 mg)	H			G-1 (06/99)	[968-81-0]	$168
1006506	Acetohydroxamic Acid (200 mg)	F-1			F (03/03)	[546-88-3]	$168
1006801	Acetone (1.5 mL/ampule; 3 ampules)	F0D028	0.997 mg/mg (ai)			[67-64-1]	$168
1007000	Acetophenazine Maleate (200 mg)	F-1				[5714-00-1]	$168
1008501	Acetylcholine Chloride (200 mg)	G				[60-31-1]	$168
1009005	Acetylcysteine (200 mg)	H1B169			H (01/04)	[616-91-1]	$168
1009901	Acetyltributyl Citrate (500 mg)	G0C120			F (05/04)	[77-90-7]	$168
1009923	Acetyltriethyl Citrate (500 mg)	G0E085		2	F-1 (01/07) F (05/02)	[77-89-4]	$168
1011007	Acitretin (200 mg)	F0E266	0.998 mg/mg (ai)			[55079-83-9]	$394
1011018	Acitretin Related Compound A (20 mg) ((2Z,4E,6E,8E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid)	F0E264				[69427-46-9]	$536
1011029	Acitretin Related Compound B (20 mg) (ethyl (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate)	F0E265				[54350-48-0]	$536
1012065	Acyclovir (300 mg)	J0C149			I (06/04)	[59277-89-3]	$213
1012134	Ademetionine Disulfate Tosylate (500 mg)	F0D073				[97540-22-2]	$563
1012101	Adenine (200 mg)	G2D279	1.000 mg/mg (dr)		G-1 (12/05) G (06/00)	[73-24-5]	$168
1012123	Adenosine (200 mg)	G0C295			F1B058 (01/05) F (04/03)	[58-61-7]	$168
1012190	Adipic Acid (100 mg)	F0D318				[124-04-9]	$168
1012145	Agigenin (25 mg)	F				n/f	$526
1012203	Agnuside (25 mg)	F0D397	0.88 mg/mg (ai)			[11027-63-7]	$920
1012509	L-Alanine (200 mg)	G0E002	1.00 mg/mg (ai)		F-2 (08/06) F-1 (04/01)	[56-41-7]	$168
1012553	Albendazole (200 mg)	H0E240	0.996 mg/mg (dr)		G (10/06) F-1 (01/00)	[54965-21-8]	$168
1012600	Albuterol (200 mg)	I			H (12/00)	[18559-94-9]	$168
1012633	Albuterol Sulfate (200 mg)	J			I (04/00)	[51022-70-9]	$168
1012757	Alclometasone Dipropionate (300 mg)	H			G (01/00)	[66734-13-2]	$168
1012768	Alcohol (1.2 mL/ampule; 5 ampules)	F0D030				[64-17-5]	$168
1012772	Dehydrated Alcohol (1.2 mL/ampule; 5 ampules)	F0D031				[64-17-5]	$168
1012699	Alcohol Determination–Acetonitrile (5 mL/ampule; 5 ampules)	F0C419	2% v/v (ai)			n/f	$168
1012688	Alcohol Determination–Alcohol (5 mL/ampule; 5 ampules)	F0C399	1.96% v/v (ai)			n/f	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1012780	Alendronate Sodium (200 mg)	G0D288	0.834 mg/mg (ai)		F0B315 (02/06)	[121268-17-5]	$168
1012906	Alfentanil Hydrochloride **CII** (500 mg)	F0B016				[70879-28-6]	$224
1012939	Allantoin (200 mg)	F0C169				[97-59-6]	$168
1012950	Alliin (25 mg)	F				[556-27-4]	$1,649
1013002	Allopurinol (250 mg)	J0C186			I-1 (01/05) I (07/02)	[315-30-0]	$168
1013024	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)	G			F-3 (05/02) F-2 (04/99)	n/f	$526
1013057	S-Allyl-L-Cysteine (25 mg)	F				n/f	$526
1014005	Alphaprodine Hydrochloride **CII** (250 mg)	F				[561-78-4]	$224
1015008	Alprazolam **CIV** (200 mg)	H1C133			H (06/05)	[28981-97-7]	$224
1016000	Alprostadil (25 mg)	H				[745-65-3]	$1,649
1017105	Altretamine (500 mg)	F				[645-05-6]	$168
1017502	Dried Aluminum Hydroxide Gel (200 mg)	F2B120			F-1 (01/04)	[21645-51-2]	$168
1017364	Aluminum Sulfate (2 g) (AS)	F0D342	55.3 % (ai)			[17927-65-0]	$168
1018505	Amantadine Hydrochloride (200 mg)	H1D207	0.998 mg/mg (ai)		H (02/06) G (04/01)	[665-66-7]	$168
1019202	Amcinonide (200 mg)	H0D346	0.995 mg/mg (ai)		G0B260 (06/06) F-1 (03/04)	[51022-69-6]	$168
1019417	Amifostine Disulfide (25 mg)	F0C152				[112901-68-5]	$526
1019508	Amikacin (300 mg)	J0E226	0.981 mg/mg (an)		I (10/06) H (08/00)	[37517-28-5]	$168
1019701	Amiloride Hydrochloride (500 mg)	H				[17440-83-4]	$168
1019712	Amiloride Related Compound A (30 mg) (AS) (Methyl 3,5-diamino-6-chloropyrazine-2-carboxylate)	F0E287				[1458-01-1]	$526
1019756	Aminobenzoate Potassium (200 mg)	F-1			F (06/01)	[138-84-1]	$168
1019767	Aminobenzoate Sodium (200 mg)	F				[55-06-6]	$168
1019803	Aminobenzoic Acid (200 mg) (p-aminobenzoic acid)	H1C083			H (10/04) G (10/00)	[150-13-0]	$168
1020008	Aminobutanol (500 mg)	G-1			G (06/99)	[96-20-8]	$421
1021000	Aminocaproic Acid (200 mg)	G0D101	0.997 mg/mg (dr)		F-4 (09/05)	[60-32-2]	$168
1022808	2-Amino-5-chlorobenzophenone (25 mg)	I			H-1 (01/03)	[719-59-5]	$526
1025205	Aminoglutethimide (200 mg)	F				[125-84-8]	$168
1025307	m-Aminoglutethimide (100 mg)	G			F (05/01)	n/f	$526
1025351	Aminohippuric Acid (200 mg)	F-1				[61-78-9]	$168
1025806	2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-d-glucose (25 mg)	F				n/f	$526
1025908	Aminopentamide Sulfate (200 mg)	F0B273				[60-46-8]	$168
1026004	m-Aminophenol (300 mg)	F				[591-27-5]	$526
1026401	Aminosalicylic Acid (125 mg)	F-1			F (03/99)	[65-49-6]	$134
1026605	3-Amino-2,4,6-triiodobenzoic Acid (50 mg)	G				[3119-15-1]	$526
1027007	5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid (50 mg)	F-1				[2280-89-9]	$526
1027302	Amiodarone Hydrochloride (200 mg)	F0D257	0.995 mg/mg (ai)			[19774-82-4]	$168
1028000	Amitraz (200 mg)	F0C042				[33089-61-1]	$168
1029002	Amitriptyline Hydrochloride (200 mg)	J0A004			I (03/03)	[549-18-8]	$168
1029501	Amlodipine Besylate (200 mg)	F0D167	0.996 mg/mg (ai)			[111470-99-6]	$168
1029909	Ammonio Methacrylate Copolymer Type A (100 mg)	F-1			F (06/01)	[33434-24-1]	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1029910	Ammonio Methacrylate Copolymer Type B (100 mg)	F2C082			F-1 (06/05) F (05/00)	[33434-24-1]	$168
1029942	Ammonium Carbonate (2 g) (AS)	F0D102	33.3% NH3 (ai)			[8000-73-5]	$168
1029953	Ammonium Chloride (200 mg)	F0C134				[12125-02-9]	$168
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	100.0 % (ai)			[7783-28-0]	$168
1030001	Amobarbital **CII** (200 mg)	F-2				[57-43-2]	$224
1031004	Amodiaquine Hydrochloride (500 mg)	H0B238			G-1 (04/03)	[6398-98-7]	$168
1031401	Amoxapine (200 mg)	G			F-1 (04/02)	[14028-44-5]	$168
1031503	Amoxicillin (200 mg)	J0C043			I (07/04)	[61336-70-7]	$168
1032007	Amphotericin B (125 mg)	J3C246	1009 ug/mg (dr)		J-2 (01/05) J-1 (07/02)	[1397-89-3]	$134
1033000	Ampicillin (200 mg)	J-1			J (12/01)	[69-53-4]	$168
1033203	Ampicillin Sodium (125 mg)	G-1			G (10/99)	[69-52-3]	$134
1033407	Ampicillin Trihydrate (200 mg)	G1D147			G (08/05)	[7177-48-2]	$168
1034002	Amprolium (200 mg)	G0C317	0.991 mg/mg (dr)		F-1 (04/05) F (04/02)	[121-25-5]	$168
1034308	Amrinone (500 mg)	G				[60719-84-8]	$168
1034320	Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyridin]-6(1H)-one)	F				[62749-46-6]	$526
1034341	Amrinone Related Compound B (100 mg) (N-(1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-yl)-2-hydroxypropanamide)	F-1			F (03/00)	n/f	$526
1034363	Amrinone Related Compound C (50 mg) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile)	F-1			F (05/00)	n/f	$526
1034909	Anecortave Acetate (200 mg)	F0E298	0.997 mg/mg (ai)			[7753-60-8]	$168
1034910	Anecortave Acetate Related Compound A (20 mg) (9(11)-dehydrocortisol)	F0E299				[10184-70-0]	$526
1036008	Anileridine Hydrochloride **CII** (250 mg)	F				[126-12-5]	$224
1036507	3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile (25 mg) (AS)	G2D383			G-1 (04/06)	[30078-48-9]	$526
1038003	Antazoline Phosphate (200 mg)	H			G-1 (04/02)	[154-68-7]	$168
1039006	Anthralin (200 mg)	I0B221			H (11/02)	[1143-38-0]	$168
1040005	Antipyrine (200 mg)	G			F-4 (09/01)	[60-80-0]	$168
1040708	Apigenin-7-glucoside (30 mg)	F				n/f	$526
1041008	Apomorphine Hydrochloride (250 mg)	H			G (01/03)	[41372-20-7]	$175
1041609	Apraclonidine Hydrochloride (100 mg)	H0B112			G (06/03)	[73218-79-8]	$518
1042000	Aprobarbital **CIII** (200 mg) (AS) **DISCONTINUED**				F-1 (02/07)	[77-02-1]	$224
1042102	L-Arabinitol (500 mg)	F0E311	1.00 mg/mg (an)	1		[7643-75-6]	$168
1042500	L-Arginine (200 mg)	G-1			G (09/00)	[74-79-3]	$168
1042601	Arginine Hydrochloride (125 mg)	G0B060			F-1 (05/03)	[1119-34-2]	$134
1042703	Arsanilic Acid (25 mg)	F				[98-50-0]	$168
1043003	Ascorbic Acid (1 g) (Vitamin C)	Q0B012			P (04/03)	[50-81-7]	$168
1043105	Ascorbyl Palmitate (2 g) (AS)	F0D326	0.988 mg/mg (ai)			[137-66-6]	$168
1043502	Asparagine Anhydrous (200 mg)	F0E013	1.00 mg/mg (dr)			[70-47-3]	$168
1043513	Asparagine Monohydrate (200 mg)	F0E012	1.00 mg/mg (ai)			[5794-13-8]	$168
1043706	Aspartame (200 mg)	H1B125			H (05/03)	[22839-47-0]	$168
1043750	Aspartame Acesulfame (200 mg)	F0C137				[106372-55-8]	$168
1043728	Aspartame Related Compound A (25 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid)	I0D208	0.99 mg/mg (ai)		H (11/05) G-1 (10/99)	[5262-10-2]	$526
1043819	Aspartic Acid (100 mg)	F0B087				[6899-03-2]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1044006	Aspirin (500 mg)	H			G-1 (11/02)	[50-78-2]	$168
1044301	Astemizole (200 mg)	F				[68844-77-9]	$168
1044403	Atenolol (200 mg)	H1C320	998 ug/mg (dr)		H (01/05) G (08/01)	[29122-68-7]	$168
1044651	Atovaquone (200 mg)	F0B190				[95233-18-4]	$168
1044662	Atovaquone Related Compound A (25 mg) (cis-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone)	F0B188				n/f	$526
1044800	Atracurium Besylate (100 mg)	F0B143				[64228-81-5]	$168
1045009	Atropine Sulfate (500 mg)	M0B098			L-2 (04/03) L-1 (06/02) L (10/00)	[5908-99-6]	$168
1045337	Avobenzone (500 mg)	G1E109	0.996 mg/mg (dr)		G0B280 (09/06) F (09/03)	[70356-09-1]	$168
1045508	Aurothioglucose (100 mg)	H0B224			G (10/03) F (12/01)	[12192-57-3]	$281
1045600	Azaerythromycin A (100 mg) (9-Deoxo-9a-aza-9a-homoerythromycin A)	G1D368			G (05/06) F-1 (02/02) F (02/99)	[76801-85-9]	$526
1045756	Azaperone (200 mg)	F				[1649-18-9]	$168
1045803	Azatadine Maleate (200 mg)	G0B300			F-1 (04/04) F (06/00)	[3978-86-7]	$168
1046001	Azathioprine (200 mg)	H			G-1 (02/00)	[446-86-6]	$168
1046056	Azithromycin (100 mg)	H0C212			G (11/04) F (06/00)	[117772-70-0]	$168
1046103	Azlocillin Sodium (200 mg)	F				[37091-65-9]	$168
1046147	Azo-aminoglutethimide (100 mg)	F				n/f	$526
1046205	Aztreonam (200 mg)	G0C077			F-1 (03/04)	[78110-38-0]	$168
1046307	Aztreonam E-Isomer (50 mg)	F1D056			F (04/05)	n/f	$526
1046409	Open Ring Aztreonam (25 mg)	G0D071			F (12/04)	[87500-74-1]	$526
1047300	Bacampicillin Hydrochloride (200 mg)	G0B053			F (11/02)	[37661-08-8]	$168
1047503	Bacitracin (1 g) (Susceptibility disk standard)	G1C254			G (07/04)	[1405-87-4]	$168
1048007	Bacitracin Zinc (200 mg)	N1E200	75.1 USP Bacitracin Units/mg (dr)		N0A024 (12/06) M-1 (11/02) M (02/00)	[1405-89-6]	$168
1048200	Baclofen (500 mg)	I				[1134-47-0]	$168
1048222	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)	H1C289			H (11/04)	n/f	$526
1048506	Beclomethasone Dipropionate (200 mg)	L0D312	0.992 mg/mg (dr)		K (02/06) J (12/00)	[5534-09-8]	$168
1048619	Benazepril Hydrochloride (125 mg)	G0E079	0.996 mg/mg (dr)		F0C250 (03/06)	[86541-74-4]	$168
1048620	Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, monohydrochloride)	F0C252				n/f	$526
1048630	Benazepril Related Compound B (15 mg) ((3S)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, monohydrochloride)	F0C256				n/f	$526
1048641	Benazepril Related Compound C (50 mg) ((3S)-3-[[(1S)-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine]-1-acetic acid)	F0C425	1.00 mg/mg (ai)			[86541-78-8]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1049000	Bendroflumethiazide (200 mg)	H0C402	0.994 mg/mg (ai)		G-1 (06/05)	[73-48-3]	$168
1050009	Benoxinate Hydrochloride (200 mg)	F-2			F-1 (10/99)	[5987-82-6]	$134
1051001	Benzalkonium Chloride (5 mL of approx. 10% aqueous solution)	L0D209	Approx. 10% (w/v)		K0B151 (10/06) J (06/03)	[8001-54-5]	$168
1051500	Benzethonium Chloride (500 mg)	F0E104				[121-54-0]	$168
1054000	Benzocaine (500 mg)	J0C130			I (12/04)	[94-09-7]	$168
1055002	Benzoic Acid (300 mg)	G0D223	1.000 mg/mg (dr)	2	F6B173 (02/07) F-5 (03/04) F-4 (07/01)	[65-85-0]	$168
1056005	Benzonatate (1 g)	I0B003			H (01/03)	[104-31-4]	$168
1056504	1,4-Benzoquinone (200 mg)	G1B145			G (01/04) F-1 (11/01) F (09/00)	[106-51-4]	$168
1057507	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)				H0B069 (02/07) G-4 (03/03)	[121-30-2]	$526
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272			F-1 (10/05)	[5411-22-3]	$224
1060002	Benzthiazide (200 mg)	F				[91-33-8]	$168
1061005	Benztropine Mesylate (200 mg)	I0C038			H (09/04)	[132-17-2]	$168
1061901	Benzyl Alcohol (500 mg/ampule)	G0B306			F0B106 (10/03)	[100-51-6]	$168
1062008	Benzyl Benzoate (5 g)	J0C060			I (05/04)	[120-51-4]	$168
1064003	1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride (25 mg)	F-1				n/f	$526
1065006	Bephenium Hydroxynaphthoate (500 mg)	F				[3818-50-6]	$168
1065210	Berberine Chloride (50 mg)	F0E185	0.81 mg/mg (ai)			[633-65-8]	$281
1065618	Betahistine Hydrochloride (200 mg)	F0C105				[5579-84-0]	$168
1065709	Betaine Hydrochloride (200 mg)	F-1			F (11/02)	[590-46-5]	$168
1066009	Betamethasone (200 mg)	K2C204			K-1 (10/04) K (11/02)	[378-44-9]	$168
1067001	Betamethasone Acetate (500 mg)	J0B079			I (08/03)	[987-24-6]	$168
1067307	Betamethasone Benzoate (200 mg)	F-1				[22298-29-9]	$168
1067704	Betamethasone Dipropionate (125 mg)	K0C229			J (04/04) I (03/99)	[5593-20-4]	$134
1068004	Betamethasone Sodium Phosphate (500 mg)	K0C358	0.993 mg/mg (an)		J0B043 (06/05) I-1 (02/03) I (01/01)	[151-73-5]	$168
1069007	Betamethasone Valerate (200 mg)	K0C330	0.997 mg/mg (ai)		J (07/05) I (05/00)	[2152-44-5]	$168
1069903	Betaxolol Hydrochloride (200 mg)	G			F-1 (06/00)	[63659-19-8]	$168
1070006	Betazole Hydrochloride (200 mg)	H				[138-92-1]	$168
1071009	Bethanechol Chloride (200 mg)	G1D088	1.00 mg/mg (dr)		G (03/05) F-3 (07/01)	[590-63-6]	$168
1071202	Bicalutamide (200 mg)	F0E321	0.999 mg/mg (ai)	1		[90357-06-5]	$168
1071213	Bicalutamide Related Compound A (25 mg) (N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfinyl]-2-hydroxy-2-methyl-propanamide)	F0E322		1		n/f	$526
1071304	Bile Salts (10 g)	I0C003			H-1 (05/04) H (05/99)	[145-42-6]	$134
1071439	Positive Bioreaction (3 strips; 10 cm x 1 cm)	F0D014				n/f	$352
1071508	Biotin (200 mg)	I0D114	0.993 mg/mg (ai)		H1B019 (11/05) H (04/03)	[58-85-5]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1072001	Biperiden (200 mg)	F2B080			F-1 (02/04)	[514-65-8]	$168
1073004	Biperiden Hydrochloride (200 mg)	G0E182	1.000 mg/mg (ai)		F-3 (08/06) F-2 (06/99)	[1235-82-1]	$168
1074007	Bisacodyl (125 mg)	I1B162			I (01/04) H-1 (02/99)	[603-50-9]	$134
1074700	2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine (25 mg)	F				n/f	$526
1075203	Bis(2-ethylhexyl)maleate (250 mg)	F-2			F-1 (01/01)	[142-16-5]	$526
1075509	p-Bis(di-n-propyl)carbamylbenzenesulfonamide (50 mg)	F				n/f	$526
1075531	Bismuth Citrate (100 mg)	F				[813-93-4]	$168
1075600	Bismuth Subcarbonate (1 g) (AS)	F0D324	98.4% (dr)			[5892-10-4]	$168
1075622	Bismuth Subgallate (2 g) (AS)	F0D323	54.2% Bi_2O_3 (dr)			[22650-86-8]	$168
1075644	Bismuth Subnitrate (1.5 g) (AS)	F0D388	81.7% Bi_2O_3 (dr)			[1304-85-4]	$168
1075553	Bismuth Subsalicylate (100 mg)	F1C394			F (08/05)	[14882-18-9]	$168
1075757	Bisoprolol Fumarate (200 mg)	G0D316	0.997 mg/mg (dr)		F0B038 (08/05)	[104344-23-2]	$168
1076206	Powdered Black Cohosh Extract (1.5 g)	F0D086				[84776-26-1]	$563
1076308	Bleomycin Sulfate (15 mg)	J0B213			I (01/04)	[9041-93-4]	$332
1076341	Boric Acid (1 g) (AS)	F0D036	100.0% (dr)			[10043-35-3]	$216
1076352	Bretylium Tosylate (200 mg)	F-1				[61-75-6]	$168
1076363	Brinzolamide (200 mg)	F0C034				[138890-62-7]	$168
1076374	Brinzolamide Related Compound A (50 mg) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide)	F0C033				n/f	$526
1076385	Brinzolamide Related Compound B (50 mg) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate)	F0C035				n/f	$526
1076501	Bromocriptine Mesylate (150 mg)	I1C197			I (09/04)	[22260-51-1]	$168
1077005	Bromodiphenhydramine Hydrochloride (200 mg)	F-1				[1808-12-4]	$168
1077708	8-Bromotheophylline (400 mg)	G			F (07/02)	[10381-75-6]	$476
1078008	Brompheniramine Maleate (125 mg)	I1A036			I (01/03) H-1 (04/99)	[980-71-2]	$134
1078201	Budesonide (200 mg)	F0E302	0.997 mg/mg (ai)			[51333-22-3]	$168
1078303	Bumetanide (250 mg)	I0C111			H0B030 (05/04) G (03/03)	[28395-03-1]	$168
1078325	Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)	F-2			F-1 (05/00)	n/f	$526
1078336	Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid)	F-2			F-1 (01/03)	[28328-53-2]	$526
1078507	Bupivacaine Hydrochloride (1 g)	H			G-2 (03/03) G-1 (08/02)	[14252-80-3]	$168
1078700	Buprenorphine Hydrochloride **CIII** (50 mg)	G0E026	0.995 mg/mg (ai)		F-1 (03/06) F (02/99)	[53152-21-9]	$224
1078711	Buprenorphine Related Compound A **CII** (50 mg) (21-[3-(1-propenyl)]-7alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine)	F1C076			F (04/04)	n/f	$526
1078733	Bupropion Hydrochloride (200 mg)	G0E048	0.998 mg/mg (ai)		F0C123 (02/06)	[31677-93-7]	$225

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1078744	Bupropion Hydrochloride Related Compound A (15 mg) (2-(tert-butylamino)-4'-chloropropiophenone hydrochloride)	F0E082				n/f	$572
1078755	Bupropion Hydrochloride Related Compound B (15 mg) (2-(tert-butylamino)-3'-bromopropiophenone hydrochloride)	F0E011				n/f	$572
1078766	Bupropion Hydrochloride Related Compound C (40 mg) (1-(3-chlorophenyl)-2-hydroxy-1-propanone)	F0D293				n/f	$572
1078799	Bupropion Hydrochloride Related Compound F (30 mg) (1-(3-chlorophenyl)-1-hydroxy-2-propanone)	F0E076				n/f	$572
1078802	Buspirone Hydrochloride (200 mg)	H0B301			G (05/05)	[33386-08-2]	$168
1079000	Butabarbital **CIII** (200 mg)	H0C007			G (03/04)	[125-40-6]	$224
1080000	Butacaine Sulfate (600 mg)	F				[149-15-5]	$168
1081002	Butalbital **CIII** (200 mg)	H0C054			G2B077 (07/04) G-2 (06/03) G (05/02)	[77-26-9]	$224
1081501	Butamben (200 mg)				F (01/07)	[94-25-7]	$168
1082300	Butoconazole Nitrate (200 mg)	F1B097			F (03/03)	[64872-77-1]	$168
1082504	Butorphanol Tartrate **CIV** (500 mg)	J			I (06/00)	[58786-99-5]	$224
1082708	Butylated Hydroxytoluene (500 mg) (AS)	F0D122	>99.0% (ai)			[128-37-0]	$168
1082800	Monotertiary-butyl-p-benzoquinone (100 mg) (FCC)	F				[3602-55-9]	$168
1082901	Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate (25 mg)	F-1				n/f	$526
1083008	2-*tert*-Butyl-4-hydroxyanisole (200 mg)	L0C028			K (09/03)	[88-32-4]	$168
1083100	3-*tert*-Butyl-4-hydroxyanisole (200 mg)				K0C239(02/07) J (03/05) I-1 (09/01)	[121-00-6]	$168
1084000	Butylparaben (200 mg)	I0C139			H-1 (03/04) H (09/01)	[94-26-8]	$168
1085003	Caffeine (200 mg)	J1D241	0.998 mg/mg (ai)		J (02/06) I (06/02)	[58-08-2]	$168
1086006	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)	K0D372			J0B204 (11/06) I (03/04)	[58-08-2]	$100
1086108	Calcifediol (75 mg)	G1E064	0.996 mg/mg (ai) (as monohydrate)		G (07/06)	[63283-36-3]	$526
1086301	Calcitriol (10 mg)	F0E062	0.993 mg/mg (ai)			[32222-06-3]	$1,352
1086312	Calcitriol Solution (5 mL)	F0D330	0.974 ug/mL			n/f	$208
1086334	Calcium Acetate (1 g) (AS)	F0D156	100.0% (an)			[62-54-4]	$168
1086356	Calcium Ascorbate (200 mg)	F-1			F (08/01)	[5743-28-2]	$168
1086403	Calcium Carbonate (1 g) (AS)	F0D099	99.1% (dr)			[471-34-1]	$168
1086436	Calcium Chloride (1 g) (AS)	F0D153	101.9% (ai)			[10035-04-8]	$168
1086800	Calcium Gluceptate (200 mg)	F-1			F (09/00)	[29039-00-7]	$168
1086855	Calcium Hydroxide (1 g) (AS)	F0D168	98.1% (ai)			[1305-62-0]	$168
1086888	Calcium Lactate (1 g)	F0D227				[63690-56-2]	$168
1086902	Calcium Lactobionate (200 mg)	G0B138			F-1 (01/04) F (11/01)	[110638-68-1]	$168
1086935	Calcium Levulinate (1 g) (AS)	F0E142	98.6% (dr)			[5743-49-7]	$168
1087009	Calcium Pantothenate (200 mg) (Vitamin B5)	O0C331	0.990 mg/mg (dr)		N-1 (06/05) N (06/00)	[137-08-6]	$168
1087031	Tribasic Calcium Phosphate (1 g) (AS)	F0D394	37.2 % Ca (ai)			[12167-74-7]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1087202	Calcium Saccharate (200 mg)	F				[5793-89-5]	$168
1087359	Calcium Stearate (2 g) (AS)	F0D255	9.8% CaO (ai)			[1592-23-0]	$168
1087406	Calcium Sulfate (1 g) (AS)	F0D236	100.0% (dr)			[10101-41-4]	$168
1087701	Candelilla Wax (250 mg)	F0D123				[8006-44-8]	$168
1088001	Candicidin (200 mg)	F				[1403-17-4]	$168
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2				[13956-29-1]	$526
1090003	Cannabinol **CI** (25 mg) (AS)				F-2 (05/02)	[521-35-7]	$224
1091006	Capreomycin Sulfate (250 mg)	G			F (06/01)	[1405-37-4]	$168
1091040	Caprylic Acid (300 mg)	F0D378				[124-07-2]	$168
1091505	Caprylocaproyl Polyoxylglycerides (200 mg)	F0C312				n/f	$189
1091108	Capsaicin (100 mg)	G2D136	0.985 mg/mg (dr)		G-1 (07/05) G (03/02) F-1 (06/00) F (03/99)	[404-86-4]	$168
1091200	Captopril (200 mg)	H				[62571-86-2]	$168
1091221	Captopril Disulfide (100 mg)	G1B066			G (01/04)	[64806-05-9]	$526
1092009	Carbachol (200 mg)	G1E010	1.000 mg/mg (dr)		G (07/06)	[51-83-2]	$168
1093001	Carbamazepine (100 mg)	K0E209	0.999 mg/mg (ai)		J (11/06) I-1 (02/00)	[298-46-4]	$168
1093205	Carbarsone (200 mg)	F				[121-59-5]	$168
1093500	Carbenicillin Indanyl Sodium (300 mg)	G				[26605-69-6]	$168
1094004	Carbenicillin Monosodium Monohydrate (200 mg)	G-2				n/f	$168
1095506	Carbidopa (400 mg)	I			H (10/99)	[38821-49-7]	$168
1095517	Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)	H0B121			G (04/03)	n/f	$526
1096000	Carbinoxamine Maleate (200 mg)	H			G-1 (11/02)	[3505-38-2]	$168
1096407	Carboplatin (100 mg)	H0C240			G (07/04) F (03/00)	[41575-94-4]	$172
1096509	Carboprost Tromethamine (25 mg)	F-1			F (02/01)	[58551-69-2]	$526
1096531	Carboxymethylcellulose Calcium (1.5 g) (AS)	F0D336				[9050-04-8]	$168
1096553	Carboxymethylcellulose Sodium (1.5 g)	F0D357				[9004-32-4]	$168
1096600	Carisoprodol (1 g)	G			F-2 (05/02)	[78-44-4]	$168
1096699	Carprofen (200 mg) (AS)	F0D335				[53716-49-7]	$168
1096757	Carteolol Hydrochloride (200 mg)	F-1			F (11/00)	[51781-21-6]	$168
1096779	Casticin (25 mg)	F0D358	0.99 mg/mg (ai)			[479-91-4]	$957
1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I				[76333-53-4]	$605
1096906	Cefaclor (400 mg)	I0E145	0.994 mg/mg HPLC (an) 1.000 mg/mg UV (an)		H (11/06)	[70356-03-5]	$168
1096917	Cefaclor, Delta-3-Isomer (30 mg)	G			F-1 (02/00)	n/f	$526
1097104	Cefadroxil (125 mg)	I1B319	935 ug/mg (ai)		I (01/05) H (04/99)	[66592-87-8]	$134
1097308	Cefamandole Lithium (200 mg)	H				n/f	$168
1097400	Cefamandole Nafate (200 mg)	H				[42540-40-9]	$168
1097501	Cefamandole Sodium (250 mg)	F				[30034-03-8]	$168
1097603	Cefazolin (400 mg)	L0C345			K (04/05) J (06/00)	[25953-19-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1097636	Cefepime Hydrochloride (500 mg)	G0D116	860 ug/mg (an)		F0C063 (06/05)	[123171-59-5]	$168
1097647	Cefepime Hydrochloride System Suitability (25 mg)	F0C095				n/f	$526
1097658	Cefixime (500 mg)	F				[79350-37-1]	$168
1097771	Cefmenoxime Hydrochloride (350 mg)	F				[75738-58-8]	$168
1097782	Cefmetazole (200 mg)	G0E260	0.988 mg/mg (ai)		F-1 (09/06) F (04/02)	[56796-20-4]	$168
1097750	Cefonicid Sodium (1 g)	H0D105	887 ug/mg (an)		G (06/05)	[61270-78-8]	$168
1097705	Cefoperazone Dihydrate (200 mg)	H			G (12/99)	[62893-19-0]	$168
1097807	Ceforanide (200 mg)	F-1			F (07/00)	[60925-61-3]	$168
1097909	Cefotaxime Sodium (250 mg)	J0C189	901 ug/mg (ai)		I (11/04)	[64485-93-4]	$134
1097975	Cefotetan (500 mg)	H0C175			G (07/04) F (09/00)	[69712-56-7]	$168
1098005	Cefotiam Hydrochloride (325 mg)	G0B050			F (01/03)	[66309-69-1]	$168
1098107	Cefoxitin (500 mg)	J0E038	0.992 mg/mg (an)		I (05/06) H (05/00)	[35607-66-0]	$168
1098118	Cefpiramide (300 mg)	F0C203				[70797-11-4]	$168
1098027	Cefpodoxime Proxetil (350 mg)	F0C192	736 ug/mg (an)			[87239-81-4]	$168
1098049	Cefprozil (E)-Isomer (50 mg)	G0D341	872 ug/mg (ai)		F2C284 (08/05) F-1 (10/04) F (05/01)	[92676-86-3]	$526
1098050	Cefprozil (Z)-Isomer (200 mg)	H0E054	927 ug/mg (ai)		G0C037(06/06) F (12/03)	[121412-77-9]	$168
1098129	Ceftazidime, Delta-3-Isomer (15 mg)	H0E106			G (06/06) F (03/00)	n/f	$526
1098130	Ceftazidime Pentahydrate (300 mg)	H			G (12/99)	[78439-06-2]	$168
1098173	Ceftizoxime (350 mg)	I0E262	0.999 mg/mg (an)		H (12/06)	[68401-81-0]	$168
1098184	Ceftriaxone Sodium (350 mg)	G1D265	925 ug/mg (an)		G0B264 (03/06) F (08/03)	[104376-79-6]	$168
1098195	Ceftriaxone Sodium E-Isomer (25 mg)	I0C190			H (07/04) G (08/01) F-1 (02/00)	n/f	$526
1098209	Cefuroxime Sodium (200 mg)	H			G-1 (05/00)	[56238-63-2]	$168
1098220	Cefuroxime Axetil (500 mg)	G			F-1 (05/02)	[64544-07-6]	$168
1098231	Cefuroxime Axetil Delta-3-Isomers (15 mg)	H1E186			H0B160 (09/06) G (03/03)	n/f	$526
1098322	Cellaburate (350 mg) (Cellulose Acetate Butyrate)	F0D220				[9004-36-8]	$168
1098300	Cellulose Acetate (125 mg)	F-1			F (11/99)	[9004-35-7]	$134
1098355	Cellulose Acetate Phthalate (125 mg)	F-1			F (03/99)	[9004-38-0]	$134
1098388	Microcrystalline Cellulose (1 g) (AS)	F0D362				[9004-34-6]	$168
1098402	Powdered Cellulose (1 g) (AS)	F0D364				[9004-34-6]	$168
1098708	Cephaeline Hydrobromide (200 mg)	G-1				n/f	$526
1099008	Cephalexin (400 mg)	J0D296	996 ug/mg (an)		I-2 (10/05) I-1 (03/00)	[23325-78-2]	$168
1102000	Cephalothin Sodium (200 mg)	I				[58-71-9]	$168
1102408	Cephapirin Benzathine (100 mg)	F				[97468-37-6]	$168
1102500	Cephapirin Sodium (200 mg)	I-1			I (07/02)	[24356-60-3]	$168
1102805	Cephradine (200 mg)	J			I (04/00)	[58456-86-3]	$168
1103003	Cetyl Alcohol (100 mg)	I1E065			I (07/06) H (03/99)	[36653-82-4]	$168
1103105	Cetyl Palmitate (50 mg)	F0B241				[540-10-3]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1104006	Cetylpyridinium Chloride (500 mg)	J0D299	1.000 mg/mg (an)		I (10/05) H-1 (06/01) H (08/99)	[6004-24-6]	$168
1105009	Powdered Chaste Tree Extract (1.5 g)	F0C406				[91722-47-3]	$563
1106001	Chlorambucil (125 mg) (FOR U.S. SALE ONLY)	G			F-1 (02/99)	[305-03-3]	$134
1107004	Chloramphenicol (200 mg)	N1C074			N (10/04) M (03/00)	[56-75-7]	$168
1107300	Chloramphenicol Palmitate (200 mg)	G-1				[530-43-8]	$168
1107401	Chloramphenicol Palmitate Nonpolymorph A (200 mg)	F-1				[530-43-8]	$526
1107503	Chloramphenicol Palmitate Polymorph A (100 mg)	G1D219			G (10/05) F (08/99)	[530-43-8]	$526
1109000	Chlordiazepoxide **CIV** (200 mg)	I0B063			H-1 (03/03)	[58-25-3]	$224
1110009	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4				[438-41-5]	$224
1110020	Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide)	G				[963-39-3]	$526
1111001	Chlorhexidine (200 mg)	F0C306				[55-56-1]	$168
1111103	Chlorhexidine Acetate (500 mg)	G0E008	0.996 mg/mg (an)		F0C281 (02/06)	[56-95-1]	$168
1111307	Chlorhexidine Related Compounds (50 mg)	F0D017				n/f	$526
1112503	Chlorobutanol (200 mg)	G1D301			G (09/05) F-3 (12/01)	[6001-64-5]	$168
1115545	Chlorogenic Acid (50 mg)	F0C420	0.97 mg/mg (ai)			[327-97-9]	$168
1115556	beta-Chlorogenin (20 mg)	F				n/f	$526
1496802	Parachlorophenol (500 mg)	F0E061	0.99 mg/mg (ai)			[106-48-9]	$168
1117008	Chloroprocaine Hydrochloride (200 mg)	G0B285			F-3 (01/04) F-2 (03/99)	[3858-89-7]	$168
1118000	Chloroquine Phosphate (500 mg)	I			H (10/99)	[50-63-5]	$168
1121005	Chlorothiazide (200 mg)	H1E231	0.992 mg/mg HPLC (dr) 1.000 mg/mg UV (dr)		H0B161 (11/06) G (04/03)	[58-94-6]	$168
1122008	Chlorotrianisene (1 g)	F				[569-57-3]	$168
1122700	Chloroxylenol (125 mg)	F2C259			F-1 (07/04) F (10/99)	[88-04-0]	$134
1122722	Chloroxylenol Related Compound A (25 mg) (2-chloro-3,5-dimethylphenol)	G0C275			F-1 (07/04)	[5538-41-0]	$526
1123000	Chlorpheniramine Maleate (125 mg)	M0B020			L-1 (06/03)	[113-92-8]	$134
1123102	Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) (60 Tablets)	G0B259			F (06/03)	[113-92-8]	$168
1124003	Chlorphenoxamine Hydrochloride (200 mg)	F-1				[562-09-4]	$168
1125006	Chlorpromazine Hydrochloride (200 mg)	J			I (04/99)	[69-09-0]	$168
1126009	Chlorpropamide (200 mg)	H				[94-20-2]	$168
1127001	Chlorprothixene (200 mg)	F-1				[113-59-7]	$168
1129007	Chlortetracycline Hydrochloride (200 mg)	K0C185	1008 ug/mg (ai)		J-1 (12/04) J (02/02)	[64-72-2]	$168
1130006	Chlorthalidone (200 mg)	I0C255			H-1 (11/04) H (07/99)	[77-36-1]	$168
1119309	Chlorthalidone Related Compound A (15 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid)	I0E270	0.99 mg/mg (ai)		H0D251 (12/06) G0C376 (09/05) F-3 (07/04)	n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1130505	Chlorzoxazone (500 mg)	I			H (07/01)	[95-25-0]	$168
1130527	Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol)	G-1			G (11/00)	[95-85-2]	$526
1131009	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157			L (10/03) K (09/99)	[67-97-0]	$172
1131803	Delta-4,6-cholestadienol (30 mg)	F				[14214-69-8]	$526
1132001	Cholesteryl Caprylate (200 mg)	F				[1182-42-9]	$168
1133004	Cholestyramine Resin (500 mg)	I				[11041-12-6]	$134
1133503	Cholic Acid (2 g) (AS)	F3B159			F-2 (01/03)	[81-25-4]	$168
1133536	Choline Bitartrate (200 mg)	F0C057				[87-67-2]	$168
1133547	Choline Chloride (200 mg)	F0C058				[67-48-1]	$168
1133570	Chondroitin Sulfate Sodium (300 mg)	G0E236	1.00 mg/mg (dr)		F0B256 (09/06)	[39455-18-0]	$168
1133638	Chromium Picolinate (100 mg)	F				[14639-25-9]	$168
1134007	Chymotrypsin (300 mg)	I			H (06/01)	[9004-07-3]	$168
1134018	Ciclopirox (50 mg)	F0E086				[29342-05-0]	$168
1134030	Ciclopirox Olamine (125 mg)	H0C207			G (05/03)	[41621-49-2]	$134
1134029	Ciclopirox Related Compound A (25 mg) (3-Cyclohexyl-4,5-dihydro-5-methyl-5-isoxazolyl acetic acid)	F0E087	1.00 mg/mg (ai)			n/f	$526
1134040	Ciclopirox Related Compound B (25 mg) (6-Cyclohexyl-4-methyl-2-pyrone)	F0E088	0.99 mg/mg (ai)			[14818-35-0]	$526
1134051	Cilastatin Ammonium Salt (100 mg)	G0C334	945 ug/mg (ai)		F-1 (05/05) F (07/00)	n/f	$168
1134062	Cimetidine (200 mg)	I1C081			I (05/04)	[51481-61-9]	$168
1134073	Cimetidine Hydrochloride (200 mg)	F				[70059-30-2]	$168
1134109	Cinoxacin (200 mg)	F				[28657-80-9]	$168
1134313	Ciprofloxacin (125 mg)				G-1 (02/07) G (05/01)	[85721-33-1]	$134
1134324	Ciprofloxacin Ethylenediamine Analog (25 mg)	J0A030			I (01/03) H-1 (02/99)	n/f	$526
1134335	Ciprofloxacin Hydrochloride (400 mg)	I0C265			H (02/05) G (04/00)	[86393-32-0]	$168
1134346	Ciprofloxacin Related Compound A (25 mg) (AS) (7-Chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride salt)	F0E333		1		n/f	$526
1134357	Cisplatin (100 mg)	H			G (03/01)	[15663-27-1]	$168
1134368	Citric Acid (200 mg)	F2E269	1.000 mg/mg (dr)		F1B092 (07/06) F-1 (01/04) F (07/02)	[77-92-9]	$168
1134379	Clarithromycin (75 mg)	G0D356	977 ug/mg (ai)		F4B183 (03/06) F-3 (01/04) F-2 (09/01)	[81103-11-9]	$168
1134390	Clarithromycin Identity (100 mg)	F0E141				[81103-11-9]	$526
1134380	Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A)	G			F (04/01)	n/f	$526
1134404	Clavam-2-carboxylate Potassium (1 Pellet)	H0C089			G0B225 (12/03) F (10/03)	n/f	$526
1134426	Clavulanate Lithium (200 mg)	I1C270	0.952 mg/mg (ai)		I (02/05) H (09/02)	n/f	$168
1134506	Clemastine Fumarate (250 mg)	J0C090	0.998 mg/mg (ai)		I (09/06) H (10/00)	[14976-57-9]	$168
1135000	Clidinium Bromide (2 g)	H0B115			G (03/05)	[3485-62-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1135021	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)	I				[76201-95-1]	$526
1136002	Clindamycin Hydrochloride (200 mg)	H0E044	867 ug/mg (ai)		G4A017 (07/06) G-3 (07/03) G-2 (05/99)	[58207-19-5]	$463
1137005	Clindamycin Palmitate Hydrochloride (500 mg)	G0D334	586 ug/mg (an)		F-2 (11/05)	[25507-04-4]	$463
1138008	Clindamycin Phosphate (125 mg)	I0C165			H-3 (04/04) H-2 (07/03) H-1 (02/99)	[24729-96-2]	$232
1138201	Clioquinol (500 mg)	N0E020	0.992 mg/mg (dr)		M (03/06) L-1 (01/03)	[130-26-7]	$168
1138405	Clobetasol Propionate (200 mg)	F2C309	980 ug/mg (ai)		F-1 (03/05) F (10/01)	[25122-46-7]	$168
1138427	Clobetasol Propionate Related Compound A (50 mg) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one])	F2C417			F-1 (12/05) F (01/03)	n/f	$526
1138507	Clocortolone Pivalate (200 mg)	G				[34097-16-0]	$168
1138904	Clofazimine (200 mg)	F				[2030-63-9]	$168
1139000	Clofibrate (1 g)	I			H (04/01)	[637-07-0]	$168
1140000	Clomiphene Citrate (500 mg)	I0E164	0.995 mg/mg (an) (HPLC) 1.000 mg/mg (an) (UV)		H (05/06) G-1 (10/99)	[50-41-9]	$168
1140101	Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine Hydrochloride)	F1B206			F (09/03)	n/f	$526
1140247	Clomipramine Hydrochloride (200 mg)	F0C075				[17321-77-6]	$168
1140305	Clonazepam **CIV** (200 mg)	H0E003	0.999 mg/mg (ai)		G1B175 (04/06) G (01/04) F-2 (01/00)	[1622-61-3]	$224
1140327	Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril)	G2B110			G-1 (01/04) G (02/99)	n/f	$526
1140338	Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone)	H			G (04/01)	[2011-66-7]	$526
1140349	Clonazepam Related Compound C (25 mg) (2-Bromo-2'-(2-chlorobenzoyl)-4'-nitroacetanilide)	F0C340				n/f	$526
1140393	Clonidine (200 mg)	F0C401				[4205-90-7]	$168
1140407	Clonidine Hydrochloride (200 mg)	H0D106	1.000 mg/mg (dr)		G (05/05)	[4205-91-8]	$168
1140418	Clonidine Related Compound A (25 mg) (Acetylclonidine)	F0C373				[54707-71-0]	$526
1140429	Clonidine Related Compound B (25 mg) (2-[(E)-2,6-Dichlorophenylimino]-1-(1-{2-[(E)-2,6-dichlorophenylimino]-imidazolidin-1-yl}-ethyl)-imidazolidine)	F0C403	0.99 mg/mg (ai)			n/f	$526
1140430	Clopidogrel Bisulfate (125 mg)	F0E115	0.995 mg/mg (ai)			[120202-66-6]	$753
1140586	Clopidogrel Related Compound A (20 mg) ((S)-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetic acid, hydrochloride)	F0E117	1.18 mg/mg (bisulfate salt equivalent) (ai)			[144750-42-5]	$640
1140597	Clopidogrel Related Compound B (20 mg) (Methyl(+/-)-(o-chlorophenyl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-acetate, hydrochloride)	F0E119	1.11 mg/mg (bisulfate salt equivalent) (ai)			[144750-52-7]	$640

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1140600	Clopidogrel Related Compound C (20 mg) (methyl (-)-(R)-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate, hydrogen sulfate)	F0E118	0.99 mg/mg (ai)			[120202-71-3]	$640
1140509	Clorazepate Dipotassium **CIV** (125 mg)	G0B027			F-1 (06/03) F (12/99)	[57109-90-7]	$224
1140702	Clorsulon (200 mg)	F1B084			F (01/04)	[60200-06-8]	$168
1141002	Clotrimazole (200 mg)	K0C282			J (02/05) I (05/99)	[23593-75-1]	$134
1141024	Clotrimazole Related Compound A (25 mg) ((o-chlorophenyl)diphenylmethanol)	I1D166	0.99 mg/mg (ai)		I (11/05) H (10/01) G-1 (02/99)	[66774-02-5]	$526
1141909	Cloxacillin Benzathine (200 mg)	F-1			F (03/02)	[23736-58-5]	$168
1142005	Cloxacillin Sodium (200 mg)	L0B086			K (01/04)	[7081-44-9]	$168
1142107	Clozapine (100 mg)	G0D315	1.000 mg/mg (dr)		F0C032 (11/05)	[5786-21-0]	$281
1143008	Cocaine Hydrochloride **CII** (250 mg)	I0B074			H-2 (01/04) H-1 (02/99)	[53-21-4]	$224
1145207	Cod Liver Oil (1 g)	F0D400				[8001-69-2]	$168
1143802	Codeine N-Oxide **CI** (50 mg)	G0A034			F-1 (11/02)	[3688-65-1]	$224
1144000	Codeine Phosphate **CII** (100 mg)	J0C200			I-1 (10/04) I (09/02) H-1 (01/00)	[41444-62-6]	$224
1145003	Codeine Sulfate **CII** (250 mg)	H-2			H-1 (01/02)	[6854-40-6]	$224
1146006	Colchicine (300 mg)	J			I (05/02)	[64-86-8]	$168
1146505	Colestipol Hydrochloride (200 mg)	F-1				[37296-80-3]	$168
1147009	Colistimethate Sodium (200 mg)	H1D234	0.420 mg/mg (dr)		H (09/05)	[8068-28-8]	$168
1148001	Colistin Sulfate (200 mg)	G-1			G (09/99)	[1264-72-8]	$168
1148500	Copovidone (100 mg)	F0C194				[2586-89-9]	$168
1148806	Corn Oil (1 g) (AS)	F0D181				[8001-30-7]	$168
1149004	Corticotropin (5.6 Units/vial; 5 vials)	M			L (06/99)	[9002-60-2]	$134
1150003	Cortisone Acetate (150 mg)	I				[50-04-4]	$168
1150207	Cottonseed Oil (1 g) (AS)	F0D173				[8001-29-4]	$168
1150353	Creatinine (100 mg)	F				[60-27-5]	$168
1150502	Cromolyn Sodium (500 mg)	J1E187	1.000 mg/mg (an)		J (11/06) I (06/00)	[15826-37-6]	$168
1150513	Cromolyn Sodium Related Compound A (25 mg) (1,3-Bis-(2-acetyl-3-hydroxyphenoxy)-2-propanol) (AS)	F0E045				[16150-44-0]	$526
1150706	Crospovidone (200 mg)	G1C273			G (12/04)	[9003-39-8]	$168
1151006	Crotamiton (200 mg)	H-1			H (07/00)	[483-63-6]	$168
1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N			M-3 (08/99)	[68-19-9]	$168
1152508	Cyclacillin (200 mg)	G				[3485-14-1]	$168
1152701	Cyclandelate (200 mg)	F0C384				[456-59-7]	$168
1154004	Cyclizine Hydrochloride (200 mg)	H0D321	1.000 mg/mg (dr)		G (10/05)	[303-25-3]	$168
1154503	Cyclobenzaprine Hydrochloride (200 mg)	G0A013			F-3 (07/03)	[6202-23-9]	$168
1154558	Alpha Cyclodextrin (50 mg)	F-1			F (10/00)	[10016-20-3]	$168
1154569	Beta Cyclodextrin (250 mg)	G			F-1 (12/02)	[7585-39-9]	$168
1154707	Cyclomethicone 4 (200 mg)	F-2			F-1 (06/02)	[69430-24-6]	$168
1154809	Cyclomethicone 5 (200 mg)	G0D052			F-2 (07/05) F-1 (09/99)	[69430-24-6]	$168
1154900	Cyclomethicone 6 (200 mg)	F2B024			F-1 (03/03)	[69430-24-6]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1156000	Cyclopentolate Hydrochloride (300 mg)	I0C424	0.999 mg/mg (dr)		H (03/05) G (04/00)	[5870-29-1]	$168
1157002	Cyclophosphamide (500 mg) (FOR U.S. SALE ONLY)	J1B200			J (02/05)	[6055-19-2]	$134
1157501	2-Cyclopropylmethylamino-5-chlorobenzophenone (50 mg)	F				n/f	$526
1158005	Cycloserine (200 mg)	G				[68-41-7]	$168
1158504	Cyclosporine (50 mg)	H-1			H (11/02) G-2 (03/00)	[59865-13-3]	$518
1158650	Cyclosporine Resolution Mixture (25 mg)	F				[108027-45-8] (U)	$445
1159008	Cyclothiazide (200 mg)	F-1				[2259-96-3]	$168
1161000	Cyproheptadine Hydrochloride (500 mg)	G			F-4 (11/02)	[41354-29-4]	$168
1161509	L-Cysteine Hydrochloride (200 mg)	H			G (05/00)	[7048-04-6]	$168
1162002	Cytarabine (250 mg)	G-2			G-1 (07/00)	[147-94-4]	$168
1162148	Cytosine (100 mg)	F0E284	1.00 mg/mg (dr)			[71-30-7]	$168
1162308	Dacarbazine (125 mg)	H			G (01/99)	[4342-03-4]	$134
1162320	Dacarbazine Related Compound A (50 mg) (5-aminoimidazole-4-carboxamide Hydrochloride)	H0C052			G (03/04) F (03/00)	[72-40-2]	$526
1162330	Dacarbazine Related Compound B (50 mg) (2-azahypoxanthine)	G0C325			F-1 (03/05) F (12/01)	[63907-29-9]	$649
1162400	Dactinomycin (50 mg)	I				[50-76-0]	$462
1162501	Danazol (200 mg)	H			G (10/00)	[17230-88-5]	$168
1164008	Dapsone (125 mg)	H0D260	0.998 mg/mg (dr)		G-3 (02/06) G-2 (08/99)	[80-08-0]	$134
1164700	Daunorubicin Hydrochloride (200 mg)	L0B307			K (11/03) J (08/00)	[23541-50-6]	$518
1165000	Decamethonium Bromide (250 mg)	F				[541-22-0]	$168
1166003	Deferoxamine Mesylate (500 mg)	I				[138-14-7]	$168
1166309	Dehydroacetic Acid (200 mg)	F				[520-45-6]	$168
1166400	Dehydrocarteolol Hydrochloride (100 mg)	F				n/f	$526
1166502	Dehydrocholic Acid (200 mg)	F-1			F (03/04)	[81-23-2]	$168
1169001	Demecarium Bromide (250 mg)	F				[56-94-0]	$168
1170000	Demeclocycline Hydrochloride (200 mg)	H1C036			H (08/04)G-1 (08/01)	[64-73-3]	$168
1046089	N-Demethylazithromycin (15 mg)	F0E068	0.92 mg/mg (ai)			n/f	$526
1171003	Denatonium Benzoate (200 mg)	I0B129			H (09/02)	[86398-53-0]	$168
1171251	2-Deoxy-D-Glucose (100 mg) (AS)	F0E006				[154-17-6]	$177
1171706	Desacetyl Diltiazem Hydrochloride (50 mg)	J0C143	1.00 mg/mg (ai)		I (07/05) H (08/00)	[23515-45-9]	$526
1171900	Desflurane (0.5 mL)	F0C187				[57041-67-5]	$168
1171910	Desflurane Related Compound A (0.1 mL) (bis-(1,2,2,2-tetrafluoroethyl) ether)	F0C031				n/f	$526
1172006	Desipramine Hydrochloride (125 mg)	I0E283	1.000 mg/mg (dr)		H-1 (11/06) H (10/99)	[58-28-6]	$134
1173009	Deslanoside (100 mg)	H-1				[17598-65-1]	$168
1173235	Desogestrel (50 mg)	G0C390			F0B282 (11/04)	[54024-22-5]	$168
1173246	Desogestrel Related Compound A (15 mg) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17alpha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer)	F0B279				n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1173257	Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel)	F0B284				n/f	$526
1173268	Desogestrel Related Compound C (25 mg) (3-Keto-desogestrel)	F0B281				[54048-10-1]	$526
1046078	Desosaminylazithromycin (15 mg)	F0E067	0.99 mg/mg (ai)			n/f	$526
1173508	Desoximetasone (200 mg)	H0B036			G (01/04)	[382-67-2]	$168
1174001	Desoxycorticosterone Acetate (200 mg)	J0C014			I (01/04) H (05/00)	[56-47-3]	$168
1175004	Desoxycorticosterone Pivalate (125 mg)	H0C276			G (01/04)	[808-48-0]	$134
1176007	Dexamethasone (125 mg)	J				[50-02-2]	$134
1176506	Dexamethasone Acetate (200 mg)	H0E339	0.996 mg/mg (dr)	2	G (12/06) F-1 (06/99)	[1177-87-3]	$168
1177000	Dexamethasone Phosphate (200 mg)	K0E275	0.996 mg/mg (dr)	2	J1B070 (01/07) J (08/03) I (03/00)	[312-93-6]	$168
1178002	Dexbrompheniramine Maleate (200 mg)	J			I (03/03)	[2391-03-9]	$168
1179005	Dexchlorpheniramine Maleate (300 mg)	H0D199	0.999 mg/mg (ai)		G1A025 (11/05) G (12/02)	[2438-32-6]	$168
1179504	Dexpanthenol (500 mg)	J0C293			I (08/04) H (02/02)	[81-13-0]	$173
1179628	Dextran 1 (50 mg)	F0D297				[9004-54-0]	$173
1179708	Dextran 40 (50 mg)	F0C247				[9004-54-0]	$168
1179741	Dextran 70 (50 mg)	F0C260				[9004-54-0]	$168
1179854	Dextran 4 Calibration (100 mg)	F0C002				[9004-54-0]	$168
1179865	Dextran 10 Calibration (100 mg)	F0C010				[9004-54-0]	$168
1179876	Dextran 40 Calibration (100 mg)	F0C011				[9004-54-0]	$168
1179720	Dextran 40 System Suitability (200 mg)	F0B181				[9004-54-0]	$168
1179887	Dextran 70 Calibration (100 mg)	F0C013				[9004-54-0]	$168
1179763	Dextran 70 System Suitability (200 mg)	F0B182				[9004-54-0]	$168
1179898	Dextran 250 Calibration (100 mg)	F0C039				[9004-54-0]	$168
1179650	Dextran T-10 (200 mg)	F0D238	1.000 mg/mg (dr)			[9004-54-0]	$168
1179800	Dextran Vo Marker (100 mg)	F0B242				[9004-54-0]	$168
1180004	Dextroamphetamine Sulfate **CII** (500 mg)	I0C311	1.000 mg/mg (dr)		H (05/05) G (08/03) F-6 (12/99)	[51-63-8]	$234
1180503	Dextromethorphan (2 g)	H			G (06/00)	[125-71-3]	$526
1181007	Dextromethorphan Hydrobromide (500 mg)	J0B167			I (07/03)	[6700-34-1]	$168
1181302	Dextrose (500 mg)	J-1			J (11/02) I (08/99)	[50-99-7]	$134
1181506	Diacetylated Monoglycerides (200 mg)	G				[68990-54-5]	$168
1182000	Diacetylfluorescein (200 mg)	H			G (01/02)	[596-09-8]	$168
1183002	Diacetylmorphine Hydrochloride **CI** (25 mg) (AS) (Heroin Hydrochloride)	J			I-1 (10/99)	[1502-95-0]	$224
1184005	Diatrizoic Acid (100 mg)	H0E084			G (04/06)	[50978-11-5]	$168
1184027	Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid)	I			H (02/00)	[1713-07-1]	$526
1185008	Diazepam **CIV** (100 mg)	I1C364	0.999 mg/mg (ai)		I (02/06) H (12/01)	[439-14-5]	$224
1185020	Diazepam Related Compound A (25 mg) (2-Methyl-amino-5-chlorobenzophenone)	I			H-1 (11/02) H (04/00)	[1022-13-5]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1023403	Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril)	I1C102			I (12/04) H (04/01)	[5220-02-0]	$526
1186000	Diazoxide (200 mg)	G1C017			G (12/03)	[364-98-7]	$168
1187003	Dibucaine Hydrochloride (200 mg)	I			H-2 (01/03)	[61-12-1]	$168
1187080	Dibutyl Phthalate (200 mg)	F0D125				[84-74-2]	$168
1187091	Dibutyl Sebacate (1 mL) (AS)	F0D128	99.2% (ai)			[109-43-3]	$168
1187207	Dichloralphenazone **CIV** (200 mg)	F0B010				[480-30-8]	$224
1187954	2,4-Dichlorophenol (100 mg)	F0E113	0.99 mg/mg (ai)			[120-83-2]	$168
1188006	Dichlorphenamide (200 mg)	G-1				[120-97-8]	$168
1188301	Dichlorvos (150 mg) (2,2-dichlorovinyl dimethyl phosphate) (AS)	F0D141				[62-73-7]	$173
1188800	Diclofenac Sodium (200 mg)	H0B150			G-1 (03/04) G (05/01)	[15307-79-6]	$168
1188811	Diclofenac Related Compound A (50 mg) (N-(2,6-dichlorophenyl)indolin-2-one)	I0D337	1.00 mg/mg (ai)		H (06/06) G (05/02)	[15362-40-0]	$530
1189009	Dicloxacillin Sodium (500 mg)	J0C182			I0B142 (09/04) H (05/03)	[13412-64-1]	$168
1190008	Dicumarol (200 mg)	G				[66-76-2]	$168
1191000	Dicyclomine Hydrochloride (125 mg)	H			G (03/99)	[67-92-5]	$134
1192003	Dienestrol (125 mg)	I				[84-17-3]	$134
1192808	Diethanolamine (3 mL)	F0D118				[111-42-2]	$168
1193006	Diethylcarbamazine Citrate (200 mg)	G-1				[1642-54-2]	$168
1193301	Diethylene Glycol Monoethyl Ether (0.5 mL/ampule)	G0C159			F0B095 (09/06)	[111-90-0]	$168
1193505	Diethyl Phthalate (200 mg)	G			F-1 (03/00)	[84-66-2]	$168
1194009	Diethylpropion Hydrochloride **CIV** (200 mg)	H				[134-80-5]	$224
1195001	Diethylstilbestrol (200 mg)	K5B291			K-4 (05/04)	[56-53-1]	$168
1197007	Diethyltoluamide (3 g)	H1D076	0.981 mg/mg (an)		H (11/06)	[134-62-3]	$134
1197302	Diflorasone Diacetate (200 mg)	G			F-1 (03/00)	[33564-31-7]	$168
1197506	Diflunisal (200 mg)	G				[22494-42-4]	$168
1198000	Digitalis (3 g)	F				[8031-42-3]	$168
1199002	Digitoxin (200 mg)	M				[71-63-6]	$168
1200000	Digoxin (250 mg)	O0B096			N-1 (04/03)	[20830-75-5]	$168
1200600	Dihydrocapsaicin (25 mg)	G0C071			F-1 (12/03) F (01/00)	[19408-84-5]	$281
1200804	Dihydrocodeine Bitartrate **CII** (200 mg)	I0D205	0.997 mg/mg (dr)		H (09/05) G (03/01)	[5965-13-9]	$224
1201002	17alpha-Dihydroequilin (50 mg)	I0C277			H (07/04)	[6639-99-2]	$225
1202005	Dihydroergotamine Mesylate (250 mg) **(List Chemical)**	J0B085			I (03/03)	[6190-39-2]	$168
1203008	Dihydrostreptomycin Sulfate (200 mg)	J				[5490-27-7]	$168
1204000	Dihydrotachysterol (30 mg/ampule; 4 ampules)	J0D250	0.996 mg/mg (ai)		I (06/05)	[67-96-9]	$168
1204102	Dihydroxyacetone (250 mg)	F				[96-26-4]	$168
1204805	Diloxanide Furoate (200 mg)	F0C026				[3736-81-0]	$168
1205003	Diltiazem Hydrochloride (200 mg)	I				[33286-22-5]	$168
1206006	Dimenhydrinate (100 mg)	J0B055			I (06/03)	[523-87-5]	$168
1208001	Dimethisoquin Hydrochloride (2 g)	G				[2773-92-4]	$168
1210105	N-(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS)	F				[41992-23-8]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1211006	Dimethyl Sulfoxide (3 g)	H0D273	0.999 mg/mg (ai)		G0C198 (10/06) F-3 (07/04) F-2 (05/02)	[67-68-5]	$225
1213001	Dinoprost Tromethamine (50 mg)	F				[38562-01-5]	$1,649
1213103	Dinoprostone (50 mg)	F0C030				[363-24-6]	$1,649
1214004	Dioxybenzone (150 mg)	F1B277			F (10/03)	[131-53-3]	$168
1217909	Diphenhydramine Citrate (125 mg)	H1C350	1.000 mg/mg (dr)		H0B128 (08/06) G (04/03)	[88637-37-0]	$134
1218005	Diphenhydramine Hydrochloride (200 mg)	J0B013			I (07/03)	[147-24-0]	$168
1219008	Diphenoxylate Hydrochloride **CII** (200 mg)	I1D339	0.998 mg/mg (dr)		I (08/06) H (03/02)	[3810-80-8]	$224
1220302	Dipivefrin Hydrochloride (200 mg)	I			H (06/99)	[64019-93-8]	$168
1220506	Dipyridamole (200 mg)	H			G-1 (01/99)	[58-32-2]	$168
1220700	Dirithromycin (200 mg)	F				[62013-04-1]	$168
1221000	Disodium Guanylate (300 mg) (FCC)	F-1				[5550-12-9]	$168
1222002	Disodium Inosinate (500 mg) (FCC)	F				[4691-65-0]	$168
1222501	Disopyramide Phosphate (200 mg)	H-1			H (03/02)	[22059-60-5]	$168
1223005	2,4-Disulfamyl-5-trifluoromethylaniline (125 mg)	G				[654-62-6]	$526
1224008	Disulfiram (200 mg)	F-3			F-2 (07/02)	[97-77-8]	$168
1224507	Dobutamine Hydrochloride (600 mg)	H-1			H (01/00)	[49745-95-1]	$168
1224700	Docusate Calcium (500 mg)	H0B044			G-1 (07/02)	[128-49-4]	$168
1224802	Docusate Sodium (500 mg)	K0D134	0.988mg/mg (an)		J (09/05) I-1 (05/02)	[577-11-7]	$168
1224904	Docusate Potassium (100 mg)	F-1			F (11/99)	[7491-09-0]	$168
1224959	Dolasetron Mesylate (200 mg)	F0C319				[115956-13-3]	$168
1224960	Dolasetron Mesylate Related Compound A (25 mg) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride)	F0C321				n/f	$526
1225204	Dopamine Hydrochloride (200 mg)	G			F-5 (05/02)	[62-31-7]	$168
1225281	Dorzolamide Hydrochloride (200 mg)	G0E278	0.998 mg/mg (ai)		F0C040 (11/06)	[130693-82-2]	$168
1225292	Dorzolamide Hydrochloride Related Compound A (20 mg) ((4R,6R)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide, monohydrochloride)	G0E029			F0C068 (12/05)	n/f	$526
1225000	Doxapram Hydrochloride (200 mg)	F4C053			F-3 (07/04)	[7081-53-0]	$168
1225419	Doxazosin Mesylate (200 mg)	G0E173	0.997 mg/mg (ai)		F0C079 (08/06)	[77883-43-3]	$168
1225500	Doxepin Hydrochloride (500 mg)	I				[1229-29-4]	$168
1225703	Doxorubicin Hydrochloride (50 mg)	K			J (06/02)	[25316-40-9]	$518
1226003	Doxycycline Hyclate (200 mg)	J0E174	859 ug/mg (ai) (chromatographic) 864 ug/mg (ai) (spectroscopic)		I (09/06) H (01/00)	[24390-14-5]	$168
1227006	Doxylamine Succinate (300 mg)	I0B266			H (01/04)	[562-10-7]	$168
1229001	Droperidol (250 mg)	I0C029			H-1 (01/05) H (04/99)	[548-73-2]	$168
1230000	Dyclonine Hydrochloride (200 mg)	G				[536-43-6]	$168
1231003	Dydrogesterone (200 mg)	I0B114			H (01/04)	[152-62-5]	$168
1231502	Dyphylline (200 mg)	G-2			G-1 (11/02)	[479-18-5]	$168
1231728	Powdered Echinacea Purpurea Extract (1 g)	F0D018				[90028-20-9]	$563
1231706	Powdered Echinacea Angustifolia Extract (1 g)	F0D019				[84696-11-7]	$563
1231808	Econazole Nitrate (200 mg)	G1C346	1.00 mg/mg (ai)		G (07/05)	[68797-31-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1232006	Edetate Calcium Disodium (200 mg)	H0B272			G-3 (11/04) G-2 (11/99)	[23411-34-9]	$168
1233009	Edetate Disodium (200 mg)	I0D405			H (06/06) G-2 (04/02)	[6381-92-6]	$168
1233508	Edetic Acid (200 mg)	F-1				[60-00-4]	$168
1234001	Edrophonium Chloride (200 mg)	H			G (08/99)	[116-38-1]	$168
1234704	Powdered Eleuthero Extract (1.5 g)	F0C291				[84696-12-5]	$563
1234668	Eleutheroside B (15 mg) (Syringin)	F0E056	95% (ai)			[118-34-3]	$884
1234680	Eleutheroside E (15 mg) (Syringaresinol diglucoside)	F0E057	98% (ai)			[96038-87-8]	$884
1234806	Emedastine Difumarate (100 mg)	F0C059				[87233-62-3]	$168
1235004	Emetine Hydrochloride (300 mg)	H0B201			G (05/03)	[316-42-7]	$168
1235274	Enalaprilat (300 mg)	J0C268			I (11/04) H (03/01) G (08/99)	[84680-54-6]	$134
1235300	Enalapril Maleate (200 mg)	J1C267	0.992 mg/mg (ai)		J (05/05) I (06/01)	[76095-16-4]	$168
1235503	Endotoxin (10,000 USP Endotoxin Units)	G3E069			G2B274 (06/06) G-1 (12/03) G (06/99)	n/f	$168
1235809	Enflurane (1 mL)	G-1			G (02/01)	[13838-16-9]	$168
1235900	Enrofloxacin (200 mg) (AS)	F0E094				[93106-60-6]	$168
1236007	Ephedrine Sulfate (200 mg) **(List Chemical)**	H-2			H-1 (11/02)	[134-72-5]	$168
1236506	4-Epianhydrotetracycline Hydrochloride (50 mg)	J0C041			I-1 (12/03) I (06/00)	[4465-65-0]	$526
1236801	Epilactose (200 mg)	H0E049	1.00 mg/mg (dr)		G (08/06) F-1 (06/00)	[50468-56-9]	$526
1237000	Epinephrine Bitartrate (200 mg)	O				[51-42-3]	$168
1237509	Epitetracycline Hydrochloride (200 mg) (AS)	G0E261			F (12/06)	[23313-80-6]	$526
1238002	Equilin (25 mg)	I1B290			I (11/04) H-1 (05/00)	[474-86-2]	$225
1239005	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275			O (02/04) N (12/99)	[50-14-6]	$182
1239504	Ergoloid Mesylates (300 mg)	I			H-1 (01/00)	[8067-24-1]	$168
1240004	Ergonovine Maleate (100 mg) **(List Chemical)**	N			M-1 (07/02)	[129-51-1]	$168
1241007	Ergosterol (50 mg)	H				[57-87-4]	$168
1241506	Ergotamine Tartrate (150 mg) **(List Chemical)**	I0B174			H (01/04)	[379-79-3]	$168
1241550	Ergotaminine (100 mg) **(List Chemical)**	G0B177			F-1 (06/04)	[639-81-6]	$168
1241903	Erythritol (200 mg)	F0E313				[149-32-6]	$168
1242000	Erythromycin (250 mg)	M1E251	96.7% Erythromycin A 978 ug/mg (ai) (microbial)	2	M (02/07) L (08/99)	[114-07-8]	$168
1242010	Erythromycin B (150 mg)	G1C080			G (11/04) F-1 (09/01) F (05/01)	[527-75-3]	$168
1242021	Erythromycin C (50 mg)	F-3			F-2 (01/03) F-1 (02/02) F (02/99)	n/f	$526
1242032	Erythromycin Related Compound N (50 mg) (N-Demethylerythromycin A)	F2A023			F-1 (06/04) F (09/99)	n/f	$526
1243002	Erythromycin Estolate (200 mg)	H			G (01/03)	[3521-62-8]	$168
1245008	Erythromycin Ethylsuccinate (200 mg)	H			G-1 (06/01)	[1264-62-6]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1246000	Erythromycin Gluceptate (200 mg)	H			G (07/03)	[23067-13-2]	$168
1247003	Erythromycin Lactobionate (200 mg)	H-1			H (01/02)	[3847-29-8]	$168
1248006	Erythromycin Stearate (200 mg)	H0B187			G-1 (05/03)	[643-22-1]	$168
1249009	Erythrosine Sodium (100 mg)	F				[49746-10-3]	$168
1250008	Estradiol (500 mg)	L0C337	0.996 mg/mg (an)		K1B007 (07/05) K (04/03)	[50-28-2]	$168
1251000	Estradiol Benzoate (250 mg) (AS)	H0C332			G-1 (01/06)	[50-50-0]	$168
1252003	Estradiol Cypionate (200 mg)	G-1			G (02/00)	[313-06-4]	$168
1254009	Estradiol Valerate (100 mg)	L1D286	0.996 mg/mg (ai)		L (04/06) K (05/02)	[979-32-8]	$168
1254508	Estriol (100 mg)	J			I-1 (06/01)	[50-27-1]	$168
1255001	Estrone (200 mg)	K1B099			K (07/03) J-1 (07/00)	[53-16-7]	$168
1255500	Estropipate (500 mg)	J0B262			I (12/03) H (09/01)	[7280-37-7]	$168
1256004	Ethacrynic Acid (200 mg)	F				[58-54-8]	$168
1257007	Ethambutol Hydrochloride (200 mg)	H			G (08/02)	[1070-11-7]	$168
1258305	Ethchlorvynol **CIV** (0.7 ml)	F0B011				[113-18-8]	$224
1260001	Ethinyl Estradiol (150 mg)	Q0C162			P1B193 (11/04) P0B052 (01/04) P (03/03) O (08/99)	[57-63-6]	$168
1260012	Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol)	F0B252				n/f	$526
1261004	Ethionamide (200 mg)	H0B148			G (03/03)	[536-33-4]	$168
1262801	Ethopabate (125 mg)	F				[59-06-3]	$168
1262823	Ethopabate Related Compound A (25 mg) (Methyl-4-acetamido-2-hydroxybenzoate)	F				n/f	$526
1263000	Ethopropazine Hydrochloride (300 mg)	G				[1094-08-2]	$168
1264002	Ethosuximide (125 mg)	H			G-2 (11/01) G-1 (05/99)	[77-67-8]	$134
1264501	Ethotoin (200 mg)	F				[86-35-1]	$168
1265005	Ethoxzolamide (200 mg)	F				[452-35-7]	$168
1265504	Ethylcellulose (1 g)	H-1			H (06/99)	[9004-57-3]	$168
1266008	Ethyl Maltol (1 g) (FCC)	H				[4940-11-8]	$168
1266507	Ethylnorepinephrine Hydrochloride (200 mg)	F				[3198-07-0]	$168
1267000	Ethylparaben (200 mg)	I0A016			H (01/04)	[120-47-8]	$168
1267500	Ethyl Vanillin (200 mg)	F2B134			F-1 (04/04)	[121-32-4]	$168
1268003	Ethynodiol Diacetate (200 mg)	I0A033			H-1 (01/03) H (04/01)	[297-76-7]	$168
1268502	Etidronate Disodium (200 mg)	G			F-2 (02/03)	[7414-83-7]	$168
1268513	Etidronate Disodium Related Compound A (300 mg) (Sodium phosphite dibasic pentahydrate)	F0E227	1.00 mg/mg (an)			[13517-23-2]	$526
1268604	Etidronic Acid Monohydrate (1 g)	G			F-1 (05/99)	[2809-21-4]	$168
1268706	Etodolac (400 mg)	G			F (10/01)	[41340-25-4]	$168
1268728	Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9-tetrahydropyrano [3,4-b]-indole-1-acetic acid)	F-1			F (05/02)	[109518-50-5]	$526
1268808	Etoposide (300 mg)	H0C315			G (11/04)	[33419-42-0]	$134
1268852	Etoposide Resolution Mixture (30 mg)	F0B209				[33419-42-0]	$526
1268965	Eugenol (500 mg) (AS)	F0D303				[97-53-0]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1269200	Famotidine (125 mg)	I0E063	0.997 mg/mg (dr)		H-1 (06/06) H (11/02) G (03/99)	[76824-35-6]	$134
1269389	Felodipine (200 mg)	G0D065	0.999 mg/mg (ai)		F-1 (04/05) F (09/02)	[72509-76-3]	$168
1269390	Felodipine Related Compound A (100 mg) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate)	F0B207				[96302-71-7]	$526
1269403	Fenbendazole (100 mg)	F				[43210-67-9]	$526
1269414	Fenbendazole Related Compound A (30 mg) (Methyl (1H-benzimidazole-2-yl)carbamate)	F0D009	0.99 mg/mg (ai)			[10605-21-7]	$526
1269425	Fenbendazole Related Compound B (30 mg) (Methyl [5(6)-chlorobenzimidazole-2-yl]carbamate)	F0D008	0.99 mg/mg (ai)			n/f	$526
1269458	Fenoldopam Mesylate (200 mg)	F0C125				[67227-57-0]	$168
1269469	Fenoldopam Related Compound A (20 mg) (N-Methyl-6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol hydrochloride)	F0C124		3		n/f	$526
1269470	Fenoldopam Related Compound B (20 mg) (1H-3-Benzazapine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate)	F0C126				n/f	$526
1269505	Fenoprofen Calcium (500 mg)	G-1				[53746-45-5]	$168
1269550	Fenoprofen Sodium (500 mg)	G			F-1 (05/02)	[66424-46-2]	$168
1270355	Ferrous Sulfate (1.5 g) (AS)	F0D196	101.0% (ai)			[7782-63-0]	$168
1270005	Fentanyl Citrate **CII** (100 mg)	K0C264			J2B227 (11/04) J-1 (09/03) J (05/02) I (06/00)	[990-73-8]	$260
1270377	Fexofenadine Hydrochloride (200 mg)	F1E289	0.996 mg/mg (ai)	2	F0D244 (02/07)	[138452-21-8]	$168
1270388	Fexofenadine Related Compound A (25 mg) (4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-alpha,alpha-dimethyl benzeneacetic acid)	F0D245	0.99 mg/mg (ai)			n/f	$526
1270399	Fexofenadine Related Compound B (25 mg) (3-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-alpha,alpha-dimethyl benzeneacetic acid hydrochloride)	F0D246				n/f	$526
1270446	Fexofenadine Related Compound C (15 mg) ((+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene) (AS)	F0E291				n/f	$526
1270402	Finasteride (200 mg)	F1E139	0.997 mg/mg (ai)		F (07/06)	[98319-26-7]	$168
1270800	Flecainide Acetate (200 mg)	F2A022			F-1 (02/05) F (06/03)	[54143-56-5]	$168
1270821	Flecainide Related Compound A (75 mg) (3-[2,5-bis(2,2,2-trifluoroethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride)	F				n/f	$526
1271008	Floxuridine (250 mg)	F-2			F-1 (08/01)	[50-91-9]	$168
1271700	Fluconazole (200 mg)	F0D262	1.00 mg/mg (ai)			[86386-73-4]	$168
1271711	Fluconazole Related Compound A (10 mg) (2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D080	0.95 mg/mg (ai)			n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1271722	Fluconazole Related Compound B (10 mg) (2-(4-fluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D081	0.92 mg/mg (ai)			[81886-51-3]	$526
1271733	Fluconazole Related Compound C (10 mg) (1,1'-(1,3-phenylene)di(1H-1,2,4-triazole))	F0D082	0.98 mg/mg (ai)			n/f	$526
1272000	Flucytosine (200 mg)	G0E151	1.000 mg/mg (dr)		F (06/05)	[2022-85-7]	$168
1272204	Fludarabine Phosphate (300 mg)	F0C374				[75607-67-9]	$168
1272907	Fludeoxyglucose (100 mg)	F0E100				[29702-43-0]	$208
1272918	Fludeoxyglucose Related Compound A (15 mg) (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane)	F0D119	1.00 mg/mg (ai)			[23978-09-8]	$578
1273003	Fludrocortisone Acetate (250 mg)	H			G (08/01)	[514-36-3]	$168
1273808	Flumazenil (200 mg)	F0C305				[78755-81-4]	$843
1273819	Flumazenil Related Compound A (20 mg) (8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazol-[1,5-alpha][1,4]benzodiazepine-3-carboxylic acid)	F0E147				n/f	$675
1273820	Flumazenil Related Compound B (20 mg) (Ethyl 8-hydroxy-5,6-dihydro-5-methyl-6-oxo-4H-imidazol-[1,5-alpha][1,4]benzodiazepine-3-carboxylate)	F0E148				n/f	$675
1274006	Flumethasone Pivalate (200 mg)	I			H (01/02)	[2002-29-1]	$168
1274505	Flunisolide (200 mg)	I			H (01/01)	[77326-96-6]	$168
1274607	Flunixin Meglumine (300 mg)	H0E241	1.000 mg/mg (dr)		G (11/06) F-1 (04/02) F (09/99)	[42461-84-7]	$168
1275009	Fluocinolone Acetonide (100 mg)	J1E014	0.993 mg/mg (dr)		J (03/06) I (11/99)	[67-73-2]	$168
1276001	Fluocinonide (100 mg)	I				[356-12-7]	$168
1277004	Fluorescein (200 mg)	G0B171			F-1 (02/03)	[2321-07-5]	$168
1277252	Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz)	J0C294			I (08/04) H (04/99)	n/f	$495
1277274	Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz)	G0D270			F (06/05)	n/f	$526
1277300	Fluoride Dentifrice: Sodium Monofluorophosphate-Calcium Carbonate (4.6 oz)	G				n/f	$526
1277354	Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz)	G				n/f	$526
1277401	Fluoride Dentifrice: Sodium Monofluorophosphate (1000 ppm)/Silica (5.25 oz)	G-1			G (08/99)	n/f	$526
1277423	Fluoride Dentifrice: Sodium Monofluorophosphate (1500 ppm)/Silica (5.25 oz)	F-1			F (07/99)	n/f	$526
1277456	Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz)	H0B105			G (11/02)	n/f	$526
1278007	Fluorometholone (200 mg)	I0B184			H-1 (11/02)	[426-13-1]	$168
1278109	Fluorometholone Acetate (200 mg)	F				[3801-06-7]	$168
1278302	Fluoroquinolonic Acid (50 mg)	H0C140			G (01/05) F-1 (12/99)	[86393-33-1]	$526
1279000	Fluorouracil (250 mg)	H2D190	1.000 mg/mg (dr)		H-1 (09/05) H (01/02)	[51-21-8]	$168
1279804	Fluoxetine Hydrochloride (200 mg)	F2C132			F-1 (02/05) F (11/99)	[59333-67-4]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1279815	Fluoxetine Related Compound A (15 mg) (N-methyl-3-phenyl-3-[(alpha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride)	H0C131			G (06/04) F-1 (05/01) F (06/00)	n/f	$526
1279826	Fluoxetine Related Compound B (5 mL of a 0.01N HCl solution, approx. 2 mg/mL) (N-methyl-3-phenylpropylamine)	G0D023	approx. 2 mg/mL (ai)		F3C085 (05/05) F-2 (06/04) F-1 (09/02) F (09/00)	[23580-89-4]	$526
1279837	Fluoxetine Related Compound C (15 mg) (N-Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid)	F0C352				n/f	$526
1280009	Fluoxymesterone **CIII** (200 mg)	G-2			G-1 (04/00)	[76-43-7]	$224
1280803	Fluphenazine Decanoate Dihydrochloride (500 mg)	G			F-1 (10/01)	n/f	$172
1281001	Fluphenazine Enanthate Dihydrochloride (125 mg)	H			G (02/99)	[3105-68-8]	$134
1282004	Fluphenazine Hydrochloride (125 mg)	H				[146-56-5]	$134
1284000	Flurandrenolide (100 mg)	I0B245			H (09/03)	[1524-88-5]	$168
1285002	Flurazepam Hydrochloride **CIV** (200 mg)	J0C365	0.996 mg/mg (ai)		I (09/03)	[1172-18-5]	$224
1285308	Flurazepam Related Compound C (50 mg) (5-chloro-2-(2-diethylaminoethylamino)-2'-fluorobenzophenone Hydrochloride)	I0D361	1.00 mg/mg (ai)		H-1 (40/06)	n/f	$526
1285603	Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one)	I0C092			H (01/04)	[2886-65-9]	$526
1285750	Flurbiprofen (200 mg)	H0D349	0.994 mg/mg (ai)		G (01/06)	[5104-49-4]	$168
1285760	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)	H			G (03/01)	n/f	$526
1285807	Flurbiprofen Sodium (200 mg)	F				[56767-76-1]	$168
1285851	Flutamide (200 mg)	H0B278			G (11/04) F-1 (06/00)	[13311-84-7]	$168
1285862	o-Flutamide (50 mg)	F-1			F (01/00)	n/f	$526
1285873	Fluticasone Propionate (100 mg)	F0F036	0.989 mg/mg (ai)	1		[80474-14-2]	$832
1285884	Fluticasone Propionate Resolution Mixture (25 mg)	F0E123				n/f	$675
1285895	Fluticasone Propionate System Suitability Mixture (25 mg) (Fluticasone Propionate and Fluticasone Propionate Related Compounds B, C and D)	F0E122				n/f	$675
1285964	Fluvastatin Related Compound B (15 mg) ([R*,S*-E]-(+/-)-7-[3-(4-fluorophenyl)-1-methylethyl-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1, dimethylethyl ester)	F0F017		1		[129332-29-2]	$526
1285942	Fluvastatin for System Suitability (25 mg) (Fluvastatin sodium and fluvastatin sodium anti-isomer ([R*,R*-E]-(+/-)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt))	F0F016		1		n/f	$526
1285909	Fluvoxamine Maleate (200 mg)	F0E016	0.996 mg/mg (dr)			[61718-82-9]	$463
1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P			O (07/00)	[59-30-3]	$168
1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176			H-1 (04/04) H (01/00)	[1492-18-8]	$168
1286060	Formononetin (50 mg)	F0C196				[485-72-3]	$563
1286300	10-Formylfolic Acid (25 mg)	F2B226			F-1 (01/04)	[134-05-4]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1286366	Fosphenytoin Sodium (250 mg)	G0E124	0.999 mg/mg (an)		F0C156 (07/06)	[92134-98-0]	$168
1286504	Fructose (125 mg)	I-2			I-1 (11/02) I (08/99)	[57-48-7]	$134
1286606	L-Fucose (200 mg) (AS)	F0E007				[2438-80-4]	$177
1286708	Fumaric Acid (200 mg)	G-1			G (04/02)	[110-17-8]	$168
1286800	Furazolidone (200 mg)	G-2			G-1 (01/01)	[67-45-8]	$168
1287008	Furosemide (125 mg)	J1B131			J (10/03)	[54-31-9]	$134
1287020	Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid)	J			I (08/02)	n/f	$526
1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)	I0C248			H (08/04) G-3 (03/01)	[3086-91-7]	$526
1287303	Gabapentin (250 mg)	G0E005	0.999 mg/mg (ai)		F (03/06)	[60142-96-3]	$168
1287325	Gabapentin Related Compound A (50 mg) (3,3-pentamethylene-5-butyrolactam)	G0E125	1.00mg/mg (ai)		F1D263 (07/06) F (10/05)	[64744-50-9]	$526
1287369	Gabapentin Related Compound E (25 mg) (Carboxymethyl-cyclohexanecarboxylic acid)	F0E190	0.99 mg/mg (ai)			n/f	$526
1287507	Gadodiamide (500 mg)	F				[131410-48-5]	$168
1287518	Gadodiamide Related Compound A (50 mg) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide)	F				n/f	$526
1287529	Gadodiamide Related Compound B (50 mg) (gadolinium disodium diethylenetriamine pentaacetic acid)	F				n/f	$526
1287609	Gadopentetate Monomeglumine (500 mg)				F (12/06)	[92923-57-4]	$168
1287631	Gadoteridol (500 mg)	F				[120066-54-8]	$168
1287642	Gadoteridol Related Compound A (50 mg) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid)	F0A002				[120041-08-9]	$526
1287653	Gadoteridol Related Compound B (50 mg) (1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt)	F0B198				[112188-16-6]	$526
1287664	Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetradecane-4,7-diacetic acid)	F0B199				[220182-19-4]	$526
1287675	Gadoversetamide (200 mg)	F0C172				[131069-91-5]	$168
1287686	Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxymethyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(4-)]gadolinium)	F0C173				n/f	$526
1287711	Galactitol (500 mg)	F0D376	0.99 mg/mg (ai)			[608-66-2]	$168
1287700	Galactose (200 mg)	F-4			F-3 (05/01)	[59-23-4]	$526
1288000	Gallamine Triethiodide (200 mg)	F				[65-29-2]	$168
1288306	Ganciclovir (200 mg)	F0C287				[82410-32-0]	$394
1288317	Ganciclovir Related Compound A (15 mg) ((RS)-2-Amino-9-(2,3-dihydroxy-propoxymethyl)-1,9-dihydro-purin-6-one)	F0C288				n/f	$675
1288463	Gemcitabine Hydrochloride (200 mg)	F0D037	0.997 mg/mg (ai)			[122111-03-9]	$168
1288500	Gemfibrozil (200 mg)	H				[25812-30-0]	$168
1288510	Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-dimethyl-4-(propene-1-yl)phenoxy]valeric acid)	G0D369	0.99 mg/mg (ai)		F0C101 (10/05)	n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1289003	Gentamicin Sulfate (200 mg)	M0D314	697 ug/mg (dr)		L0C279 (08/04) K (12/04) J-1 (04/00)	[1405-41-0]	$168
1290002	Gentian Violet (650 mg)	G0E112	1.000 mg/mg (an)		F (08/06)	[548-62-9]	$168
1291005	Gibberellic Acid (200 mg) (FCC)	G			F (04/01)	[77-06-5]	$168
1291504	Powdered Ginger (500 mg)	F				n/f	$281
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289				[50647-08-0]	$563
1292008	Gitoxin (50 mg)	G			F-3 (07/00)	[4562-36-1]	$526
1292303	Glimepiride (200 mg)	F0E228	0.994 mg/mg (ai)			[93479-79-1]	$260
1292314	Glimepiride Related Compound A (20 mg) (glimepiride cis-isomer)	F0E232				n/f	$526
1292325	Glimepiride Related Compound B (20 mg) (glimepiride sulfonamide)	F0E233				[119018-29-0]	$526
1292336	Glimepiride Related Compound C (20 mg) (Glimepiride urethane)	F0E234				[119018-30-3]	$526
1292347	Glimepiride Related Compound D (20 mg) (Glimepiride-3-isomer)	F0E235				n/f	$526
1292507	Glipizide (125 mg)	G1C174			G (07/04)	[29094-61-9]	$134
1292609	Glipizide Related Compound A (25 mg) (N-{2-[(4-aminosulfonyl)phenyl]ethyl}-5-methyl-pyrazinecarboxamide)	G-1			G (04/99)	n/f	$526
1294207	Glucosamine Hydrochloride (200 mg)	F0C363				[66-84-2]	$168
1294976	Glutamic Acid (200 mg)	F0C069				[56-86-0]	$168
1294808	Glutamine (100 mg)	F0B244				[56-85-9]	$168
1294848	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F				n/f	$730
1295006	Glutethimide **CII** (500 mg)	F				[77-21-4]	$224
1295505	Glyburide (200 mg)	G1C347	0.990 mg/mg (dr)		G (04/06) F-2 (11/02)	[10238-21-8]	$168
1295516	Glyburide Related Compound A (25 mg) (5-chloro-2-methoxy-N-[2-(4-sulfamoylphenyl)-ethyl]benzamide)	F0E224				[16673-34-0]	$526
1295607	Glycerin (2 mL)	H0C073			G1A001 (04/04) G (12/02) F (04/99)	[56-81-5]	$168
1295709	Glyceryl Behenate (200 mg)	F3B113			F-2 (03/03)	[18641-57-1]	$168
1295800	Glycine (200 mg)	G0E099	0.999 mg/mg (dr)		F-3 (05/06) F-2 (02/00)	[56-40-6]	$168
1296009	Glycopyrrolate (200 mg)	H0B304			G (05/04)	[596-51-0]	$168
1295888	Glycyrrhizic Acid (25 mg)	F0C006				[1405-86-3]	$526
1297001	Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package)	H			G (07/00)	[9002-61-3]	$1,082
1298004	Gramicidin (200 mg)	I			H-1 (07/02)	[1405-97-6]	$168
1299007	Griseofulvin (200 mg)	I			H-1 (09/02)	[126-07-8]	$168
1299200	Griseofulvin Permeability Diameter (2 g)	J0C380			I0C138 (10/04) H (08/03)	[126-07-8]	$168
1300004	Guaiacol (1 g)	K			J (04/00)	[90-05-1]	$168
1301007	Guaifenesin (200 mg)	I1C098	0.993 mg/mg (dr)		I (11/05) H (09/02)	[93-14-1]	$168
1301404	Guanabenz Acetate (200 mg)	G			F-1 (06/00)	[23256-50-0]	$168
1301608	Guanadrel Sulfate (200 mg)	F-1				[22195-34-2]	$168
1301801	Guanethidine Monosulfate (200 mg)	F				[645-43-2]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1302000	Guanethidine Sulfate (500 mg)	G-1				[60-02-6]	$168
1302101	Guanfacine Hydrochloride (125 mg)	G0B123			F-1 (02/03) F (11/99)	[29110-48-3]	$134
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224			F (12/04)	[23092-17-3]	$224
1302509	Halcinonide (300 mg)	F				[3093-35-4]	$168
1303002	Haloperidol (200 mg)	I			H-1 (05/02)	[52-86-8]	$168
1303013	Haloperidol Related Compound A (15 mg) (4,4'-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone)	K0C362			J (12/04)	[67987-08-0]	$526
1303308	Haloprogin (200 mg)	F				[777-11-7]	$168
1303501	Halothane (1 mL)	G0D068			F-1 (03/05)	[151-67-7]	$168
1304005	Heparin Sodium (10 x 1 mL)	K-5			K-4 (08/03) K-3 (02/99)	[9041-08-1]	$168
1305008	Hexachlorophene (500 mg)	I			H-2 (01/01)	[70-30-4]	$168
1305507	2E, 4E-Hexadienoic Acid Isobutylamide (25 mg)	F0C353	1.00 mg/mg (ai)			[82240-09-3]	$584
1307003	Hexobarbital **CIII** (500 mg)	F				[56-29-1]	$224
1308006	Hexylcaine Hydrochloride (1 g)	F-1				[532-76-3]	$168
1308200	Hexylene Glycol (125 mg)	G			F-2 (04/02) F-1 (04/99)	[107-41-5]	$168
1308307	Hexylresorcinol (200 mg)	F				[136-77-6]	$168
1308505	L-Histidine (200 mg)	G0A018			F-2 (01/03) F-1 (04/00)	[71-00-1]	$168
1309009	Histamine Dihydrochloride (250 mg)	M0C280			L (07/04)	[56-92-8]	$168
1310008	Homatropine Hydrobromide (200 mg)	H2C049			H-1(02/05) H (08/02)	[51-56-9]	$168
1311000	Homatropine Methylbromide (250 mg)	J			I-1 (06/01)	[80-49-9]	$168
1311306	Homopolymer Polypropylene (3 Strips)	F0C096				[9003-07-0]	$168
1311408	Homosalate (500 mg)	H0D322	0.994 mg/mg (ai)		G0D072 (09/06) F0B102 (04/05)	[118-56-9]	$168
1313006	Hydralazine Hydrochloride (200 mg)	K1E183	0.998 mg/mg (dr)		K (10/06) J-1 (09/02)	[304-20-1]	$168
1313210	Hydrastine (10 mg)	F0E204	0.99 mg/mg (ai)			[118-08-1]	$281
1314009	Hydrochlorothiazide (200 mg)	I			H (05/02)	[58-93-5]	$168
1315001	Hydrocodone Bitartrate **CII** (250 mg)	L0E176	0.997 mg/mg (dr)		K0C217 (11/06) J0A026 (01/05) I-1 (12/02) I (07/02) H-2 (11/99)	[34195-34-1]	$224
1315012	Hydrocodone Bitartrate Related Compound A **CII** (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl)	F0C214				[847-86-9]	$555
1316004	Hydrocortisone (200 mg)	M1C110			M (10/04) L (09/00)	[50-23-7]	$168
1317007	Hydrocortisone Acetate (200 mg)	K			J (10/99)	[50-03-3]	$168
1317302	Hydrocortisone Butyrate (200 mg)	H				[13609-67-1]	$168
1318000	Hydrocortisone Cypionate (200 mg)	F				[508-99-6]	$168
1319002	Hydrocortisone Hemisuccinate (200 mg)	I0D343	0.998 mg/mg (dr)		H (03/06) G-3 (03/02) G-2 (08/99)	[83784-20-7]	$168
1320001	Hydrocortisone Phosphate Triethylamine (200 mg)	F-1				n/f	$168
1321004	Hydrocortisone Valerate (200 mg)	F-1			F (07/02)	[57524-89-7]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1322007	Hydroflumethiazide (200 mg)	F-2				[135-09-1]	$168
1323000	Hydromorphone Hydrochloride **CII** (50 mg)	J0C372			I (01/05) H-2 (03/01)	[71-68-1]	$224
1324002	Hydroquinone (500 mg)	H0C249			G-1 (10/04) G (11/01) F-4 (02/99)	[123-31-9]	$168
1325005	Hydroxyamphetamine Hydrobromide (200 mg)	G			F (06/01)	[306-21-8]	$168
1327000	Hydroxychloroquine Sulfate (200 mg)	J0B297			I (05/04)	[747-36-4]	$168
1329006	Hydroxyprogesterone Caproate (200 mg)	H				[630-56-8]	$168
1329709	Hydroxypropyl Betadex (200 mg)	F0B295				[128446-35-5]	$168
1329800	Hydroxypropyl Cellulose (200 mg)	F-1				[9004-64-2]	$168
1332000	Hydroxyurea (200 mg)	H			G (01/00)	[127-07-1]	$168
1333003	Hydroxyzine Hydrochloride (500 mg)	I0C385	0.998 mg/mg (dr)		H (05/05)	[2192-20-3]	$168
1333058	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)	H1E248			H (09/06)	[303-26-4]	$526
1334006	Hydroxyzine Pamoate (500 mg)	H0C016			G-1 (07/03)	[10246-75-0]	$168
1335009	Hyoscyamine Sulfate (125 mg)	H0C193			G2A007 (09/04) G-1 (08/02) G (10/99)	[6835-16-1]	$134
1335010	Hyoscyamine Related Compound A (10 mg) (Norhyoscyamine Sulfate)	F0E250				[537-29-1]	$526
1335202	Hyperoside (50 mg)	F				[482-36-0]	$925
1330005	Hypromellose (250 mg) (Hydroxypropyl Methylcellulose)	H0C387			G-1 (11/04) G (02/02)	[9004-65-3]	$168
1335279	Hypromellose Acetate Succinate (100 mg)	F0D275				[71138-97-1]	$168
1335304	Hypromellose Phthalate (100 mg)	F-1			F (12/00)	[9050-31-1]	$168
1335508	Ibuprofen (750 mg)	J1E043	0.999 mg/mg (ai)		J (08/06) I (06/02)	[15687-27-1]	$168
1335701	Idarubicin Hydrochloride (50 mg)	I0D309	955 ug/mg (ai)		H0C061 (11/05) G (11/03) F (06/00)	[57852-57-0]	$518
1336001	Idoxuridine (250 mg)	H1B230			H (07/04)	[54-42-2]	$168
1336205	Ifosfamide (500 mg)	G1C371	1.000 mg/mg (an)		G (03/06) F-1 (11/00) F (02/99)	[3778-73-2]	$168
1336500	Imidazole (200 mg)	G2E031	1.00 mg/mg (ai)		G1B132 (10/06) G (01/04)	[288-32-4]	$526
1336806	Imidurea (200 mg)	H			G (10/99)	[39236-46-9]	$168
1337004	Iminodibenzyl (25 mg)	I0C253			H (11/04)	[494-19-9]	$526
1337809	Imipenem Monohydrate (100 mg)	H0E040	0.929 mg/mg (ai)		G1C296 (05/06) G (01/05) F (01/01)	[74431-23-5]	$168
1338007	Imipramine Hydrochloride (200 mg)	I			H (09/01)	[113-52-0]	$168
1338801	Indapamide (250 mg)	H1E103	0.998 mg/mg (dr)		H (07/06) G (07/02)	[26807-65-8]	$168
1338812	Indapamide Related Compound A (50 mg) (4-Chloro-N-(2-methyl-indol-1-yl)-3-sulfamoylbenzamide) (AS)	F0E052				[63968-75-2]	$526
1339000	Indigotindisulfonate Sodium (500 mg)	H1B153			H (06/03)	[860-22-0]	$168
1339178	Indinavir (100 mg)	F0D308	0.971 mg/mg (ai)			[180683-37-8]	$168
1339189	Indinavir System Suitability (100 mg)	F0D352				[180683-37-8]	$526
1340009	Indocyanine Green (200 mg)	I0B045			H (09/01)	[3599-32-4]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1341001	Indomethacin (200 mg)	J0B165			I (01/04) H (05/99)	[53-86-1]	$168
1342004	Insulin (100 mg)	H				[9004-10-8]	$168
1342106	Insulin Human (100 mg)	I0C383	26.6 USP Insulin Human Units/mg (ai)		H1A031 (07/05) H (11/02) G (04/00)	[11061-68-0]	$168
1342321	Insulin Lispro (5.97 mg)	F0E140	172 USP Insulin Lispro Units/vial			[133107-64-9]	$168
1342208	Insulin (Beef) (100 mg)	F				[11070-73-8]	$168
1342300	Insulin (Pork) (100 mg)	F				[12584-58-6]	$168
1342503	Iocetamic Acid (200 mg)	F				[16034-77-8]	$168
1343007	Iodipamide (200 mg)	G				[606-17-7]	$168
1343517	Iodixanol (200 mg)	F0B240				[92339-11-2]	$168
1343540	Iodixanol Related Compound C (25 mg) (5-Acetyl[3-[[3,5-bis[[(2,3-dihydroxypropyl)amino]-carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxy-propyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B236				n/f	$526
1343550	Iodixanol Related Compound D (50 mg) (5-[Acetyl(2-hydroxy-3-methylpropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B231				[89797-00-2]	$526
1343561	Iodixanol Related Compound E (25 mg) (5-[[3-[[3-[[(2,3-Dihydoxypropyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimino)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B229				n/f	$526
1344305	o-Iodohippuric Acid (100 mg)	F				[147-58-0]	$168
1344509	Iodoquinol (100 mg)	I0D285			H (07/06) G (07/02)	[83-73-8]	$168
1344600	Iohexol (100 mg)	F-1			F (01/99)	[66108-95-0]	$134
1344622	Iohexol Related Compound A (100 mg) (5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F-1			F (10/01)	n/f	$526
1344644	Iohexol Related Compound B (50 mg) (5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F-1			F (01/04)	[76801-93-9]	$526
1344666	Iohexol Related Compound C (100 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide)	F-1			F (09/03)	n/f	$526
1344702	Iopamidol (200 mg)	G				[60166-93-0]	$168
1344724	Iopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoiso-phthalamide)	G				[60166-98-5]	$526
1344735	Iopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide)	F				n/f	$526
1344804	Iopromide (400 mg)	F				[73334-07-3]	$168
1344826	Iopromide Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide)	F				n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1344837	Iopromide Related Compound B (50 mg) (5-(Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide)	F				n/f	$526
1345002	Iothalamic Acid (200 mg)	G				[2276-90-6]	$168
1345104	Ioversol (200 mg)	F				[87771-40-2]	$168
1345115	Ioversol Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide)	F				[76801-93-9]	$526
1345126	Ioversol Related Compound B (50 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide)	F				n/f	$526
1345159	Ioxaglic Acid (100 mg)	F				[59017-64-0]	$168
1345206	Ioxilan (400 mg)	F				[107793-72-6]	$168
1345228	Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2-hydroxyethyl)carbamoyl benzoic acid)	F				[22871-58-5]	$526
1346005	Ipodate Calcium (200 mg)	F-1			F (06/06)	[1151-11-7]	$168
1347008	Ipodate Sodium (200 mg)	F-1				[1221-56-3]	$168
1347755	Isoamyl Methoxycinnamate (750 mg/ampule)	F0B017				[71617-10-2]	$168
1348000	Isocarboxazid (200 mg)	F-1				[59-63-2]	$168
1348500	Isoetharine Hydrochloride (250 mg)	F-2				[2576-92-3]	$168
1348907	Isoflupredone Acetate (200 mg)	F0C109				[338-98-7]	$168
1349003	Isoflurane (1 mL)	H1C199			H (12/04)	[26675-46-7]	$168
1349014	Isoflurane Related Compound A (0.1 mL) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether)	F0C232				n/f	$526
1349025	Isoflurane Related Compound B (0.1 mL) (2,2,2-Trifluoroethyldifluoromethyl ether)	F0C233				n/f	$526
1349502	L-Isoleucine (200 mg)	F-2			F-1 (09/02)	[73-32-5]	$168
1349604	Isomalathion (50 mg)	G0D311	0.97 mg/mg (ai)		F1B107 (11/05) F (01/03)	[3344-12-5]	$526
1349626	Isomalt (200 mg)	F0E263	0.511 mg/mg 1,6-GPS; 0.453 mg/mg 1,1-GPM (ai)			[64519-82-0]	$168
1349659	Isometheptene Mucate (200 mg)	F				[7492-31-1]	$168
1349706	Isoniazid (200 mg)	H				[54-85-3]	$168
1350002	Isopropamide Iodide (200 mg)	F-2				[71-81-8]	$168
1350308	Isopropyl Alcohol (1.5 mL/ampule; 3 ampules) (AS)	F0D261	99.9% (ai)			[67-63-0]	$168
1350400	Isopropyl Myristate (500 mg)	J0D247			I1C183 (06/06) I (01/05)	[110-27-0]	$168
1350603	Isopropyl Palmitate (500 mg)	I			H (10/99)	[142-91-6]	$168
1351005	Isoproterenol Hydrochloride (125 mg)	K				[51-30-9]	$134
1352008	Isosorbide (75% solution, 1 g)	I			H-2 (10/00)	[652-67-5]	$168
1353000	Diluted Isosorbide Dinitrate (500 mg of 25% mixture with mannitol)	I2E153	25.1 % (ai)		I-1 (08/06) I (10/99)	[87-33-2]	$168
1353500	Isotretinoin (200 mg)	I1E066	0.998 mg/mg (ai)		I (08/06) H (10/00)	[4759-48-2]	$168
1354003	Isoxsuprine Hydrochloride (200 mg)	F-3				[579-56-6]	$168
1354207	Isradipine (200 mg)	H0E252	0.995 mg/mg (dr)	2	G0B054 (01/07) F (05/03)	[75695-93-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1354218	Isradipine Related Compound A (25 mg) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate)	F1D243			F (02/06)	n/f	$526
1354309	Ivermectin (200 mg)	G0D408	0.906 mg/mg (ai)		F0B196 (02/06)	[70288-86-7]	$168
1355006	Kanamycin Sulfate (200 mg)	J			I (06/99)	[25389-94-0]	$168
1355709	Powdered Kava Extract (1 g)	F0C161				n/f	$281
1355753	Kawain (200 mg)	F0C160				[500-64-1]	$225
1356009	Ketamine Hydrochloride **CIII** (250 mg)	H0E091	0.998 mg/mg (ai)		G-2 (06/06) G-1 (07/00)	[1867-66-9]	$224
1356020	Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol)	F0C118				[6740-87-0]	$526
1356508	Ketoconazole (200 mg)	G4B179			G-3 (01/04) G-2 (06/01) G-1 (01/99)	[65277-42-1]	$168
1356632	Ketoprofen (200 mg)	H0B216			G (07/04) F-2 (05/99)	[22071-15-4]	$168
1356643	Ketoprofen Related Compound A (25 mg) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) (AS)	H0E028			G (11/05)	[107257-20-5]	$526
1356665	Ketorolac Tromethamine (200 mg)	G			F-2 (04/99)	[74103-07-4]	$168
1356654	Labetalol Hydrochloride (200 mg)				G (02/07) F-2 (01/02) F-1 (03/01)	[32780-64-6]	$168
1356698	Lactase (200 mg)	F0D032	105,000 USP units/g (ai)			[9031-11-2]	$168
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	88.5% (ai)			[50-21-5]	$168
1356676	Anhydrous Lactose (100 mg)	G1C004			G (12/04) F (06/01)	[63-42-3]	$168
1356687	Lactitol (500 mg)	G0E254	0.997 mg/mg (an)		F0B005 (09/06)	[81025-04-9]	$168
1356701	Lactose Monohydrate (500 mg)	H0C151			G-1 (07/05) G (08/02)	[5989-81-1]	$168
1356803	Lactulose (1 g)	H			G-1 (08/00)	[4618-18-2]	$168
1356836	Lamivudine (200 mg)	F0C361				[134678-17-4]	$168
1356847	Lamivudine Resolution Mixture A (10 mg)	F0D024				[134678-17-4]	$526
1356880	Lanolin (20 g)	F				[8006-54-0]	$168
1356905	Lanolin Alcohols (5 g)	G0C421	1.00 mg/mg (ai)		F (11/04)	[8027-33-6]	$168
1356916	Lansoprazole (150 mg)	G0D307	0.995 mg/mg (ai)		F0B310 (10/05)	[103577-45-3]	$168
1356927	Lansoprazole Related Compound A (25 mg) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]-methyl]sulfonyl]benzimidazole)	F0B311				n/f	$526
1356950	Lauroyl Polyoxylglycerides (500 mg)	F1E144			F0D020 (08/06)	n/f	$168
1356971	Letrozole (200 mg)	F0B170				[112809-51-5]	$168
1356982	Letrozole Related Compound A (25 mg) (4,4'-(1H-1,3,4-triazol-1-ylmethylene)dibenzonitrile)	G0D298			F0B168 (10/05)	n/f	$526
1357001	L-Leucine (200 mg)	H0B237			G-1 (04/04) G (08/00)	[61-90-5]	$168
1358004	Leucovorin Calcium (500 mg)	J2B219			J-1 (07/04) J (05/02)	[1492-18-8]	$173
1358503	Leuprolide Acetate (200 mg)	F0C430	0.907 mg/mg (an,fb)			[74381-53-6]	$1,649
1359302	Levamisole Hydrochloride (125 mg)	F2C122			F-1 (05/04)	[16595-80-5]	$134
1359506	Levmetamfetamine **CII** (75 mg)	F1C113	98% (ai)		F(08/05)	[33817-09-3]	$224
1359801	Levobunolol Hydrochloride (200 mg)	H0E047	0.999 mg/mg (dr)		G (04/06)	[27912-14-7]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1359903	Levocarnitine (400 mg)	G0B197			F-2 (06/03) F-1 (12/00)	[541-15-1]	$168
1359925	Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride)	F-1			F (08/01)	[6538-82-5]	$526
1361009	Levodopa (200 mg)	I			H (09/00)	[59-92-7]	$168
1361010	Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)-alanine)	K			J (01/03) I (06/00)	[27244-64-0]	$526
1420006	Levodopa Related Compound B (50 mg) (3-Methoxytyrosine)	I0C300			H (07/04)		$526
1362500	Levonordefrin (200 mg)	F-1				[829-74-3]	$168
1363004	Levopropoxyphene Napsylate (300 mg)	G				[55557-30-7]	$168
1364007	Levorphanol Tartrate **CII** (500 mg)	I0D138	1.000 mg/mg (an)		H (07/05) G (03/01)	[5985-38-6]	$224
1365000	Levothyroxine (500 mg)	L0D226	0.994 mg/mg (dr)	2	K (12/06) J (10/00)	[51-48-9]	$168
1366002	Lidocaine (250 mg)	L				[137-58-6]	$168
1367005	Lincomycin Hydrochloride (200 mg)	H2B130			H-1 (01/04)	[7179-49-9]	$168
1367504	Lindane (200 mg)	F-2				[58-89-9]	$168
1367708	Linoleoyl Polyoxylglycerides (100 mg)	F0C283				n/f	$168
1368008	Liothyronine (250 mg)	M0D338	0.993 mg/mg (dr)		L1C262 (12/05) L (08/04) K (08/01)	[6893-02-3]	$168
1368609	Lisinopril (300 mg)	I1C045			I (11/04) H (09/01) G (10/99)	[83915-83-7]	$168
1369000	Lithium Carbonate (300 mg)	G0B031			F-2 (01/03) F-1 (01/01)	[554-13-2]	$168
1370000	Loperamide Hydrochloride (200 mg)	H0C202			G-2 (09/04) G-1 (02/03)	[34552-83-5]	$168
1370203	Loracarbef (200 mg)	F				[121961-22-6]	$168
1370225	Loracarbef L-Isomer (25 mg)	F				n/f	$526
1370270	Loratadine (200 mg)	G0D344	0.999 mg/mg (ai)		F0C414 (12/05)	[79794-75-5]	$281
1370280	Loratadine Related Compound A (15 mg) (8-Chloro-6,11-dihydro-11(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b] pyridine)	F0D229				[100643-71-8]	$526
1370291	Loratadine Related Compound B (15 mg) (8-Chloro-6,11-dihydro-11(N-methyl-4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine)	F0D230				n/f	$526
1370305	Lorazepam **CIV** (200 mg)	I1D404	0.998 mg/mg (ai)		I0C048 (06/06) H0B023 (06/04)	[846-49-1]	$224
1370327	Lorazepam Related Compound A (25 mg) (7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-acetoxy-2H-1,4-benzodiazepin-2-one)	G			F-1 (06/01)	[2848-96-6]	$526
1370338	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)	G			F-2 (01/04)	[2958-36-3]	$526
1370349	Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde)	H			G (01/03) F-3 (01/02)	n/f	$526
1370350	Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid)	G0A014			F-2 (01/04)	[54643-79-7]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1370360	Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol)	H0D254	0.98 mg/mg (ai)		G (02/06) F-3 (07/02) F-2 (04/99)	n/f	$526
1370462	Losartan Potassium (250 mg)	F0D287	0.998 mg/mg (ai)			[124750-99-8]	$168
1370600	Lovastatin (125 mg)	H2C012			H1B067 (01/04) H (08/03)	[75330-75-5]	$134
1370611	Lovastatin Related Compound A (10 mg) (dihydro-lovastatin)	H0D274			G0C326 (11/05) F0B235 (09/04)	n/f	$526
1370702	Loxapine Succinate (125 mg)	H0C094	0.998 mg/mg (dr)		G0B026 (11/05) F-2 (06/03) F-1 (07/01) F (03/99)	[27833-64-3]	$134
1370804	Lutein (1 mL)	F0D291	0.056 mg/mg in corn oil (ai)			[127-40-2]	$919
1370906	Lynestrenol (20 mg)	F0B314				[52-76-6]	$219
1371002	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) (AS) (LSD)	I				[50-37-3]	$584
1371501	L-Lysine Acetate (200 mg)	F1C027			F (11/04)	[57282-49-2]	$168
1372005	L-Lysine Hydrochloride (200 mg)	H			G (07/00)	[657-27-2]	$168
1373008	Mafenide Acetate (400 mg)	F1D216	0.999 mg/mg (an)		F (07/05)	[13009-99-9]	$168
1286209	Mafenide Related Compound A (50 mg) (4-Formylbenzenesulfonamide)	G0C351	1.00 mg/mg (dr)		F (08/05)	n/f	$526
1374000	Magaldrate (200 mg)	F-1				[74978-16-8]	$168
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	41.8% MgO (ai)			[546-93-0]	$168
1374248	Magnesium Chloride (1 g) (AS)	F0D157	100.3% (ai)			[7791-18-6]	$168
1374260	Magnesium Hydroxide (1 g) (AS)	F0D158	98.5% (dr)			[1309-42-8]	$168
1374292	Magnesium Phosphate (2 g) (AS)	F0E107	99.8% (ig)			[7757-87-1]	$168
1374306	Magnesium Salicylate (200 mg)	F2B081			F-1 (01/04)	[18917-95-8]	$168
1374340	Magnesium Stearate (5 g) (AS)	F0D214	65% Stearate 29% Palmitate 4.8% Mg (ai)			[577-04-0]	$168
1374361	Magnesium Sulfate (1 g) (AS)	F0D160	99.8% (ig)			[10034-99-8]	$168
1374408	Malathion (500 mg)	G0D143	0.993 mg/mg (ai)		F-1 (11/05) F (08/01)	[121-75-5]	$168
1374500	Maleic Acid (300 mg)	G			F-2 (12/00)	[110-16-7]	$526
1374601	Malic Acid (200 mg)	G0B158			F-1 (04/03)	[6915-15-7]	$168
1374907	Maltitol (200 mg)	G			F-1 (12/99)	[585-88-6]	$168
1375003	Maltol (4 g) (FCC)	G			F-1 (12/99)	[118-71-8]	$168
1375025	Maltose Monohydrate (500 mg)	F0E035	0.947 mg/mg (ai)			[6363-53-7]	$168
1375058	Mandelic Acid (500 mg)	F				[90-64-2]	$168
1375069	Mangafodipir Trisodium (200 mg)	F0D272	0.996 mg/mg (an)			[140678-14-4]	$168
1375070	Mangafodipir Related Compound A (15 mg) (manganese (II) dipyridoxyl monophosphate sodium salt)	F0D266				n/f	$526
1375080	Mangafodipir Related Compound B (15 mg) (manganese (II) dipyridoxyl diphosphate mono-overalkylated sodium salt)	F0D267				n/f	$526
1375091	Mangafodipir Related Compound C (15 mg) (manganese (III) dipyridoxyl diphosphate sodium salt)	F0D283				n/f	$526
1375127	Manganese Chloride (1 g) (AS)	F0D150	99.6% (dr)			[13446-34-9]	$168
1375149	Manganese Sulfate (1 g) (AS)	F0D151	99.8% (ai)			[10034-96-5]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1375105	Mannitol (200 mg)	I0B212			H (03/04)	[69-65-8]	$168
1375207	Maprotiline Hydrochloride (200 mg)	H			G (07/02)	[10347-81-6]	$168
1375309	Mazindol **CIV** (350 mg)	H			G (02/03)	[22232-71-9]	$224
1375502	Mebendazole (200 mg)	G1C195			G (11/04)	[31431-39-7]	$168
1375706	Mebrofenin (100 mg)	F				[78266-06-5]	$168
1376006	Mecamylamine Hydrochloride (200 mg)	F-2				[826-39-1]	$168
1376505	Mechlorethamine Hydrochloride (100 mg) (FOR U.S. SALE ONLY)	F-1			F (09/00)	[55-86-7]	$168
1377009	Meclizine Hydrochloride (500 mg)	I-1				[31884-77-2]	$168
1377508	Meclocycline Sulfosalicylate (300 mg)	G				[73816-42-9]	$168
1377803	Meclofenamate Sodium (500 mg)	H				[6385-02-0]	$168
1378001	Medroxyprogesterone Acetate (200 mg)	I0D013	0.995 mg/mg (ai)		H-2 (09/05) H-1 (04/03)	[71-58-9]	$168
1378012	Medroxyprogesterone Acetate Related Compound A (25 mg) (4,5-beta-Dihydromedroxyprogesterone acetate)	F0C427	1.00 mg/mg (ai)			n/f	$541
1379004	Medrysone (500 mg)	F				[2668-66-8]	$168
1379605	Mefenamic Acid (200 mg)	G0C025			F3A032 (08/04) F-2 (01/03)	[61-68-7]	$168
1379059	Mefloquine Hydrochloride (100 mg)	F0E165				[51773-92-3]	$168
1379060	Mefloquine Related Compound A (20 mg) (threo-mefloquine)	F0E166				n/f	$526
1379106	Megestrol Acetate (500 mg)	I			H (05/00)	[595-33-5]	$168
1379140	Meglumine (500 mg) (AS)	F0D385	99.5% (dr)			[6284-40-8]	$168
1380105	Melatonin (100 mg) (AS)	F0E027	0.999 mg/mg (dr)			[73-31-4]	$179
1379254	Melengestrol Acetate (125 mg)	F0D304	0.993 mg/mg (ai)			[2919-66-6]	$168
1379265	Melengestrol Acetate Related Compound A (25 mg) (17-hydroxy-16-methylenepregna-4-ene-3,20-dione 17-acetate)	F0D305	1.00 mg/mg (ai)			n/f	$526
1379276	Melengestrol Acetate Related Compound B (25 mg) (6,16-dimethylene-17-hydroxypregna-4-ene-3,20-dione 17-acetate)	F0D306	0.98 mg/mg (ai)			n/f	$526
1379401	Meloxicam (400 mg)	F0E158	0.999 mg/mg (ai)			[71125-38-7]	$281
1379412	Meloxicam Related Compound A (25 mg) (4-Hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylic acid ethyl ester 1,1-dioxide)	F0E167				[24683-26-9]	$526
1379423	Meloxicam Related Compound B (25 mg) (2-Amino-5-methyl-thiazole)	F0E168	1.00 mg/mg (ai)			[7305-71-7]	$526
1379434	Meloxicam Related Compound C (30 mg) (Isopropyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide)	F0E159	0.99 mg/mg (ai)			n/f	$526
1379445	Meloxicam Related Compound D (30 mg) (4-Methoxy-2-methyl-(5-methyl-1,3-thiazol-2yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide)	F0E160	1.00 mg/mg (ai)			n/f	$526
1379300	Melphalan Hydrochloride (100 mg) (FOR U.S. SALE ONLY)	H0B296	0.975 mg/mg (ai)		G (01/05)	[3223-07-2]	$168
	Melting Point Standards - See Cross Reference Section						
1381006	Menadione (200 mg) (Vitamin K3)	H-3			H-2 (02/00)	[58-27-5]	$168
1381709	Menthol (250 mg)	I0B049			H (04/03)	[2216-51-5]	$168
1381742	Menthyl Anthranilate (500 mg/ampule)	F0B103				[134-09-8]	$168
1382009	Mepenzolate Bromide (200 mg)	F				[76-90-4]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1383001	Meperidine Hydrochloride **CII** (200 mg)	I			H-1 (12/99)	[50-13-5]	$224
1385007	Mephenytoin (250 mg)	G				[50-12-4]	$168
1386000	Mephobarbital **CIV** (250 mg)	G			F (01/01)	[115-38-8]	$224
1387002	Mepivacaine Hydrochloride (200 mg)	H			G-4 (02/99)	[1722-62-9]	$168
1388005	Meprednisone (200 mg)	G				[1247-42-3]	$168
1389008	Meprobamate **CIV** (200 mg)	G-1			G (03/02)	[57-53-4]	$224
1390007	Meprylcaine Hydrochloride (200 mg)	F				[956-03-6]	$168
1391000	3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt (75 mg)	G				n/f	$526
1392002	Mercaptopurine (500 mg)	I2C263			I-1 (10/04) I (07/02) H (12/99)	[6112-76-1]	$168
1392454	Meropenem (300 mg)	F0C201				[119478-56-7]	$197
1392705	Mesalamine (200 mg)	H0C341			G1B001 (06/05) G (01/03) F-1 (03/00)	[89-57-6]	$168
1393005	Mesoridazine Besylate (250 mg)	J0C117			I-1 (12/04)	[32672-69-8]	$168
1394008	Mestranol (200 mg)	K0C065			J (07/04) I-1 (09/99)	[72-33-3]	$168
1395500	Metaproterenol Sulfate (200 mg)	F-3				[5874-97-5]	$168
1396003	Metaraminol Bitartrate (200 mg)	F-3				[33402-03-8]	$168
1396309	Metformin Hydrochloride (200 mg)	H0E136	1.00 mg/mg (ai)		G0D271 (07/06) F0C209 (08/05)	[1115-70-4]	$197
1396310	Metformin Related Compound A (50 mg) (1-Cyanoguanidine)	F0C210				[461-58-5]	$526
1396331	Metformin Related Compound B (25 mg) (1-Methylbiguanide hydrochloride)	F0F019		1		[1674-62-0]	$526
1396342	Metformin Related Compound C (25 mg) (N,N-Dimethyl-[1,3,5]triazine-2,4,6-triamine)	F0E343		1		[1985-46-2]	$526
1396364	Methacholine Chloride (500 mg) (AS)	F0D222	100.0% (dr)			[62-51-1]	$182
1396400	Methacrylic Acid Copolymer Type A (200 mg)	G0B140			F-2 (04/03)	n/f	$168
1396502	Methacrylic Acid Copolymer Type B (200 mg)	G0B141			F-2 (04/03)	n/f	$168
1396604	Methacrylic Acid Copolymer Type C (100 mg)	G1B088			G (08/03)	n/f	$134
1397006	Methacycline Hydrochloride (200 mg)	I0C348	903 ug/mg (ai)		H (10/05) G (04/01)	[3963-95-9]	$168
1398009	Methadone Hydrochloride **CII** (200 mg)	I0B163			H-1 (08/03)	[1095-90-5]	$224
1399001	Methamphetamine Hydrochloride **CII** (125 mg)	I				[51-57-0]	$224
1401001	Methantheline Bromide (200 mg)	F-1				[53-46-3]	$168
1402004	Methapyrilene Fumarate (200 mg)	F-1				[33032-12-1]	$168
1404000	Methaqualone **CI** (500 mg)	F-1				[72-44-6]	$224
1405002	Metharbital **CIII** (200 mg)	F-2			F-1 (07/99)	[50-11-3]	$224
1406005	Methazolamide (500 mg)	H0B239			G-1 (05/04)	[554-57-4]	$168
1407008	Methdilazine (200 mg)	F-1				[1982-37-2]	$168
1408000	Methdilazine Hydrochloride (200 mg)	G				[1229-35-2]	$168
1409003	Methenamine (500 mg)	H0C047			G (05/04)	[100-97-0]	$168
1409502	Methenamine Hippurate (200 mg)	F				[5714-73-8]	$168
1409604	Methenamine Mandelate (200 mg)	G0C304			F-2 (01/05) F-1 (11/00)	[587-23-5]	$168
1410002	Methicillin Sodium (500 mg) (AS)	J0C333			I1B186 (11/04) I (03/03) H (03/00)	[7246-14-2]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1411005	Methimazole (200 mg)	G			F (02/01)	[60-56-0]	$168
1411504	L-Methionine (200 mg)	G1D398	1.00 mg/mg (ai)		G (08/06) F-2 (11/99)	[63-68-3]	$168
1412008	Methocarbamol (200 mg)	H2B029			H-1 (03/04)	[532-03-6]	$168
1413000	Methohexital **CIV** (500 mg)	G0D252	1.000 mg/mg (an)		F-2 (08/05)	[18652-93-2]	$224
1414003	Methotrexate (500 mg)	I1D108	0.999 mg/mg (an)		I (01/06)	[59-05-2]	$168
1415006	Methotrimeprazine (125 mg)	F-2			F-1 (05/99)	[60-99-1]	$134
1416009	Methoxamine Hydrochloride (200 mg)	F				[61-16-5]	$168
1417001	Methoxsalen (500 mg)	H				[298-81-7]	$168
1418004	Methoxyflurane (1 mL)	G				[76-38-0]	$168
1419007	Methoxyphenamine Hydrochloride (250 mg)	F				[5588-10-3]	$168
1421009	Methscopolamine Bromide (200 mg)	G1D004	0.999 mg/mg (dr)		G (02/05)	[155-41-9]	$168
1422001	Methsuximide (500 mg)	F-2			F-1 (08/99)	[77-41-8]	$168
1424007	Methyclothiazide (200 mg)	G				[135-07-9]	$168
1424018	Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide)	G			F-2 (12/00)	n/f	$526
1424109	Methyl Alcohol (3 x 1.5 mL)	F0D015	0.999 mg/mg (ai)			[67-56-1]	$168
1424211	Methylbenzethonium Chloride (500 mg)	F0E101				[25155-18-4]	$177
1424222	Methyl Benzylidene Camphor (200 mg)	F0B118				[36861-47-9]	$168
1424233	Methyl Caprate (300 mg)	G0D087			F (04/06)	[110-42-9]	$168
1424244	Methyl Caproate (300 mg)	F				[106-70-7]	$168
1424255	Methyl Caprylate (300 mg)	G0D064	1.00 mg/mg (ai)		F (07/05)	[111-11-5]	$168
1424506	Methylcellulose (1 g) (AS)	G0B222			F-2 (05/03)	[9004-67-5]	$168
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) (AS) (STP)	F				[15589-00-1]	$224
1426002	Methyldopa (500 mg)	I1E059	0.999 mg/mg (an)		I (02/06)	[41372-08-1]	$168
1427005	Methyldopate Hydrochloride (200 mg)	G-2				[2508-79-4]	$168
1428008	Methylene Blue (250 mg)	H0D163	1.000 mg/mg (dr) (Colorimetric) 0.90 mg/mg (dr) (TLC)		G (08/05)	[7220-79-3]	$168
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) (AS) (MDA)	F-1				[6292-91-7]	$224
1430000	Methylergonovine Maleate (50 mg) **(List Chemical)**	J			I (05/02)	[57432-61-8]	$168
1430305	Methyl Laurate (500 mg)	G0C356	0.998 mg/mg (ai)		F (03/05)	[111-82-0]	$168
1430327	Methyl Linoleate (5 x 50 mg)	G0D107	0.99 mg/mg (ai)		F (07/06)	[112-63-0]	$168
1430349	Methyl Linolenate (5 x 50 mg)				F (09/06)	[301-00-8]	$168
1430509	3-O-Methylmethyldopa (50 mg)	G-1				n/f	$526
1431002	Methyl 5-methyl-3-isoxazolecarboxylate (25 mg)	F-1			F (01/01)	n/f	$526
1431501	Methyl Myristate (300 mg)	G0C357	0.998 mg/mg (ai)		F (03/05)	[124-10-7]	$168
1431556	Methyl Oleate (500 mg)	G0C148			F (04/04)	[112-62-9]	$168
1431603	Methyl Palmitate (300 mg)	G0E329	1.00 mg/mg (ai)	2	F(02/07)	[112-39-0]	$168
1431625	Methyl Palmitoleate (300 mg)	F				n/f	$168
1432005	Methylparaben (125 mg)	K0C382	0.999 mg/mg (dr)		J-1 (10/05) J (03/03))	[99-76-3]	$134
1433008	Methylphenidate Hydrochloride **CII** (125 mg)	I1C241			I (04/05) H (05/01)	[298-59-9]	$179

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)	F0C368	0.5 mg/mL (ai)			n/f	$605
1434022	Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride)	G			F-2 (10/99)	n/f	$526
1435003	Methylprednisolone (200 mg)	I0E170	0.995 mg/mg (dr)		H (07/06)	[83-43-2]	$168
1436006	Methylprednisolone Acetate (200 mg)	H0D148	0.995 mg/mg (ai)		G-2 (05/05) G-1 (02/00)	[53-36-1]	$168
1437009	Methylprednisolone Hemisuccinate (200 mg)	I0C146			H (07/04)	[2921-57-5]	$168
1437450	Methyl Salicylate (2 mL) (AS)	F0D070	99.1 % (ai)			[119-36-8]	$168
1437508	Methyl Stearate (300 mg)	G0E290	1.0 mg/mg (ai)		F (11/06)	[112-61-8]	$168
1438001	Methyltestosterone **CIII** (200 mg)	J1E324	0.996 mg/mg (dr)	2	J (02/07) I (11/01)	[58-18-4]	$224
1440003	Methysergide Maleate (350 mg)	H1F038	0.997 mg/mg (dr)	2,3	H (12/06)	[129-49-7]	$260
1440808	Metoclopramide Hydrochloride (500 mg)	H0D121	0.999 mg/mg (an)		G (06/05) F-2 (06/99)	[54143-57-6]	$168
1441006	Metocurine Iodide (300 mg)	G				[7601-55-0]	$168
1441200	Metolazone (200 mg)	G0B246			F-1 (05/03)	[17560-51-9]	$168
1441287	Metoprolol Fumarate (200 mg)	F				[119637-66-0]	$168
1441232	Metoprolol Related Compound A (20 mg) ((+/-)-1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol)	F0C343				n/f	$563
1441243	Metoprolol Related Compound B (50 mg) ((+/-)-1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane)	F0C377				n/f	$563
1441254	Metoprolol Related Compound C (20 mg) ((+/-)-4-[2-Hydroxy-3-(1-methylethyl)aminopropoxy]-benzaldehyde)	F0C344				n/f	$563
1441265	Metoprolol Related Compound D (50 mg) ((+/-)-N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine hydrochloride)	G0E188			F0C378 (12/06)	n/f	$563
1441298	Metoprolol Succinate (200 mg)	F0C415	0.998 mg/mg (ai)			[98418-47-4]	$168
1441301	Metoprolol Tartrate (200 mg)	H1B059			H (01/04) G-1 (11/99)	[56392-17-7]	$168
1441505	Metrizamide (500 mg)	F				[31112-62-6]	$168
1442009	Metronidazole (100 mg)	J0C316	1.000 mg/mg (dr)		I (07/05)	[443-48-1]	$168
1443001	Metyrapone (200 mg)	H			G (06/01)	[54-36-4]	$168
1443205	Metyrosine (200 mg)	F				[672-87-7]	$168
1443250	Mexiletine Hydrochloride (200 mg)	F3E098	0.999 mg/mg (dr)		F-2 (02/06) F-1 (09/02)	[5370-01-4]	$168
1443307	Mezlocillin Sodium (350 mg)	G				[59798-30-0]	$168
1443409	Miconazole (200 mg)	G-1			G (07/02)	[22916-47-8]	$168
1443500	Miconazole Nitrate (200 mg)	J0D011	0.997 mg/mg (dr)		I (06/06) H (06/99)	[22832-87-7]	$168
1443850	Powdered Milk Thistle Extract (250 mg)	F0B321				[84604-20-6]	$281
1443908	Milrinone (500 mg)	G0D340	0.998 mg/mg (an)		F0C050 (09/05)	[78415-72-2]	$281
1443919	Milrinone Related Compound A (50 mg) (1,6-Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide)	F0C051				[80047-24-1]	$526
1444004	Minocycline Hydrochloride (200 mg)	I0C178			H-3 (04/04) H-2 (07/02)	[13614-98-7]	$168
1444208	Minoxidil (125 mg)	H1C168			H (03/04) G (05/99)	[38304-91-5]	$134

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1444279	Mirtazapine (350 mg)	F0D155	0.999 mg/mg (an)			[61337-67-5]	$865
1444707	Mitomycin (50 mg)	K			J (07/01)	[50-07-7]	$518
1445007	Mitotane (500 mg)	G0C044			F (07/04)	[53-19-0]	$168
1445200	Mitoxantrone Hydrochloride (400 mg)	I0D174	0.990 mg/mg (an)		H (05/05) G (03/01)	[70476-82-3]	$539
1445211	Mitoxantrone System Suitability Mixture (0.3 mg)	F0D010				n/f	$541
1445404	Modafinil **CIV** (200 mg)	F0D351	0.997 mg/mg (ai)			[68693-11-8]	$270
1445459	Molindone Hydrochloride (500 mg)	F				[15622-65-8]	$168
1445470	Mometasone Furoate (200 mg)	H0E009	0.998 mg/mg (dr)	2	G0B073 (01/07) F-1 (04/03) F (02/01)	[83919-23-7]	$168
1445481	Monensin Sodium (200 mg)	F0B293				[22373-78-0]	$168
1445506	Monobenzone (200 mg)	F				[103-16-2]	$168
1445925	Monoethanolamine (1 mL)	F0D149				[141-43-5]	$168
1445801	Mono- and Di-acetylated Monoglycerides (200 mg)	F				[68990-54-5]	$168
1446000	Monoglycerides (125 mg)	H1D232	0.963 mg/mg (ai)		H (11/05)	[68990-53-4]	$134
1446600	Monosodium Glutamate (1 g) (AS)	F0D387	99.7% (ai)			[6106-04-3]	$168
1446804	Monostearyl Maleate (100 mg)	G			F-2 (04/00)	[2424-62-6]	$526
1446906	Morantel Tartrate (100 mg)	F0D295	0.997 mg/mg (ai)			[26155-31-7]	$168
1446950	Moricizine Hydrochloride (250 mg)	F1D057	0.999 mg/mg (an)		F (03/05)	[29560-58-5]	$422
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G				[6009-81-0]	$224
1448005	Morphine Sulfate **CII** (500 mg)	N0E161	0.999 mg/mg (an)		M0D016 (09/06) L0B056 (04/05) K (06/03) J-1 (07/00)	[6211-15-0]	$359
1448504	Moxalactam Disodium (500 mg)	F-1				[64953-12-4]	$168
1448901	Mupirocin (50 mg)	F2C158			F-1 (12/04) F (03/02)	[12650-69-0]	$168
1448923	Mupirocin Lithium (100 mg)	H0C176	926 ug/mg (ai)		G (03/05) F (02/01)	[73346-79-9]	$168
1448990	Myristic Acid (200 mg)	F0E120				[544-63-8]	$168
1449008	Myristyl Alcohol (1 g)	G			F (02/02)	[112-72-1]	$168
1449518	Nabumetone (200 mg)	F0C072				[42924-53-8]	$168
1449530	Nabumetone Related Compound A (15 mg) (1-(6-Methoxy-2-naphthyl)-but-1-en-3-one)	F0D165				n/f	$526
1449700	Nadolol (200 mg)	G0C308	0.995 mg/mg (ai)		F-3 (04/05) F-2 (04/02)	[42200-33-9]	$168
1450007	Nafcillin Sodium (200 mg)	H				[7177-50-6]	$168
1450404	Naftifine Hydrochloride (200 mg)	F				[65473-14-5]	$168
1451000	Nalidixic Acid (200 mg)	G				[389-08-2]	$168
1452002	Nalorphine Hydrochloride **CIII** (250 mg)	I				[57-29-4]	$224
1453005	Naloxone (125 mg)	M0D085	0.999 mg/mg (dr)		L0B124 (09/06) K-1 (12/02) K (07/01)	[465-65-6]	$134
1453504	Naltrexone (200 mg)	H0C150			G1B039 (03/04) G (02/03)	[16590-41-3]	$168
1453526	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride)	F				n/f	$526
1454008	Nandrolone **CIII** (50 mg)	F4D144	1.00 mg/mg (ai)		F-3 (04/05)	[434-22-0]	$605
1455000	Nandrolone Decanoate **CIII** (250 mg)	J0D218	0.999 mg/mg (dr)		I (06/06)	[360-70-3]	$224

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1456003	Nandrolone Phenpropionate **CIII** (250 mg)	H				[62-90-8]	$224
1457006	Naphazoline Hydrochloride (200 mg)	L0E207	0.989 mg/mg (dr)	2	K (02/07)	[550-99-2]	$168
1457301	Naproxen (200 mg)	I-1			I (03/03) H-1 (01/01)	[22204-53-1]	$168
1457403	Naproxen Sodium (200 mg)	J0C379	0.999 mg/mg (dr)		I (07/05)	[26159-34-2]	$168
1457469	Naratriptan Hydrochloride (125 mg)	F0C360	0.998 mg/mg (ai)			[143388-64-1]	$225
1457505	Natamycin (200 mg)	J0D180	0.917 mg/mg (ai)		I (06/05) H (11/99)	[7681-93-8]	$168
1458009	Neomycin Sulfate (200 mg)	L3E135	782 ug/mg (dr)	2	L-2 (01/07) L-1 (09/01) L (02/99)	[1405-10-3]	$168
1459001	Neostigmine Bromide (200 mg)	G				[114-80-7]	$168
1460000	Neostigmine Methylsulfate (200 mg)	I			H (07/00)	[51-60-5]	$168
1460204	Neotame (200 mg)	F0F044	0.954 mg/mg (ai)	1		[165450-17-9]	$168
1460215	Neotame Related Compound A (15 mg) (N-[N-(3,3-dimethylbutyl)-L-alpha-aspartyl]-L-phenylalanine)	F0F045	1.00 mg/mg (ai)	1		n/f	$526
1460500	Netilmicin Sulfate (500 mg)	I0C388	653 ug/mg (dr)		H (01/05) G (05/02)	[56391-57-2]	$168
1460703	Nevirapine Anhydrous (100 mg)	F0D159	0.997 mg/mg (ai)			[129618-40-2]	$168
1460714	Nevirapine Hemihydrate (100 mg)	F0D034				n/f	$168
1460725	Nevirapine Related Compound A (15 mg) (5,11-Dihydro-6H-11-ethyl-4-methyl-dipyrido[3,2-b2',3'-e][1,4]diazepin-6-one)	F0D035				n/f	$526
1460736	Nevirapine Related Compound B (15 mg) (5,11-Dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one)	F0D033				n/f	$526
1461003	Niacin (200 mg)	I0E295	0.998 mg/mg (ai)	2	H2C121 (02/07) H-1 (01/05)	[59-67-6]	$168
1462006	Niacinamide (500 mg) (Vitamin B3)	N0E024	0.999 mg/mg (dr)		M-1 (04/06) M (02/01)	[98-92-0]	$168
1463304	Nicotine Bitartrate Dihydrate (500 mg)	G1C070			G (05/05) F (05/99)	[6019-06-3]	$168
1463508	Nifedipine (125 mg)	K0D401	0.998 mg/mg (ai)		J0B243 (03/06) I-1 (04/04)	[21829-25-4]	$134
1463600	Nifedipine Nitrophenylpyridine Analog (25 mg)	K			J (04/01)	n/f	$526
1463701	Nifedipine Nitrosophenylpyridine Analog (25 mg)	K			J (07/02)	n/f	$526
1464001	Nitrofurantoin (500 mg)	J			I-1 (11/02)	[67-20-9]	$168
1021703	Nitrofurantoin Related Compound A (25 mg) (N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine)	F2E037	0.98 mg/mg (ai)		F-1 (08/06)	n/f	$526
1465004	Nitrofurazone (200 mg)	I0E149	0.995 mg/mg (ai)		H-1 (11/06) H (09/01)	[59-87-0]	$168
1465503	Nitrofurfural Diacetate (100 mg)	G0D066	0.99 mg/mg (ai)		F-1 (12/04)	[92-55-7]	$526
1466007	Nitrofurazone Related Compound A (500 mg) (5-Nitro-2-furfuraldazine)	H0B100			G (07/03)	n/f	$526
1466506	Diluted Nitroglycerin (5 ampules, approx. 200 mg of a 0.948% solution in propylene glycol each)	G				[55-63-0]	$168
1467804	Nizatidine (200 mg)	G			F-1 (06/00)	[76963-41-2]	$168
1467950	Nonoxynol 9 (0.5 mL)	H-1			H (03/02)	[26027-38-3]	$168
1468002	Nonoxynol 10 (200 mg)	F				[26027-38-3]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)	H1B035			H (03/03) G (03/00)	[1088-11-5]	$605
1468501	Norepinephrine Bitartrate (125 mg)	I0C381			H (04/05)	[69815-49-2]	$134
1469005	Norethindrone (200 mg)	K0C307	0.998 mg/mg (ai)		J1B065 (09/05) J-1 (05/03) J (07/02) I-1 (03/01)	[68-22-4]	$168
1470004	Norethindrone Acetate (100 mg)	J1E102	0.997mg/mg (dr)		J0B072 (09/06) I (04/03) H (06/99)	[51-98-9]	$168
1471007	Norethynodrel (200 mg)	G				[68-23-5]	$168
1471506	Norfloxacin (200 mg)	H1D317	0.995 mg/mg (dr)		H (12/06) G (04/01)	[70458-96-7]	$168
1471914	Norgestimate (200 mg)	F0C086				[35189-28-7]	$168
1472000	Norgestrel (125 mg)	J0C269			I (07/04) H (05/99)	[6533-00-2]	$134
1473002	Noroxymorphone Hydrochloride **CII** (50 mg)	H1C177			H (11/04)	n/f	$605
1473206	Norphenylephrine Hydrochloride (25 mg)	F0E205				[15308-34-6]	$526
1474005	Nortriptyline Hydrochloride (200 mg)	I1D054	1.000 mg/mg (dr)		I (05/05) H (04/00)	[894-71-3]	$168
1474504	Noscapine (500 mg)	G				[128-62-1]	$168
1475008	Novobiocin (200 mg)	H0D327	1012 ug/mg (dr)		G-2 (05/05)	[303-81-1]	$168
1476000	Nylidrin Hydrochloride (200 mg)	F-2				[849-55-8]	$168
1477003	Nystatin (200 mg)	O0D177	5751 Nystatin units/mg (dr)		N1B004 (09/05) N (01/03)	[1400-61-9]	$168
1477900	Octinoxate (500 mg) (Octyl Methoxycinnamate)	H0D213	0.987 mg/mg (ai)		G0C024 (09/05) F0B032 (12/03)	[5466-77-3]	$168
1477943	Octisalate (400 mg) (Octyl Salicylate)	G0D278	0.995 mg/mg (ai)		F0B091 (12/05)	[118-60-5]	$168
1477411	Octocrylene (500 mg)	G0C211			F0B104 (05/04)	[6197-30-4]	$168
1477502	Octoxynol 9 (200 mg)	G			F-2 (07/00)	[9002-93-1]	$168
1477808	Octyldodecanol (200 mg)	H0D059			G (03/06) F-1 (07/99)	[5333-42-6]	$168
1478108	Ofloxacin (200 mg)	G0E180	0.999 mg/mg (ai)		F-2 (07/06) F-1 (08/02)	[82419-36-1]	$168
1478119	Ofloxacin Related Compound A (25 mg) ((RS)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-10-(piperazin-1-yl)-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid)	F0E276				[82419-52-1]	$526
1478130	Oleic Acid (1 g)	F0E001				[112-80-1]	$168
1478152	Oleoyl Polyoxylglycerides (100 mg)	F0C313				n/f	$168
1478254	Olive Oil (1 g) (AS)	F0D175				[8001-25-0]	$168
1478505	Omeprazole (200 mg)	H1B211			H (05/04) G-1 (04/02) G (09/01)	[73590-58-6]	$168
1478516	Omeprazole Related Compound A (15 mg) (Omeprazole Sulfone) (AS)	F0D363				[88546-55-8]	$526
1478571	Ondansetron (300 mg)	F0E281	0.999 mg/mg (an)			[99614-02-5]	$225
1478582	Ondansetron Hydrochloride (300 mg)	G0D154	0.993 mg/mg (an)		F0C222 (05/05)	[103639-04-9]	$225
1478593	Ondansetron Related Compound A (50 mg) (3[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride)	F0C191				[119812-29-2]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1478618	Ondansetron Related Compound C (50 mg) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one)	F0C251				[27397-31-1]	$526
1478629	Ondansetron Related Compound D (50 mg) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one)	F0C226				n/f	$526
1478630	Ondansetron Resolution Mixture (50 mg)	F0D242				n/f	$526
1479009	Orphenadrine Citrate (200 mg)	G			F-4 (05/02)	[4682-36-4]	$168
1481000	Oxacillin Sodium (200 mg)	J			I (03/02)	[7240-38-2]	$168
1482003	Oxandrolone **CIII** (50 mg)	H0E223	0.994 mg/mg (ai)		G0B220 (08/06) F-4 (07/03)	[53-39-4]	$224
1482207	Oxaprozin (200 mg)	F0C115				[21256-18-8]	$168
1483006	Oxazepam **CIV** (200 mg)	H0D259	1.000 mg/mg (dr)		G-1 (08/05) G (12/00)	[604-75-1]	$224
1483301	Oxfendazole (200 mg)	F0C128				[53716-50-0]	$168
1483505	Oxprenolol Hydrochloride (200 mg)	I0C344			H (02/05)	[6452-73-9]	$168
1484009	Oxtriphylline (500 mg)	G				[4499-40-5]	$168
1485001	Oxybenzone (150 mg)	H0B263			G (11/03) F-2 (12/99)	[131-57-7]	$168
1485103	Oxybutynin Chloride (200 mg)	H0E080	0.998 mg/mg (dr)		G-1 (05/06) G (11/02)	[1508-65-2]	$168
1485114	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)	H0E169	1.00 mg/mg (dr)		G (07/06) F-2 (01/00)	[4335-77-7]	$526
1485125	Oxybutynin Related Compound B (20 mg) (Cyclohexyl mandelic acid methyl ester)	F0D061				[10399-13-0]	$526
1485136	Oxybutynin Related Compound C (20 mg) (4-(Ethylmethylamino)but-2-ynyl(+/-)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride)	F0D062				n/f	$526
1485191	Oxycodone **CII** (200 mg)	I1D206	0.990 mg/mg (dr)		I0B046 (08/05) H (01/03) G-1 (01/01)	[76-42-6]	$224
1486004	Oxymetazoline Hydrochloride (200 mg)	J0C206			I (03/05)	[2315-02-8]	$168
1487007	Oxymetholone **CIII** (200 mg)	G1B247			G (10/03)	[434-07-1]	$224
1488000	Oxymorphone **CII** (500 mg)	H0B214			G (03/03)	[76-41-5]	$224
1490103	Oxyquinoline Sulfate (200 mg)	F-1			F (07/02)	[134-31-6]	$168
1491004	Oxytetracycline (200 mg)	J0C084	913 ug/mg (ai)		I-1 (10/04)	[6153-64-6]	$168
1491015	Oxytetracycline Hydrochloride (200 mg) (AS)	F0E258				[2058-46-0]	$168
1491300	Oxytocin (5 vials, 46 USP units per vial)	F				[50-56-6]	$168
1491332	Paclitaxel (200 mg)	G0E018	0.989 mg/mg (ai)		F0C180 (04/06)	[33069-62-4]	$1,631
1491343	Paclitaxel Related Compound A (20 mg) (Cephalomannine)	F0C179				[71610-00-9]	$815
1491354	Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel)	G0E019	0.98 mg/mg (ai)		F0C181 (03/06)	nf	$815
1491503	Padimate O (300 mg)	H0B154			G (04/03)	[21245-02-3]	$168
1492040	Palm Oil (1 g) (AS)	F0D179				[8002-75-3]	$168
1492007	Palmitic Acid (500 mg)				J0D329(01/07) I (12/05)	[57-10-3]	$168
1493000	Pamoic Acid (250 mg)	G-4			G-3 (01/03)	[130-85-8]	$168
1494057	Pancreatin Amylase and Protease (2 g)	I1E218	174 USP Units of amylase activity/mg 124 USP Units of protease activity/mg		I (09/06) H (10/00)	[8049-47-6]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1494079	Pancreatin Lipase (2 g)	I1E327	21.2 USP Units of Lipase Activity/mg (ai)	2	I (12/06) H-1 (03/01)	[8049-47-6]	$168
1494217	Pancuronium Bromide (200 mg)	F0D377	0.99 mg/mg (an)			[15500-66-0]	$303
1494501	Panthenol, Racemic (200 mg)	G			F-1 (02/00)	[16485-10-2]	$168
1494807	Pantolactone (500 mg)	F				[599-04-2]	$526
1495005	Papain (1 g)	I0C389	6700 USP units/mg (ai)		H (06/04) G (12/01)	[9001-73-4]	$168
1496008	Papaverine Hydrochloride (200 mg)	H				[61-25-6]	$168
1497000	Paramethadione (500 mg)	G				[115-67-3]	$168
1498003	Paramethasone Acetate (200 mg)	G			F-1 (05/01)	[1597-82-6]	$168
1498706	Parbendazole (200 mg)	F				[14255-87-9]	$168
1499006	Pargyline Hydrochloride (200 mg)	F-1				[306-07-0]	$168
1500003	Paromomycin Sulfate (125 mg)	G			F-3 (01/01)	[1263-89-4]	$168
1500218	Paroxetine Hydrochloride (350 mg)	G0D003	0.972 mg/mg (ai)		F0B288 (09/04)	[110429-35-1]	$168
1500230	Paroxetine Related Compound B (10 mg) (trans-4-phenyl-3-[(3,4-methylenedioxy)phenoxymethyl]piperidine hydrochloride)	G0D137	0.92 mg/mg (ai)		F0B189 (10/05)	n/f	$526
1500240	Paroxetine Related Compound C (15 mg) ((+)-trans-Paroxetine hydrochloride)	G0D053	0.96 mg/mg (ai)		F0B192 (05/05)	[130855-30-0]	$526
1500251	Paroxetine Related Compound D (10 mg) (AS) (cis-Paroxetine hydrochloride)	G0E096		2,3	F0C228 (12/06)	n/f	$526
1500262	Paroxetine Related Compound E Mixture (25 mg) (1-Methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine in Paroxetine Hydrochloride Matrix)	F1F028	0.86 ng/mg (ai)	2	F0D225 (11/06)	n/f	$526
1500273	Paroxetine Related Compound F (10 mg) (trans(-)-1-Methyl-3-[(1,3-benzodioxol-5-yloxy)-methyl]-4-(4-fluorophenyl)piperidine)	F0D237	1.00 mg/mg (ai)			n/f	$526
1500284	Paroxetine Related Compound G (0.4 mg) ((+/-)-trans-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4''-fluorophenyl-4'-phenyl)piperidine hydrochloride)	G0E121	0.4 mg in ~1.5 mg povidone	2,3	F0D110 (12/06)	n/f	$526
1500353	Paroxetine System Suitability Mixture A (50 mg)	F0E150				n/f	$526
1500400	Parthenolide (25 mg)	F				[20554-84-1]	$168
1500502	Particle Count Set (2 blanks and 2 suspensions)	J0D067			I (12/05) H (09/02)	n/f	$526
1500557	Peanut Oil (1 g) (AS)	F0D171				[8002-03-7]	$168
1500808	Penbutolol Sulfate (200 mg)	F				[38363-32-5]	$168
1501006	Penicillamine (200 mg)	H1B164			H (01/04)	[52-67-5]	$168
1501108	Penicillamine Disulfide (100 mg)	H			G (07/00)	[20902-45-8]	$526
1502009	Penicillin G Benzathine (200 mg)	J1D164			J (04/06)	[41372-02-5]	$168
1502508	Penicillin G Potassium (200 mg)	J0C349	89.3%/1595 USP Penicillin G units/mg (ai)		I (07/05) H (02/99)	[113-98-4]	$168
1502552	Penicillin G Procaine (200 mg)	G0C271			F-1 (08/04) F (03/99)	[6130-64-9]	$168
1502701	Penicillin G Sodium (150 mg)	L4C366			L-3 (08/06) L-2 (09/01)	[69-57-8]	$168
1504489	Penicillin V (200 mg)	F1C318			F (08/05)	[87-08-1]	$168
1504503	Penicillin V Potassium (200 mg)	H0C213			G-1 (06/04) G (06/00)	[132-98-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1505007	Pentazocine **CIV** (500 mg)	I0C418	0.998 mg/mg (dr)		H (01/05) G-1 (11/00)	[359-83-1]	$224
1505506	Pentetic Acid (100 mg)	F-1			F (09/01)	[67-43-6]	$168
1507002	Pentobarbital **CII** (200 mg)	I0D359	0.997 mg/mg (ai)		H3C144 (12/04) H-2 (07/04) H-1 (08/02)	[76-74-4]	$224
1508901	Pentoxifylline (200 mg)	F1D350	0.999 mg/mg (dr)		F0B202 (12/05)	[6493-05-6]	$168
1510007	Pepsin (5 g)	F-2				[9001-75-6]	$168
1510801	Perflubron (0.5 mL)	G0C103			F (04/04)	[423-55-2]	$168
1510845	Pergolide Mesylate (200 mg)	F1C225			F (07/04)	[66104-23-2]	$210
1510867	Pergolide Sulfoxide (50 mg)	F0B014				[72822-01-6]	$210
1511000	Perphenazine (200 mg)	J0B249			I (10/03)	[58-39-9]	$168
1511203	Perphenazine Sulfoxide (100 mg)	G-1			G (07/02)	[10078-25-8]	$526
1512002	Phenacemide (250 mg)	F				[63-98-9]	$168
1513005	Phenacetin (500 mg)	H-1			H (09/00)	[62-44-2]	$168
1514008	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)	H3A009			H-2 (02/03) H-1 (06/01)	[62-44-2]	$100
1515000	Phenazopyridine Hydrochloride (200 mg)	H0C426	0.998 mg/mg (dr)		G-4 (12/04)	[136-40-3]	$168
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025			G (12/02)	[956-90-1]	$224
1516502	Phendimetrazine Tartrate **CIII** (350 mg)	G			F (01/01)	[50-58-8]	$224
1517006	Phenelzine Sulfate (200 mg)	G			F-1 (04/02)	[156-51-4]	$168
1517301	D-Phenethicillin Potassium (200 mg)	F				n/f	$526
1517607	L-Phenethicillin Potassium (200 mg)	F				n/f	$168
1520000	Phenformin Hydrochloride (200 mg)	G				[834-28-6]	$168
1522006	Phenindione (250 mg)	F				[83-12-5]	$168
1522301	Pheniramine Maleate (100 mg)	F1C342			F (08/04)	[132-20-7]	$168
1523009	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2				[1707-14-8]	$224
1524001	Phenobarbital **CIV** (200 mg)	J				[50-06-6]	$224
1524908	Phenolphthalein (250 mg)	F-3				[77-09-8]	$168
1525004	Phenolsulfonphthalein (100 mg)	F-2				[143-74-8]	$168
1525707	Phenothiazine (500 mg) (AS)	F0D231	0.994 mg/mg (dr)			[92-84-2]	$168
1526007	Phenoxybenzamine Hydrochloride (250 mg)	G				[63-92-3]	$168
1526200	Phenoxyethanol (500 mg) (2-Phenoxyethanol)	F0D069	0.998 mg/mg (ai)			[122-99-6]	$168
1528002	Phensuximide (500 mg)	G			F-1 (03/01)	[86-34-0]	$168
1528501	Phentermine Hydrochloride **CIV** (200 mg)	H0B309			G (08/03)	[1197-21-3]	$224
1529005	Phentolamine Hydrochloride (300 mg)	F				[73-05-2]	$168
1530004	Phentolamine Mesylate (200 mg)	I				[65-28-1]	$168
1530503	L-Phenylalanine (200 mg)	H			G (02/02)	[63-91-2]	$168
1530809	Phenylbenzimidazole Sulfonic Acid (200 mg)	F				[27503-81-7]	$168
1531007	Phenylbutazone (250 mg)	J0A008			I-1 (02/03)	[50-33-9]	$168
1533002	Phenylephrine Hydrochloride (125 mg)	K1C290			K (03/05) J (02/99)	[61-76-7]	$134
1533250	Phenylethyl Alcohol (1 mL)	F0D395				[60-12-8]	$168
1533308	5-Phenylhydantoin (100 mg)	F				[89-24-7]	$526
1533851	Phenylpropanediol (100 mg)	F				n/f	$526
1533909	Phenylpropanolamine Bitartrate (100 mg) **(List Chemical)**	F				[67244-90-0]	$168
1534005	Phenylpropanolamine Hydrochloride (250 mg) **(List Chemical)**	J			I (02/02)	[154-41-6]	$168
1534402	Phenyltoloxamine Citrate (100 mg)	F0E127				[1176-08-5]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1534413	Phenyltoloxamine Related Compound A (50 mg) (2-(2-benzylphenoxy)ethylmethylamine hydrochloride)	F0E128				n/f	$526
1535008	Phenytoin (200 mg)	J0E090	0.999 mg/mg (ai)		I2B233 (05/06) I-1 (03/04) I (04/01)	[57-41-0]	$168
1535507	Phenytoin Sodium (200 mg)	H1E335	1.000 mg/mg (dr) (UV)	2	H (02/07) G (05/99)	[630-93-3]	$168
1535019	Phenytoin Related Compound A (50 mg) (2,2-Diphenylglycine)	F0C155				[3060-50-2]	$526
1535020	Phenytoin Related Compound B (50 mg) (alpha-((aminocarbonyl)amino)-alpha-phenyl benzeneacetic acid)	F0C157				[6802-95-5]	$526
1535700	Phosphated Riboflavin (100 mg)	G1B286			G (07/04)	[6184-17-4]	$134
1535802	Phosphoric Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D026	86.8% (ai)			[7664-38-2]	$168
1537003	Physostigmine Salicylate (200 mg)	H-1			H (06/00)	[57-64-7]	$168
1538006	Phytonadione (500 mg) (Vitamin K1)	N0B303			M-1 (07/04) M (09/01)	[84-80-0]	$168
1538505	Pilocarpine (300 mg)	F				[92-13-7]	$168
1538902	Pilocarpine Hydrochloride (200 mg)	I0D055	0.998 mg/mg (dr)		H (09/05)	[54-71-7]	$168
1539009	Pilocarpine Nitrate (200 mg)	I1E138	0.991 mg/mg (dr)		I (11/06)	[148-72-1]	$168
1539508	Pimozide (200 mg)	G				[2062-78-4]	$168
1539701	Pindolol (200 mg)	I0B210			H-1 (12/04)	[13523-86-9]	$168
1541000	Piperacetazine (250 mg)	F				[3819-00-9]	$168
1541500	Piperacillin (500 mg)	H				[66258-76-2]	$168
1541703	Piperazine Adipate (200 mg)	F				[142-88-1]	$168
1541805	Piperazine Citrate (200 mg)	F				[144-29-6]	$168
1541907	Piperazine Dihydrochloride (200 mg)	F				[142-64-3]	$168
1542003	Piperazine Phosphate (200 mg)	F				[14538-56-8]	$168
1543006	Piperidolate Hydrochloride (200 mg)	F				[129-77-1]	$168
1544508	Piroxicam (200 mg)	H1D038	0.998 mg/mg (ai)		H (07/05) G (01/99)	[36322-90-4]	$168
1545205	Plicamycin (50 mg)	H			G (04/00)	[18378-89-7]	$518
1545409	Polacrilex Resin (100 mg)	F1D233			F (05/06)	n/f	$168
1545500	Polacrilin Potassium (200 mg)	F-2			F-1 (09/00)	n/f	$168
1546106	Poloxalene (500 mg)	F0C009				[9003-11-6]	$168
1546300	Polydimethylsiloxane (500 mg)	H0C020			G-5 (05/04) G-4 (06/01)	[9016-00-6]	$168
1546707	Polyethylene, High Density (3 strips)	G1D115			G (06/05) F-1 (04/01)	[9002-88-4]	$168
1546809	Low-Density Polyethylene (3 strips)	H0E114			G1B166 (10/06) G (06/04) F-2 (12/99)	[9002-88-4]	$168
1546401	Polyethylene Glycol 200 (1 g)	F0E316		1		[25322-68-3]	$168
1546423	Polyethylene Glycol 300 (1 g)	F0E336		1		[25322-68-3]	$168
1546445	Polyethylene Glycol 400 (1 g)	F0E344		1		[25322-68-3]	$168
1546525	Polyethylene Glycol 3000 (1 g)	F0F013		1		[25322-68-3]	$168
1546547	Polyethylene Glycol 3350 (1 g)	F0F012		1		[25322-68-3]	$168
1546853	Polyethylene Oxide (100 mg)	F-1				[25322-68-3]	$168
1546900	Polyethylene Terephthalate (PET) (3 Strips)	F				[25038-59-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1546922	Polyethylene Terephthalate G (PETG) (3 Strips)	F				[25640-14-6]	$168
1546966	Polyisobutylene (1 g)	F0E108		1		[9003-27-4]	$168
1547007	Polymyxin B Sulfate (200 mg)	K			J-1 (09/99)	[1405-20-5]	$168
1547200	Polyoxyl 35 Castor Oil (1 g)	F0E116				[61791-12-6]	$168
1547801	Polyoxyl 20 Cetostearyl Ether (100 mg)	F0C292				[9004-95-9]	$168
1372402	Polyoxyl Lauryl Ether (500 mg)	F0E253				[9002-92-0]	$168
1547903	Polyoxyl 40 Stearate (200 mg)	F-2			F-1 (05/00)	[9004-99-3]	$168
1547404	Polyoxyl 50 Stearate (200 mg)	F				[9004-99-3]	$168
1547346	Polyoxyl 2 Stearyl Ether (1 g) (AS)	F0D353				[9005-00-9]	$168
1372606	Polyoxyl 10 Stearyl Ether (1 g)	F0D354				[9005-00-9]	$168
1547368	Polyoxyl 20 Stearyl Ether (1 g) (AS)	F0D355				[9005-00-9]	$168
1547925	Polysorbate 20 (2 g) (AS)	F0D130				[9005-64-5]	$168
1547936	Polysorbate 40 (2 g) (AS)	F0D204				[9005-66-7]	$168
1547947	Polysorbate 60 (2 g) (AS)	F0D131				[9005-67-8]	$168
1547969	Polysorbate 80 (2 g) (AS)	F0D132				[9005-65-6]	$168
1548000	Polythiazide (200 mg)	F-1				[346-18-9]	$168
1549807	Potassium Acetate (500 mg) (AS)	F0E083	99.7% (dr)			[127-08-2]	$168
1548101	Potassium Benzoate (1 g) (AS)	F0D161	0.999 mg/mg (an)			[582-25-2]	$168
1548134	Potassium Bicarbonate (1 g) (AS)	F0D074	99.9% (dr)			[298-14-6]	$168
1549840	Potassium Bitartrate (3 g) (AS)	F0D384	99.9% (dr(			[868-14-4]	$168
1548167	Potassium Carbonate (1 g) (AS)	F0D075	99.8% (dr)			[584-08-7]	$168
1548190	Potassium Chloride (1 g) (AS)	F0D127	100.0% (dr)			[7447-40-7]	$168
1548225	Potassium Citrate (1 g) (AS)	F0D201	100.0% (dr)			[6100-05-6]	$168
1550001	Potassium Gluconate (200 mg)	H0C064			G (06/04)	[299-27-4]	$168
1551004	Potassium Guaiacolsulfonate (500 mg)	J0B292			I-1 (07/03) I (11/00)	[78247-49-1]	$168
1548280	Potassium Iodide (1 g) (AS)	F0D078	100.0% (dr)			[7681-11-0]	$168
1548349	Potassium Nitrate (5 g) (AS)	F0D325	100.0% (ai)			[7757-79-1]	$168
1551128	Dibasic Potassium Phosphate (5 g) (AS)	F0D281	99.7% (dr)			[7758-11-4]	$168
1551139	Monobasic Potassium Phosphate (5 g) (AS)	F0D313	100.0% (dr)			[7778-77-0]	$168
1551140	Potassium Sodium Tartrate (2 g) (AS)	F0D380	99.8% (an)			[6381-59-5]	$168
1548407	Potassium Sorbate (1 g) (AS)	F0D264	99.6% (dr)			[24634-61-5]	$168
1551150	Potassium Sucrose Octasulfate (300 mg)	I0B283			H0B119 (04/04) G-1 (04/03) G (02/01)	[76578-81-9]	$168
1551300	Potassium Trichloroammineplatinate (20 mg)	I0D022	0.84 mg/mg (dr)		H0B149 (12/04) G-1 (01/03) G (07/99)	[13820-91-2]	$526
1551503	Povidone (100 mg)	F-1			F (11/01)	[9003-39-8]	$168
1553000	Pralidoxime Chloride (200 mg)	G-2			G-1 (03/01) G (08/99)	[51-15-0]	$168
1554002	Pramoxine Hydrochloride (500 mg)	I1D197	0.998 mg/mg (dr)		I (10/05) H (11/02)	[637-58-1]	$168
1554501	Prazepam **CIV** (500 mg)	G0C066			F-1 (11/02)	[2955-38-6]	$224
1554603	Praziquantel (200 mg)	G			F-3 (07/02) F-2 (09/00)	[55268-74-1]	$168
1554658	Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a]isoquinolin-4-one)	F-1				n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1554669	Praziquantel Related Compound B (50 mg) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4H-pyrazino [2,1-alpha]isoquinolin-4-one)	G0E039	0.98 mg/mg (dr)		F-2 (12/05) F-1 (06/00)	n/f	$526
1554670	Praziquantel Related Compound C (50 mg) (2-(N-formylhexahydrohippuroyl)-1,2,3,4-tetrahydroisoquinolin-1-one)	F-2			F-1 (06/00)	n/f	$526
1554705	Prazosin Hydrochloride (500 mg)	H0B254			G-1 (02/05) G (02/01)	[19237-84-4]	$168
1555005	Prednisolone (200 mg)	N0D212	1.000 mg/mg (dr)		M (02/06) L-1 (04/02)	[50-24-8]	$168
1556008	Prednisolone Acetate (200 mg)	J			I-1 (02/02)	[52-21-1]	$168
1556507	Prednisolone Hemisuccinate (125 mg)	H-1			H (02/99)	[2920-86-7]	$134
1557000	Prednisolone Sodium Phosphate (100 mg)	F0E300				[125-02-0]	$168
1558003	Prednisolone Tebutate (200 mg)	F				[7681-14-3]	$168
1559006	Prednisone (250 mg)	M0D211	0.994 mg/mg (ai) (HPLC) 0.999 mg/mg (ai) (Spectrophotometric)		L1B251 (11/05) L (11/04) K-1 (01/02) K (02/00)	[53-03-2]	$168
1559505	Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets)	O0C056			N (06/04) M (09/02) L (11/00)	[53-03-2]	$194
1560990	Prilocaine (200 mg)	F0E073				[721-50-6]	$168
1561008	Prilocaine Hydrochloride (200 mg)	F3B215			F-2 (03/04)	[1786-81-8]	$168
1561019	Prilocaine Related Compound A (100 mg) (o-toluidine hydrochloride)	F0E074	1.00 mg/mg (ai)			[636-21-5]	$526
1561020	Prilocaine Related Compound B (50 mg) ((RS)-N-(4-methylphenyl)-2-(propylamino)propanamide)	F0E075				n/f	$526
1561507	Primaquine Phosphate (200 mg)	F-1				[63-45-6]	$168
1562000	Primidone (200 mg)	H0D399	1.000 mg/mg (dr)		G (07/06) F-6 (04/99)	[125-33-7]	$168
1563003	Probenecid (200 mg)	I0A011			H-1 (03/03)	[57-66-9]	$168
1563309	Probucol (200 mg)	G			F-1 (01/02)	[23288-49-5]	$168
1563320	Probucol Related Compound A (25 mg) (2,2',6,6'-tetra-*tert*-butyldiphenoquinone)	F-2			F-1 (11/04)	n/f	$526
1563331	Probucol Related Compound B (25 mg) (4,4'-dithio-bis(2,6-di-*tert*-butylphenol))	F-2			F-1 (08/03)	n/f	$526
1563342	Probucol Related Compound C (25 mg) (4-[(3,5-di-*tert*-butyl-2-hydroxyphenylthio)isopropylidenethio]-2,6-di-*tert*-butylphenol)	F-2			F-1 (05/00)	n/f	$526
1563502	Procainamide Hydrochloride (200 mg)	H1B117			H (04/03)	[614-39-1]	$168
1564006	Procaine Hydrochloride (200 mg)	I0E089	0.998 mg/mg (dr)		H (12/06)	[51-05-8]	$168
1565009	Procarbazine Hydrochloride (200 mg)	F				[366-70-1]	$168
1566001	Prochlorperazine Maleate (200 mg)	H-1				[84-02-6]	$168
1567004	Procyclidine Hydrochloride (200 mg)	G				[1508-76-5]	$168
1568007	Progesterone (200 mg)	I0D373	0.998 mg/mg (ai)		H6C088(03/06) H-5 (11/04) H-4 (07/02)	[57-83-0]	$134
1568506	L-Proline (200 mg)	G0D146	1.00 mg/mg (dr)		F-2 (09/05) F-1 (01/02)	[147-85-3]	$168
1569000	Promazine Hydrochloride (200 mg)	H0B261			G (10/03)	[53-60-1]	$168
1570009	Promethazine Hydrochloride (500 mg)	K			J-1 (10/00)	[58-33-3]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1570304	Propafenone Hydrochloride (200 mg)	G1C184			G (12/04) F-1 (01/01)	[34183-22-7]	$168
1570508	Propantheline Bromide (200 mg)	I0A019			H (11/02)	[50-34-0]	$168
1329505	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)	G0B258			F-1 (12/03)	n/f	$526
1571001	Proparacaine Hydrochloride (200 mg)	G				[5875-06-9]	$168
1572208	Propionic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D029	99.8 % w/w (ai)			[79-09-4]	$168
1572503	Propofol (200 mg)	F0D379	0.999 mg/mg (ai)			[2078-54-8]	$168
1572536	Propofol Related Compound A (25 mg) (3,3'-5,5'-Tetraisopropyldiphenol)	F0E060	1.00 mg/mg (ai)			n/f	$526
1572547	Propofol Related Compound B (50 mg) (2,6-diisopropylbenzoquinone)	F0D239	0.99 mg/mg (ai)			n/f	$526
1572558	Propofol Related Compound C (50 mg) (2,6-diisopropylphenyl isopropylether)	F0D240				n/f	$526
1572525	Propofol Resolution Mixture (100 mg) (Propofol, 2,6-diisopropylphenyl isopropylether, and 2-isopropyl-6-n-propylphenol)	F0D193				n/f	$526
1573007	Propoxycaine Hydrochloride (200 mg)	F				[550-83-4]	$168
1574000	Propoxyphene Hydrochloride **CII** (1 g)	L0C285			K (09/04)	[1639-60-7]	$224
1575002	Propoxyphene Napsylate **CII** (1 g)	H1C323	0.993 mg/mg (an)		H (05/05)	[26570-10-5]	$224
1575206	Propoxyphene Related Compound A (50 mg) (alpha-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride)	G6D124	0.99 mg/mg (ai)		G-5 (01/06)	n/f	$526
1008002	Propoxyphene Related Compound B (50 mg) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane)	H0D012	0.94 mg/mg (ai)		G-3 (05/05)	n/f	$526
1576005	Propranolol Hydrochloride (200 mg)	I0C170			H-1 (12/04) H (09/01)	[318-98-9]	$168
1576504	Propylene Carbonate (200 mg)	F				[108-32-7]	$168
1576708	Propylene Glycol (1 mL)	I0C022			H (03/04) G (02/99)	[57-55-6]	$168
1576800	Propyl Gallate (200 mg)	G2D203	1.000 mg/mg (dr)		G-1 (10/05) G (01/03)	[121-79-9]	$168
1577008	Propylparaben (200 mg)	J0D402	1.000 mg/mg (ai)		I (08/06) H (02/00)	[94-13-3]	$168
1578000	Propylthiouracil (200 mg)	G			F-1 (01/00)	[51-52-5]	$168
1578500	Prostaglandin A1 (25 mg)	H0B108			G (04/03)	[14152-28-4]	$572
1578554	Prostaglandin B1 (25 mg) ((13E,15S)-15-Hydroxy-9-oxoprosta-8(12),13-dien-1-oic Acid)	F0E022	1.00 mg/mg (ai)			[1345-51-2]	$1,352
1580002	Protriptyline Hydrochloride (200 mg)	G0E034	0.999 mg/mg (dr)		F-1 (12/05)	[1225-55-4]	$168
1581005	Pseudoephedrine Hydrochloride (125 mg) **(List Chemical)**	J1B203			J (01/04) I (05/02)	[345-78-8]	$134
1581504	Pseudoephedrine Sulfate (200 mg) **(List Chemical)**	G1C135			G (06/04) F-2 (05/02)	[7460-12-0]	$168
1584003	Pyrantel Pamoate (1 g)	I			H-1 (04/00)	[22204-24-6]	$168
1585006	Pyrazinamide (200 mg)	G			F-2 (02/00)	[98-96-4]	$168
1586009	Pyridostigmine Bromide (200 mg)	I0C324	0.999 mg/mg (dr)		H (01/05)	[101-26-8]	$168
1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P			O-1 (04/00)	[58-56-0]	$168
1588004	Pyrilamine Maleate (200 mg)	I0B276			H (12/03)	[59-33-6]	$168
1589007	Pyrimethamine (200 mg)	H			G (07/02)	[58-14-0]	$168
1592001	Pyrvinium Pamoate (500 mg)	G				[3546-41-6]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1592205	Quazepam **CIV** (200 mg)	F				[36735-22-5]	$224
1592227	Quazepam Related Compound A (30 mg) (7-Chloro-1-(2,2,2-trifluoroethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one)	F				n/f	$526
1592409	Quercetin (500 mg)	G0D407	1.000 mg/mg (an)		F0B015	[6151-25-3]	$168
1593004	Quinacrine Hydrochloride (200 mg)	F-1				[6151-30-0]	$168
1593412	Quinapril Related Compound A (50 mg) (Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate)	F0C114				[103733-49-9]	$526
1593423	Quinapril Related Compound B (50 mg) (3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-,[3S-[2[R*(R*)],3R*]]-)	F0C116				[82768-85-2]	$526
1594007	Quinethazone (1.5 g)	G				[73-49-4]	$168
1594506	Quinic Acid (200 mg)	F				[77-95-2]	$168
1595000	Quinidine Gluconate (200 mg)	H1A028			H (04/03)	[7054-25-3]	$168
1595509	Quinidine Sulfate (500 mg)	H-1			H (12/99)	[6591-63-5]	$168
1596807	Quinine Hydrochloride Dihydrate (1 g)	F0C108				[6119-47-7]	$168
1597005	Quinine Sulfate (500 mg)	I0E071	0.984 mg/mg (an) (HPLC) 1.000 mg/mg (an) (Spectrophotometric)		H (06/06)	[6119-70-6]	$168
1597504	Quininone (50 mg)	H0B034			G-1 (03/04)	[84-31-1]	$526
1598008	3-Quinuclidinyl Benzilate (25 mg) (FOR U.S. SALE ONLY)	H			G (11/01)	[6581-06-2]	$557
1598303	Ramipril (200 mg)	G0D345	0.998 mg/mg (ai)		F0C099 (11/05)	[87333-19-5]	$168
1598314	Ramipril Related Compound A (20 mg) ((2S,3aS,6aS)-1-[(S)2-[[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[b]pyrrole-2-carboxylic acid)	F0C100				[91224-69-0]	$526
1598338	Ramipril Related Compound C (20 mg) (Hexahydroramipril Hydrochloride)	F0E157				n/f	$526
1598347	Ramipril Related Compound D (20 mg) (Ramipril Diketopiperazine)	F0E036				n/f	$526
1598405	Ranitidine Hydrochloride (200 mg)	H0B268			G (01/04)	[66357-59-3]	$168
1598507	Ranitidine Related Compound A (50 mg) (5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate)	H1B137			H (01/04) G (01/01)	[91224-69-0]	$526
1598609	Ranitidine Related Compound B (50 mg) (N,N'-bis[2-[[[5-[(dimethylamino)methyl]-2-furanyl]-methyl]thio]ethyl]-2-nitro-1,1-ethenediamine)	G1D347			G (03/06) F-4 (04/02)	[72126-78-4]	$526
1598700	Ranitidine Related Compound C (50 mg) (N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]-sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine)	I1B136			I (01/04) H (05/01)	[73851-70-4]	$526
1598450	Ranitidine Resolution Mixture (20 mg)	F0E323		1		n/f	$1,052
1599000	Rauwolfia Serpentina (15 g)	G				[8063-17-0]	$168
1599500	Powdered Red Clover Extract (500 mg)	F0C188				n/f	$281
1600813	Repaglinide (200 mg)	G0D276	0.999 mg/mg (ai)		F0B265 (02/06)	[135062-02-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1600824	Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N-acetyl-L-glutamate salt)	F0B267				n/f	$526
1600835	Repaglinide Related Compound B (50 mg) (3-Ethoxy-4-ethoxycarbonyl-phenylacetic acid)	F0B269				[99469-99-5]	$526
1600846	Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)-phenyl]ethyl]amino]-2-oxoethyl] benzoic acid)	F0B271				[107362-12-9]	$526
1601000	Reserpine (200 mg)	O0C106			N (06/03)	[50-55-5]	$168
1601102	Residual Solvents Mixture - Class 1 (1.2 mL/ampule; 3 ampules)	F0C407				n/f	$168
1601146	Residual Solvent Class 1 - Benzene (1.2 mL/ampule; 3 ampules)	F0C408	10.1 mg/mL (ai)			n/f	$168
1601168	Residual Solvent Class 1 - Carbon Tetrachloride (1.2 mL/ampule; 3 ampules)	F0C409	19.7 mg/mL (ai)			n/f	$168
1601180	Residual Solvent Class 1 - 1,2-Dichloroethane (1.2 mL/ampule; 3 ampules)	F0C412	25.1 mg/mL (ai)			n/f	$168
1601204	Residual Solvent Class 1 - 1,1-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0C411	37.9 mg/mL (ai)			n/f	$168
1601226	Residual Solvent Class 1 - 1,1,1-Trichloroethane (1.2 mL/ampule; 3 ampules)	F0C410	49.1 mg/mL (ai)			n/f	$168
1601281	Residual Solvents Class 2 - Mixture A (1.2 mL/ampule; 3 ampules)	F0D051				n/f	$168
1601292	Residual Solvents Class 2 - Mixture B (1.2 mL/ampule; 3 ampules)	F0D248				n/f	$168
1601306	Residual Solvent Class 2 - Mixture C (1.2 mL/ampule; 3 ampules)	F0D182				n/f	$168
1601340	Residual Solvent Class 2 - Acetonitrile (1.2 mL/ampule; 3 ampules)	F0D049	2.00 mg/mL (ai)			n/f	$168
1601361	Residual Solvent Class 2 - Chlorobenzene (1.2 mL/ampule; 3 ampules)	F0D048	1.81 mg/mL (ai)			n/f	$168
1601383	Residual Solvent Class 2 - Chloroform (1.2 mL/ampule; 3 ampules)	F0D186	0.293 mg/mL (ai)			n/f	$168
1601408	Residual Solvent Class 2 - Cyclohexane (1.2 mL/ampule; 3 ampules)	F0D047	18.0 mg/mL (ai)			n/f	$168
1601420	Residual Solvent Class 2 - 1,2-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0D040	9.2 mg/mL (ai)			n/f	$168
1601463	Residual Solvent Class 2 - 1,2-Dimethoxyethane (1.2 mL/ampule; 3 ampules)	F0D185	0.479 mg/mL (ai)			n/f	$168
1601485	Residual Solvent Class 2 - N,N-Dimethylacetamide (1.2 mL/ampule; 3 ampules)	F0D169	5.44 mg/mL (ai)			n/f	$168
1601500	Residual Solvent Class 2 - N,N-Dimethylformamide (1.2 mL/ampule; 3 ampules)	F0D189	4.42 mg/mL (ai)			n/f	$168
1601521	Residual Solvent Class 2 - 1,4-Dioxane (1.2 mL/ampule; 3 ampules)	F0D050	1.89 mg/mL (ai)			n/f	$168
1601543	Residual Solvent Class 2 - 2-Ethoxyethanol (1.2 mL/ampule; 3 ampules)	F0D195	0.80 mg/mL (ai)			n/f	$168
1601565	Residual Solvent Class 2 - Ethylene Glycol (1.2 mL/ampule; 3 ampules)	F0D191	3.07 mg/mL (ai)			n/f	$168
1601587	Residual Solvent Class 2 - Formamide (1.2 mL/ampule; 3 ampules)	F0D188	1.10 mg/mL (ai)			n/f	$168
1601601	Residual Solvent Class 2 - Hexane (1.2 mL/ampule; 3 ampules)	F0D268	0.256 mg/mL (ai)			n/f	$168

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1601623	Residual Solvent Class 2 - Methanol (1.2 mL/ampule; 3 ampules)	F0D045	14.8 mg/mL (ai)			n/f	$168
1601645	Residual Solvent Class 2 - 2-Methoxyethanol (1.2 mL/ampule; 3 ampules)	F0D194	0.253 mg/mL (ai)			n/f	$168
1601667	Residual Solvent Class 2 - Methylbutylketone (1.2 mL/ampule; 3 ampules)	F0D202	0.248 mg/mL (ai)			n/f	$168
1601689	Residual Solvent Class 2 - Methylcyclohexane (1.2 mL/ampule; 3 ampules)	F0D044	5.46 mg/mL (ai)			n/f	$168
1601441	Residual Solvent Class 2 - Methylene Chloride (1.2 mL/ampule; 3 ampules)	F0D046	2.90 mg/mL (ai)			n/f	$168
1601703	Residual Solvent Class 2 - N-Methylpyrrolidone (1.2 mL/ampule; 3 ampules)	F0D183	2.63 mg/mL (ai)			n/f	$168
1601725	Residual Solvent Class 2 - Nitromethane (1.2 mL/ampule; 3 ampules)	F0D210	0.248 mg/mL (ai)			n/f	$168
1601747	Residual Solvent Class 2 - Pyridine (1.2 mL/ampule; 3 ampules)	F0D215	0.99 mg/mL (ai)			n/f	$168
1601769	Residual Solvent Class 2 - Sulfolane (1.2 mL/ampule; 3 ampules)	F0D187	0.80 mg/mL (ai)			n/f	$168
1601770	Residual Solvent Class 2 - Tetrahydrofuran (1.2 mL/ampule; 3 ampules)	F0D043	3.49 mg/mL (ai)			n/f	$168
1601780	Residual Solvent Class 2 - Tetralin (1.2 mL/ampule; 3 ampules)	F0D228	0.493 mg/mL (ai)			n/g	$168
1601805	Residual Solvent Class 2 - Toluene (1.2 mL/ampule; 3 ampules)	F0D042	4.39 mg/mL (ai)			n/f	$168
1601827	Residual Solvent Class 2 - Trichloroethylene (1.2 mL/ampule; 3 ampules)	F0D221	0.391 mg/mL (ai)			n/f	$168
1601849	Residual Solvent Class 2 - Xylenes (1.2 mL/ampule; 3 ampules)	F0D041	10.7 mg/mL (ai)			n/f	$168
1602003	Resorcinol (200 mg)	I0D135	0.998 mg/mg (ai)		H-1 (10/05) H (04/01)	[108-46-3]	$168
1602706	Ribavirin (200 mg)	H1C335			H (03/05) G (08/01)	[36791-04-5]	$313
1603006	Riboflavin (500 mg) (Vitamin B2)	N0C021			M-1 (09/04) M (11/00)	[83-88-5]	$168
1603800	Rifabutin (50 mg)	G0B040			F (11/02)	[72559-06-9]	$168
1604009	Rifampin (300 mg)	J			I (09/00)	[13292-46-1]	$168
1604202	Rifampin Quinone (50 mg)	H			G (12/01)	[13983-13-6]	$526
1604508	Rimantadine Hydrochloride (300 mg)	F0C266				[1501-84-4]	$168
1604600	Rimexolone (100 mg)	F				[49697-38-3]	$168
1604701	Ritodrine Hydrochloride (200 mg)	G-1				[23239-51-2]	$168
1605500	Ropivacaine Hydrochloride (200 mg)	F0E334	0.943 mg/mg (ai)	1		[132112-35-7]	$168
1605512	Ropivacaine Related Compound A (25 mg) (2,6-dimethylaniline hydrochloride)	F0E315	1.00 mg/mg (ai)	1		[21436-98-6]	$526
1605523	Ropivacaine Related Compound B (50 mg) ((R)-(+)-1-Propylpiperidine-2-carboxylic acid (2,6-dimethylphenyl)-amide hydrochloride monohydrate)	F0E318		1		[112773-90-7]	$526
1606208	Roxarsone (200 mg)	F				[121-19-7]	$168
1606503	Rutin (100 mg)	G0C355			F (09/05)	[153-18-4]	$168
1607007	Saccharin (200 mg)	G4C375			G-3 (03/06) G-2 (12/01)	[81-07-2]	$168
1608000	Salicylamide (200 mg)	F-4			F-3 (05/03)	[65-45-2]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1609002	Salicylic Acid (125 mg)	J3C400	0.994 mg/mg (ai)		J2B147 (01/06) J-1 (10/03) J (10/02) I (07/99)	[69-72-7]	$134
1609501	Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (30 tablets)	Q0D200			P0C404 (10/06) O (01/06) N (02/02)	[69-72-7]	$168
1609807	Salsalate (125 mg)	G				[552-94-3]	$134
1609829	Saquinavir Mesylate (200 mg)	F0B008				[149845-06-7]	$168
1609831	Saquinavir Related Compound A (25 mg) (N-*tert*-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide)	F0B009				n/f	$526
1610001	Scopolamine Hydrobromide (250 mg)	J0B051			I-1 (01/03)	[6533-68-2]	$168
1610090	Scopoletin (20 mg)	F0C329				[92-61-5]	$168
1611004	Secobarbital **CII** (200 mg)	H				[76-73-3]	$224
1611900	Selegiline Hydrochloride (200 mg)	G				[14611-52-0]	$168
1611955	Selenomethionine (100 mg)	F0B006				[1464-42-2]	$168
1612007	Sennosides (250 mg)	H1B223			H (04/04)	[81-27-6] (A) [128-57-4] (B)	$168
1612506	L-Serine (200 mg)	G			F-3 (11/00)	[56-45-1]	$168
1612404	Sesame Oil (1 mL/ampule; 2 ampules) (AS)	F0E134				[8008-74-0]	$168
1612415	Sesame Oil Related Compound A (6 mg/vial; 3 vials) (1,2-dilinoleoyl-3-oleoyl-rac-glycerol)	F0E131				[2190-21-8]	$526
1612426	Sesame Oil Related Compound B (6 mg/vial; 3 vials) (1,2-dilinoleoyl-3-palmitoyl-rac-glycerol, PLL)	F0E132				[64550-34-1]	$526
1612540	Sevoflurane (1 mL)	F0C219				[28523-86-6]	$168
1612550	Sevoflurane Related Compound A (0.2 mL) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether)	F0C261				[58109-34-5]	$526
1612572	Sevoflurane Related Compound B (0.2 mL) (1,1,1,3,3,3-hexafluoro-2-methoxypropane)	F0D140	1.00 mg/mg (ai)			[13171-18-1]	$526
1612594	Sevoflurane Related Compound C (0.2 mL) (1,1,1,3,3,3-hexafluoro-2-propanol)	F0D142	1.00 mg/mg (ai)			[920-66-1]	$526
1612608	Silver Sulfadiazine (200 mg)	I			H (04/01)	[22199-08-2]	$168
1612630	Silybin (50 mg)	G0D392	0.94 mg/mg (ai)		F (01/06)	[22888-70-6]	$168
1612641	Silydianin (20 mg)	F				[29782-68-1]	$168
1612652	Simethicone (50 g)	H0D084	5.3% SiO2 (ai)		G (11/04) F (07/00)	[8050-81-5]	$168
1612700	Simvastatin (200 mg)	I0D382	0.994 mg/mg (ai)		H1B093 (02/06) H (07/03) G (02/02) F-1 (05/99)	[79902-63-9]	$168
1612801	Sisomicin Sulfate (500 mg)	I0C238			H (04/04) G (10/00)	[53179-09-2]	$168
1612947	Beta-Sitosterol (300 mg)	F0D217	0.98 mg/mg (an)			[83-46-5]	$563
1613407	Sodium Acetate (1 g) (AS)	F0D083	99.8% (dr)			[127-09-3]	$168
1613509	Sodium Ascorbate (200 mg)	G2C067			G-1 (03/05)	[134-03-2]	$168
1613564	Sodium Benzoate (1 g)	F0E025				[532-32-1]	$168
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	99.7% (dr)			[144-55-8]	$168
1613600	Sodium Butyrate (25 mg)	F				[156-54-7]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1613757	Sodium Carbonate Anhydrous (1 g) (AS)	F0D100	100.0% (dr)			[497-19-8]	$168
1613804	Sodium Chloride (1 g) (AS)	F0D269	100.0% (ai)			[7647-14-5]	$168
1613859	Sodium Citrate (1 g) (AS)	F0D172	100.0% (an)			[6132-04-3]	$168
1614002	Sodium Fluoride (1 g)	I0E033	1.000 mg/mg (ai)		H-1 (03/06) H (05/01)	[7681-49-4]	$168
1614308	Sodium Lactate (200 mg)	J0E249	1.000 mg/mg (dr)		I0C299 (12/06) H (04/05) G (06/00)	[867-56-1]	$168
1614363	Sodium Lauryl Sulfate (1 g) (AS)	F0D381		1		[151-21-3]	$168
1614396	Sodium Metabisulfite (1 g) (AS)	F0D111	98.6% (ai)			[7681-57-4]	$168
1614454	Sodium Nitrite (1 g) (AS)	F0D117	99.6% (dr)			[7632-00-0]	$168
1614501	Sodium Nitroprusside (500 mg)	H			G (11/99)	[13755-38-9]	$168
1614603	Sodium Propionate (200 mg)	F-1			F (03/02)	[6700-17-0]	$168
1614669	Sodium Starch Glycolate Type A (400 mg)	G0E221			F0C087 (11/06)	[9063-38-1]	$168
1614670	Sodium Starch Glycolate Type B (400 mg)	F0E222				[9063-38-1]	$168
1614705	Sodium Stearyl Fumarate (200 mg)	G			F-2 (05/01)	[4070-80-8]	$168
1614807	Sodium Sulfate Anhydrous (1 g) (AS)	F0D112	99.8% (dr)			[7757-82-6]	$168
1615107	Sodium Thiosulfate (1 g) (AS)	F0D178	100.2% (an)			[10102-17-7]	$168
1615708	Somatropin (8.63 USP Somatropin Units/vial)	F0E191				[12629-01-5]	$182
1615956	Sorbic Acid (1 g) (AS)	F0D129	99.4% (ai)			[110-44-1]	$168
1616008	1,4-Sorbitan (200 mg)	I0A003			H (04/03) G (02/00)	[27299-12-3]	$168
1617000	Sorbitol (125 mg)	H1B139			H (01/04)	[50-70-4]	$134
1617408	Sotalol Hydrochloride (300 mg)	G0E198	0.997 mg/mg (ai)		F0C234 (09/06)	[959-24-0]	$197
1617419	Sotalol Related Compound A (50 mg) (N-[4-[[(1-Methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride)	F0C235				n/f	$526
1617420	Sotalol Related Compound B (50 mg) (N-(4-Formylphenyl)methanesulfonamide)	F0C236				n/f	$526
1617430	Sotalol Related Compound C (50 mg) (N-[4-[2-[(1-Methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride)	F0C237				n/f	$526
1618003	Spectinomycin Hydrochloride (200 mg)	G0C310	650 ug/mg (ai)		F-2 (01/05)	[22189-32-8]	$168
1619006	Spironolactone (125 mg)	J-1				[52-01-7]	$134
1619017	Spironolactone Related Compound A (100 mg) (Canrenone (3-Oxo-17-alpha-pregna-4,6-diene-21, 17-carbolactone)) (AS)	F0E184				[976-71-6]	$526
1619505	Squalane (500 mg)	G-1				[111-01-3]	$168
1620005	Stanozolol **CIII** (200 mg)	F-3			F-2 (02/01)	[10418-03-8]	$224
1620209	Stavudine (250 mg)	F0E050	0.997 mg/mg (ai)			[3056-17-5]	$260
1620220	Stavudine System Suitability Mixture (20 mg)	F0E051				n/f	$526
1621008	Stearic Acid (500 mg)	J1D360			J (02/06) I (10/01)	[57-11-4]	$168
1621507	Stearoyl Polyoxyglycerides (100 mg)	F0C286				n/f	$168
1622000	Stearyl Alcohol (125 mg)	H2B217			H-1 (12/04) H (09/99)	[112-92-5]	$134
1623003	Streptomycin Sulfate (200 mg)	J0B195			I (04/03)	[3810-74-0]	$168
1623502	Succinylcholine Chloride (500 mg)	H1E325	0.995 mg/mg (an)	2	H (12/06)	[71-27-2]	$168
1623604	Succinylmonocholine Chloride (150 mg)	G			F-1 (02/01)	n/f	$526
1623626	Sucralose (400 mg)				G0B028 (02/07) F (04/03)	[56038-13-2]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1623637	Sucrose (100 mg)	H1C223			H0B002 (11/04) G-1 (03/03) G (05/99)	[57-50-1]	$168
1623648	Sufentanil Citrate **CII** (25 mg)	H1E105	1.000 mg/mg (dr)		H0B208 (09/06) G (05/03) F-1 (04/02) F (09/99)	[60561-17-3]	$238
1623670	Sulbactam (250 mg)	H0C396	0.976 mg/mg (ai)		G (05/05) F-1 (05/00)	[68373-14-8]	$168
1623681	Sulconazole Nitrate (200 mg)	F-1			F (05/02)	[61318-91-0]	$168
1623706	Sulfabenzamide (200 mg)	G				[127-71-9]	$168
1623808	Sulfacetamide (300 mg)	G-2			G-1 (11/06)	[144-80-9]	$168
1624006	Sulfacetamide Sodium (500 mg)	I1B318			I (09/04) H (08/01)	[6209-17-2]	$168
1624505	Sulfachlorpyridazine (200 mg)	F				[80-32-0]	$168
1625009	Sulfadiazine (200 mg)	J			I (03/04)	[68-35-9]	$168
1626001	Sulfadimethoxine (200 mg)	G0D249	0.998 mg/mg (ai)		F4C298 (09/05) F-3 (11/04) F-2 (03/99)	[122-11-2]	$168
1626500	Sulfadoxine (200 mg)	F3C336	0.999 mg/mg (ai)		F-2 (10/05) F-1 (07/02)	[2447-57-6]	$168
1628007	Sulfamerazine (500 mg)	H1C171			H (12/04)	[127-79-7]	$168
1629000	Sulfamethazine (1 g)	G-3				[57-68-1]	$168
1630009	Sulfamethizole (200 mg)	F-3			F-2 (01/03)	[144-82-1]	$168
1631001	Sulfamethoxazole (200 mg)	I-1			I (04/02)	[723-46-6]	$168
1631500	Sulfamethoxazole N4-glucoside (25 mg)	H1D290	0.98 mg/mg (ai)		H (01/06) G (11/01)	n/f	$526
1632004	Sulfanilamide (5 g)	O0B047			N (01/04)	[63-74-1]	$168
1633007	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)	K0B133			J-1 (03/04) J (09/99)	[63-74-1]	$81
1633506	Sulfanilic Acid (200 mg)	G			F-2 (09/00)	[121-57-3]	$526
1634000	Sulfapyridine (200 mg)	I0B298			H (07/04)	[144-83-2]	$168
1635002	Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees)	J1E042			J (11/06) I (07/00)	[144-83-2]	$100
1635206	Sulfaquinoxaline (200 mg)	F0A005				[59-40-5]	$168
1635228	Sulfaquinoxaline Related Compound A (25 mg) (N1,N2-diquinoxalin-2-ylsulfanilamide)	F0E093	0.96 mg/mg (ai)			n/f	$526
1636005	Sulfasalazine (125 mg)	G3F035	1.000 mg/mg (dr)	2	G-2 (02/07) G-1 (06/99)	[599-79-1]	$134
1636504	Sulfathiazole (350 mg)	H			G (08/00)	[72-14-0]	$168
1637008	Sulfinpyrazone (200 mg)	H0C416	0.992 mg/mg (ai)		G (03/05)	[57-96-5]	$168
1638000	Sulfisoxazole (200 mg)	J			I-1 (06/99)	[127-69-5]	$168
1639003	Sulfisoxazole Acetyl (200 mg)	H-1				[80-74-0]	$168
1640002	Sulfisoxazole Diolamine (500 mg) **DISCONTINUED**			9	F (02/07)	[4299-60-9]	$168
1642008	Sulindac (200 mg)	H			G-1 (12/01)	[38194-50-2]	$168
1642019	Sulindac Related Compound A (20 mg) (trans-sulindac)	F0E314		1		[53933-60-1]	$526
1642154	Sumatriptan (50 mg)	F0C220				[103628-46-2]	$225
1642201	Sumatriptan Succinate (200 mg)	F1E256	0.989 mg/mg (ai)		F0C231 (10/06)	[103628-48-4]	$225

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1642212	Sumatriptan Succinate Related Compound A (15 mg) ([3-[2-(dimethylamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-indol-5-yl]-N-methylmethansulfonamide, succinate salt)				F0C221 (01/07)	n/f	$675
1642223	Sumatriptan Succinate Related Compound C (50 mg) ([3-[2-(dimethylamino)ethyl]-1-(hydroxymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt)	F0C230				n/f	$675
1642256	Sumatriptan Succinate Related Impurities (25 mg)	F0E046				n/f	$675
1642507	Suprofen (200 mg)	F				[40828-46-4]	$168
1642700	Tacrine Hydrochloride (500 mg)	F0C119				[1684-40-8]	$168
1642904	Tagatose (200 mg)	F0E017	0.996 mg/mg (dr)			[87-81-0]	$189
1643000	Talbutal **CIII** (250 mg)	F				[115-44-6]	$224
1643306	Tamoxifen Citrate (200 mg)	I0D294	0.994 mg/mg (ai)		H (10/05) G-2 (09/01) G-1 (05/00)	[54965-24-1]	$168
1643328	Tannic Acid (2 g) (AS)	F0D292				[1401-55-4]	$168
1643340	Tartaric Acid (1 g) (AS)	F0D176	100.0% (dr)			[87-69-4]	$168
1643361	Taurine (100 mg)	F0C104				[107-35-7]	$168
1643408	Temazepam **CIV** (200 mg)	H0C205			G (06/04) F (12/99)	[846-50-4]	$224
1643452	Terazosin Hydrochloride (200 mg)	F0C244				[70024-40-7]	$168
1643463	Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride)	F0C245				n/f	$526
1643474	Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine)	F0C218				n/f	$526
1643485	Terazosin Related Compound C (25 mg) (1,4-bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride)	F0C257				n/f	$526
1643500	Terbutaline Sulfate (125 mg)	H			G (04/99)	[23031-32-5]	$134
1643510	Terbutaline Related Compound A (50 mg) (tert-butylamino-3,5-dihydroxyacetophenone sulfate)	F0D289				n/f	$526
1643703	Terconazole (200 mg)	H0E229			G3C322 (09/06) G-2 (08/05) G-1(04/01) G (03/99)	[67915-31-5]	$168
1643805	Terfenadine (200 mg)	H			G (12/99)	[50679-08-8]	$168
1643907	Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanone)	G				n/f	$526
1643929	Terfenadine Related Compound B (50 mg) (Terfenadine-N-oxide)	F				n/f	$526
1644003	Terpin Hydrate (750 mg)	H0C395	0.999 mg/mg (an)		G (06/06)	[2451-01-6]	$168
1645006	Testolactone **CIII** (125 mg)	F-1				[968-93-4]	$179
1646009	Testosterone **CIII** (125 mg)	I1B253			I (08/04)	[58-22-0]	$179
1647001	Testosterone Cypionate **CIII** (200 mg)	H0D162	1.000 mg/mg (ai)		G-1 (03/05) G (08/01)	[58-20-8]	$224
1648004	Testosterone Enanthate **CIII** (200 mg)	K0D253	0.998 mg/mg (ai)		J (07/06)	[315-37-7]	$224

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1649007	Testosterone Propionate **CIII** (200 mg)	L1C005			L (08/04) K-1 (11/01)	[57-85-2]	$224
1650006	Tetracaine Hydrochloride (200 mg)	J				[136-47-0]	$168
1651009	Tetracycline Hydrochloride (200 mg)	L0C216	976 ug/mg (ai)		K (12/04)	[64-75-5]	$168
1652001	Tetrahydrozoline Hydrochloride (200 mg)	G1A015			G (03/03)	[522-48-5]	$168
1652500	Thalidomide (200 mg)	F0C107				[50-35-1]	$197
1653004	Theophylline (200 mg)	J0B180			I (01/04)	[58-55-9]	$168
1655000	Thiabendazole (100 mg)	G0A027			F-1 (04/03) F (04/01)	[148-79-8]	$168
1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O			N (11/02) M-1 (04/99)	[67-03-8]	$168
1656308	Thiamylal **CIII** (200 mg)	F				[77-27-0]	$224
1657005	Thiethylperazine Malate (200 mg)	G			F-1 (09/00)	[52239-63-1]	$168
1658008	Thiethylperazine Maleate (200 mg)	F-1				[1179-69-7]	$168
1659000	Thimerosal (500 mg)	H1B205			H (09/04) G (12/99)	[54-64-8]	$168
1660000	Thioguanine (200 mg)	F-1				[154-42-7]	$168
1661002	Thiopental **CIII** (250 mg)	I1D198	1.000mg/mg (dr)		I (09/05)	[76-75-5]	$224
1662504	Thioridazine (200 mg)	H				[50-52-2]	$168
1663008	Thioridazine Hydrochloride (200 mg)	H				[130-61-0]	$168
1663700	Thiostrepton (200 mg)	G0E175	1075 USP Thiostrepton Units/mg (dr)		F1B022 (10/06) F (11/02)	[1393-48-2]	$168
1664000	Thiotepa (500 mg)	I			H (01/99)	[52-24-4]	$168
1665003	Thiothixene (250 mg)	G				[3313-26-6]	$168
1666006	(E)-Thiothixene (100 mg)	H			G-1 (05/00)	[3313-27-7]	$526
1667100	Thonzonium Bromide (200 mg)	F				[553-08-2]	$168
1667202	L-Threonine (200 mg)	G			F-3 (12/00)	[72-19-5]	$168
1667213	Thymol (500 mg)	F0D391				[89-83-8]	$168
1667280	Tiagabine Hydrochloride (300 mg)	F0E178	0.998 mg/mg (an)			[145821-59-6]	$260
1667235	Racemic Tiagabine Hydrochloride Mixture (25 mg) ((S)-(+),(R)-(-)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid, hydrochloride)	F0E179				n/f	$526
1667224	Tiagabine Related Compound A (15 mg) ((R)-ethyl 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate, hydrochloride)	F0E177				n/f	$526
1667355	Tiamulin (100 mg)	F0E219				[55297-95-5]	$168
1667290	Tiamulin Fumarate (250 mg)	F0C327				[55297-96-6]	$168
1667337	Tiamulin Related Compound A (50 mg) (Tosyl pleuromutilin)	F0C328				n/f	$535
1667304	Ticarcillin Monosodium Monohydrate (200 mg)	H			G-1 (03/99)	[74682-62-5]	$168
1667359	Tiletamine Hydrochloride (200 mg)	F0C019				[14176-50-2]	$168
1667370	Tilmicosin (400 mg)	F0D393	830 ug/mg cis (an) 126 ug/mg trans (an)			[108050-54-0]	$168
1667406	Timolol Maleate (200 mg)	G-1				[26921-17-5]	$168
1667520	Tinidazole (200 mg)	F0C093				[19387-91-8]	$168
1667530	Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole)	F0C091				[696-23-1]	$526
1667541	Tinidazole Related Compound B (20 mg) (1-(2-ethyl-sulfonylethyl)-2-methyl-4-nitroimidazole)	F0E274	1.00 mg/mg (ai)			[25459-12-5]	$526
1667439	Tioconazole (200 mg)	H			G (04/02)	[65899-73-2]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1667450	Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride)				G (02/07)	n/f	$526
1667461	Tioconazole Related Compound B (25 mg) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]-phenethyl]imidazole Hydrochloride)	G				n/f	$526
1667472	Tioconazole Related Compound C (25 mg) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride)	G				n/f	$526
1667585	Titanium Dioxide (1 g) (AS)	F0D079	99.6% (dr)			[13463-67-7]	$168
1667508	Tobramycin (350 mg)	L0E077	970 ug/mg (an)		K0B248 (07/06) J (08/03)	[32986-56-4]	$182
1667552	Tocainide Hydrochloride (125 mg)	F-1			F (04/99)	[35891-93-1]	$134
1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M			L-1 (01/00)	[10191-41-0]	$168
1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K			J (06/99)	[7695-91-2]	$168
1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)	G0D077	0.995 mg/mg GC 0.978 mg/mg HPLC (ai)		F-5 (05/05) F-4 (01/02)	[4345-03-3]	$168
1668001	Tolazamide (200 mg)	G-2			G-1 (06/00)	[1156-19-0]	$168
1669004	Tolazoline Hydrochloride (300 mg)	F				[59-97-2]	$168
1670003	Tolbutamide (200 mg)	I			H (06/00)	[64-77-7]	$168
1670207	Tolcapone (200 mg)	F0D280	0.999 mg/mg (ai)			[134308-13-7]	$168
1670218	Tolcapone Related Compound A (25 mg) (4'-methyl-3,4-dihydroxybenzophenone)	F0D282				n/f	$526
1670229	Tolcapone Related Compound B (25 mg) (4-hydroxy-3-methoxy-4'-methyl-5-nitrobenzophenone)	F0D284				n/f	$526
1670502	Tolmetin Sodium (500 mg)	I0B064			H (09/03)	[64490-92-2]	$168
1671006	Tolnaftate (200 mg)	J0C405	1.000 mg/mg (dr)		I (02/05)	[2398-96-1]	$168
1672010	o-Toluenesulfonamide (200 mg)	F0E163	1.00 mg/mg (ai)			[88-19-7]	$263
1672020	p-Toluenesulfonamide (200 mg)	F0E162	1.00 mg/mg (ai)			[70-55-3]	$263
1672304	Torsemide (200 mg)	F0B090				[56211-40-6]	$168
1672315	Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B071				n/f	$526
1672326	Torsemide Related Compound B (75 mg) (N-[(n-butylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B083				n/f	$526
1672337	Torsemide Related Compound C (75 mg) (N-[(ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B078				n/f	$526
1672803	Transplatin (25 mg)	H0B287			G (03/04)	[14913-33-8]	$526
1673500	Trazodone Hydrochloride (200 mg)	F-2				[25332-39-2]	$168
1673806	Trenbolone **CIII** (50 mg)	F0D389	0.99 mg/mg (ai)			[10161-33-8]	$179
1673828	Trenbolone Acetate **CIII** (200 mg)	F0D390	0.999 mg/mg (ai)			[10161-34-9]	$179
1674004	Tretinoin (30 mg/vial; 5 vials)	J0D145	0.996 mg/mg (ai)		I2B185 (01/06) I-1 (01/04) I (01/02) H (06/01)	[302-79-4]	$168
1675007	Triacetin (1 g)	H0C413			G-1 (02/05) G (06/01)	[102-76-1]	$168
1676000	Triamcinolone (250 mg)	H-1				[124-94-7]	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1677002	Triamcinolone Acetonide (500 mg)	K			J (03/99)	[76-25-5]	$168
1678005	Triamcinolone Diacetate (200 mg)	G				[67-78-7]	$168
1679008	Triamcinolone Hexacetonide (125 mg)	G				[5611-51-8]	$134
1680007	Triamterene (200 mg)	I				[396-01-0]	$168
1680506	Triazolam **CIV** (200 mg)	H0B041			G-1 (03/03)	[28911-01-5]	$224
1680608	Tributyl Citrate (500 mg)	G0C227			F (01/05)	[77-94-1]	$168
1680801	Trichlorfon (200 mg)	F				[52-68-6]	$168
1681000	Trichlormethiazide (200 mg)	H				[133-67-5]	$168
1682206	Triclosan (200 mg)	G0D001	0.997 mg/mg (ai)		F0B135 (05/05)	[3380-34-5]	$168
1682217	Triclosan Related Compounds Mixture A (1.2 mL/ampule; 3 ampules)	F0E292				n/f	$526
1683005	Tridihexethyl Chloride (200 mg)	F-1				[4310-35-4]	$168
1683504	Trientine Hydrochloride (125 mg)	F2B257			F-1 (09/03) F (08/96)	[38260-01-4]	$134
1683606	Triethyl Citrate (500 mg)	G0C393			F-1 (10/05) F (03/02)	[77-93-0]	$168
1685000	Trifluoperazine Hydrochloride (200 mg)	H0A010			G (03/03)	[440-17-5]	$168
1685500	2-[N-(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone (25 mg)	F				n/f	$526
1686003	Triflupromazine Hydrochloride (200 mg)	F-2			F-1 (03/04)	[1098-60-8]	$168
1686309	Trifluridine (200 mg)	F				[70-00-8]	$194
1686310	Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine)	G0E004	1.00 mg/mg (ai)		F (02/06)	[14599-46-3]	$526
1687006	Trihexyphenidyl Hydrochloride (200 mg)	J			I (07/01)	[52-49-3]	$168
1689001	Trimeprazine Tartrate (200 mg)	F-3			F-2 (08/01)	[4330-99-8]	$168
1690000	Trimethadione (200 mg)	G				[127-48-0]	$168
1692006	Trimethobenzamide Hydrochloride (500 mg)	H-2			H-1 (06/02)	[554-92-7]	$168
1692505	Trimethoprim (300 mg)	J0B228			I (01/04)	[738-70-5]	$168
1693009	Trioxsalen (200 mg)	H0C278			G (04/04)	[3902-71-4]	$168
1694001	Tripelennamine Citrate (200 mg) **DISCONTINUED**			9	G (02/07) F (02/03)	[6138-56-3]	$168
1695004	Tripelennamine Hydrochloride (200 mg)	J				[154-69-8]	$168
1696007	Triprolidine Hydrochloride (500 mg)	I			H-1 (02/02)	[6138-79-0]	$168
1696109	Triprolidine Hydrochloride Z-Isomer (100 mg)	G			F-1 (02/02)	n/f	$526
1696200	Trisalicylic Acid (100 mg)	G			F-1 (10/99)	n/f	$526
1696958	Trolamine (3 mL)	F0D120				[102-71-6]	$168
1697000	Troleandomycin (250 mg)	F-1				[2751-09-9]	$168
1698002	Tromethamine (125 mg)	G			F-3 (07/99)	[77-86-1]	$134
1699005	Tropicamide (200 mg)	H0E307	0.99 mg/mg (ai)	2,3	G-1 (01/07) G (02/99)	[1508-75-4]	$134
1700002	Trypsin Crystallized (300 mg)	I0E055	3250 USP Trypsin Units/mg (dr)		H (01/06) G (12/99)	[9002-07-7]	$168
1700501	L-Tryptophan (200 mg)	G2E237			G-1 (12/06) G (09/00)	[73-22-3]	$168
1702008	Tubocurarine Chloride (250 mg)	K-1				[6989-98-6]	$168
1703805	Tylosin (250 mg)	F0C008				[1401-69-0]	$168
1703850	Tylosin Tartrate (100 mg)	F0D333				[1405-54-5]	$168
1704003	Tyloxapol (600 mg)	I0E111			H (07/06) G (02/00)	[25301-02-4]	$168
1704502	Tyropanoate Sodium (500 mg)	F				[7246-21-1]	$168
1705006	L-Tyrosine (500 mg)	K0C141	1.00 mg/mg (ai)		J (05/05)	[60-18-4]	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1705301	Ubidecarenone (200 mg)	G0E154	0.999 mg/mg (ai)		F0B191 (04/06)	[303-98-0]	$270
1705323	Ubidecarenone Related Compound A (15 mg) (Coenzyme Q9)	F0E210				[303-97-9]	$526
1705312	Ubidecarenone for System Suitability (25 mg)	F0B194				[303-98-0]	$526
1705505	Undecylenic Acid (200 mg)	G2C018			G-1 (11/04) G (01/02)	[112-38-9]	$168
1705800	Uracil Arabinoside (50 mg)	G			F-1 (06/99)	[3083-77-0]	$168
1706009	Uracil Mustard (500 mg) (FOR U.S. SALE ONLY)	F				[66-75-1]	$168
1706698	Urea (200 mg)	F0D331	1.00 mg/mg (ai)			[57-13-6]	$168
1706701	Urea C 13 (100 mg)	H0E110	0.999 mg/mg (dr)		G0D374 (11/06) F0C078 (12/05)	[58069-82-2]	$197
1707806	Ursodiol (125 mg)	G			F-1 (11/01) F (09/99)	[128-13-2]	$134
1707908	Valerenic Acid (15 mg)	H0D126	1.00 mg/mg (ai)		G0B146 (05/05) F (01/04)	[3569-10-6]	$753
1708503	L-Valine (200 mg)	F-2			F-1 (05/02)	[72-18-4]	$168
1708707	Valproic Acid (500 mg)	K0D224	0.999 mg/mg (ai)		J1B127 (08/05) J (01/04) I-1 (11/00)	[99-66-1]	$168
1708729	Valproic Acid Related Compound A (0.25 mL) (diallylacetic acid)	G0C398			F2C386 (02/06) F1B156 (05/05) F (01/03)	[99-67-2]	$526
1708718	Valproic Acid Related Compound B (50 mg) ((2RS)-2-(1-methylethyl)pentanoic acid) (AS)	F0E201		1		[62391-99-5]	$526
1708762	Valsartan (350 mg)	F0C147	0.995 mg/mg (an)			[137862-53-4]	$168
1708773	Valsartan Related Compound A (10 mg) ((R)-N-Valeryl-N-([2'-(1H-tetrazole-5-yl)-biphen-4-yl]-methyl)-valine)	F1E272	0.96 mg/mg (ai)		F0C215 (10/06)	n/f	$675
1708795	Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole-5-yl)biphenyl-4-yl]-methyl)valine benzyl ester)	F1D025	0.99 mg/mg (ai)		F0C208 (09/05)	n/f	$675
1709007	Vancomycin Hydrochloride (4 vials, each vial contains 100,500 mcg of vancomycin activity)	L1D039			L (07/05) K (08/01)	[1404-93-9]	$168
1710006	Vanillin (200 mg)	J0A021			I (03/05) H (04/99)	[121-33-5]	$168
1711009	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)	J1C303			J (06/05) I-1 (03/03) I (11/00)	[121-33-5]	$100
1711155	Vecuronium Bromide (50 mg)	F0C367				[50700-72-6]	$168
1711166	Vecuronium Bromide Related Compound A (25 mg) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan)	F0B178				n/f	$526
1711202	Verapamil Hydrochloride (200 mg)	G1E095	0.999 mg/mg (dr)		G (08/06) F-4 (06/00)	[152-11-4]	$168
1711304	Verapamil Related Compound A (50 mg) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-alpha-(1-methylethyl)-benzeneacetonitrile mono-Hydrochloride)	H			G (01/01)	n/f	$526
1711406	Verapamil Related Compound B (50 mg) (alpha-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-alpha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride)	G				[1794-55-4]	$526

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1711428	Verapamil Related Compound D (50 mg) (5,5'-[[2-(3,4)dimethoxyphenyl)ethyl]imino]bis[2-(3,4-dimethoxyphenyl)-2-(1-methylethyl)pentanenitrile] hydrochloride)	F0E342		1		[190850-50-1]	$526
1711461	Verteporfin (200 mg)	F0C166				[129497-78-5]	$168
1711472	Verteporfin Related Compound A (50 mg) ((+/-)-18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-benzo[b]-prophine-9,13-dipropanoic acid)	F0C167				n/f	$526
1711508	Vidarabine (200 mg)	G-2	939 ug/mg (ai)		G-1 (09/05)	[24356-66-9]	$168
1713004	Vinblastine Sulfate (50 mg)	M0B308			L (12/04) K (05/99)	[143-67-9]	$383
1714007	Vincristine Sulfate (50 mg/ampule)	O0B062			N (01/03) M (04/99)	[2068-78-2]	$518
1714506	Vinorelbine Tartrate (200 mg)	F1E133	0.994 mg/mg (an)		F0C243 (08/05)	[125317-39-7]	$1,631
1714528	Vinorelbine Related Compound A (25 mg) (4-O-Deacetylvinorelbine tartrate)	F0C242				n/f	$815
1715000	Viomycin Sulfate (200 mg)	F				[37883-00-4]	$168
1716002	Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil)				V0C258 (12/05) U (04/04)	[127-47-9]	$168
1717504	Vitamin D Assay System Suitability (1.5 g)	F-1			F (08/06)	[67-97-0]	$168
1717708	Vitexin (30 mg)	F0C142				[3681-93-4]	$563
1719000	Warfarin (200 mg)	I0B305			H-2 (08/04) H-1 (11/01)	[81-81-2]	$168
1719102	Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one)	H0E268		2	G1B111 (02/07) G (01/04)	[37209-23-7]	$168
1720000	Xanthanoic Acid (100 mg)	G-1			G (12/00)	[82-07-5]	$526
1720203	Xanthone (100 mg)	F-1				[90-47-1]	$526
1720407	Xylazine (200 mg)	F1C001			F (02/05)	[7361-61-7]	$168
1720429	Xylazine Hydrochloride (200 mg)	F				[23076-35-9]	$168
1720600	Xylitol (1 g)	G0B037			F-3 (11/02) F-2 (05/00)	[87-99-0]	$168
1721002	Xylometazoline Hydrochloride (125 mg)	I0B101			H-1 (05/03)	[1218-35-5]	$134
1722005	Xylose (1 g)	F				[58-86-6]	$168
1724000	Yohimbine Hydrochloride (200 mg)	F				[65-19-0]	$168
1724306	Zalcitabine (200 mg)	F				[7481-89-2]	$168
1724317	Zalcitabine Related Compound A (50 mg) (2',3'-Didehydro-2',3'-dideoxycytidine)	F0B234				[7481-88-1]	$526
1724500	Zidovudine (400 mg)	G1D319	0.991 mg/mg (ai)		G (10/05) F (09/01)	[30516-87-1]	$168
1724521	Zidovudine Related Compound B (25 mg) (3'-chloro-3'-deoxythymidine)	G0B116			F-1 (03/03) F (06/01)	[25526-94-7]	$526
1724532	Zidovudine Related Compound C (100 mg) (thymine)	F-1			F (09/01)	[65-71-4]	$526
1724656	Zileuton (150 mg)	F0C062				[111406-87-2]	$168
1724667	Zileuton Related Compound A (50 mg) (N-(1-Benzo[b]thien-2-ylethyl) urea)	F0B316				n/f	$526
1724678	Zileuton Related Compound B (50 mg) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene)	F0B313				n/f	$526
1724689	Zileuton Related Compound C (50 mg) (1-Benzo[b]thien-2-ylethanone)	F0B299				n/f	$526
1724747	Zinc Oxide (2 g) (AS)	F0D170	99.7% (ig)			[1314-13-2]	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1724769	Zinc Sulfate (1 g) (AS)	F0D133	56.4% (ai)			[7446-20-2]	$168
1724805	Zolazepam Hydrochloride (500 mg)	G0C023			F-1 (03/04) F (05/02)	[33754-49-3]	$168

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
00200-6	5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid (50 mg) (Limit Test)	1184027	Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid)
1008002	alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane	1008002	Propoxyphene Related Compound B (50 mg) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane)
1021703	N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine (25 mg)	1021703	Nitrofurantoin Related Compound A (25 mg) (N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine)
02200-3	3-Amino-4-carboxamidopyrazole Hemisulfate (50 mg) **(Limit Test)**	1013024	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)
02250-2	4-Amino-6-chloro-1,3-benzenedisulfonamide (100 mg) **(Limit Test)**	1057507	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)
1023403	3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg)	1023403	Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril)
02380-0	2-Amino-2'-chloro-5-nitrobenzophenone (25 mg) **(Limit Test)**	1140338	Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone)
02420-2	4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide (100 mg) (Limit Test)	1424018	Methyclothiazide Related Compound A (100 mg) (4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide)
02240-6	2-Amino-4-chlorophenol (50 mg) **(Limit Test)**	1130527	Chlorzoxazone Related Compound A (25 mg) (2-Amino-4-chlorophenol)
02460-0	3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril (25 mg) **(Limit Test)**	1140327	Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril)
02490-5	2-Amino-2',5-dichlorobenzophenone (25 mg) **(Limit Test)**	1370338	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)
02610-6	3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) **(Limit Test)**	1078325	Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)
02620-8	alpha-Aminopropiophenone Hydrochloride (50 mg) **(Limit Test)**	1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)
1042000	Aprobarbital **CIII** (200 mg) (AS) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/07)
06300-0	5-Benzyl-3,6-dioxo-2-piperazineacetic Acid (250 mg) **(Limit Test)**	1043728	Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid)
07350-3	2-(4-Biphenylyl)propionic Acid (100 mg) **(Limit Test)**	1285760	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)
07480-1	N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide (50 mg) **(Limit Test)**	1344724	Iopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide)
07500-4	4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone (25 mg) (Limit Test)	1303013	Haloperidol Related Compound A (25 mg) (4,4-Bis[4-p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone
1076002	4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone (25 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: G (05/03)
08650-5	Calcium Formyltetrahydrofolate (50 mg) (AS) (For Qualitative Use Only)	1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)
11230-0	p-Chlorobenzhydrylpiperazine (25 mg)	1333058	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)
11310-9	6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde (25 mg) **(Limit Test)**	1370349	Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde)
11320-0	6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid (25 mg) **(Limit Test)**	1370350	Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid)
11330-2	6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol (25 mg) **(Limit Test)**	1370360	Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol)
11400-0	7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (50 mg) **(Limit Test)**	1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)
11500-2	7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (25 mg) **(Limit Test)**	1110020	Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide)
11510-4	2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid (50 mg) **(Limit Test)**	1287020	Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid)
11550-1	2-Chloro-3,5-dimethyl-phenol (50 mg) **(Limit Test)**	1122722	Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5-dimethyl-phenol)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
11650-4	(o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test)	1141024	Clotrimazole Related Compound A (25 mg) ((o-Chlorophenyl)diphenyl-methanol)
11670-8	4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) **(Limit Test)**	1048222	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)
11900-3	4-Chloro-5-sulfamoylanthranilic Acid (100 mg) **(Limit Test)**	1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)
1119309	4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid (100 mg)	1119309	Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid)
1153001	Cyclizine (1 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (04/04)
15870-8	Cyclosporine U (25 mg) **DISCONTINUED**	1158650	Cyclosporine Resolution Mixture (25 mg) (Replaces Cat. No. 15870-8 Cyclosporine U (25 mg))
21000-3	alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (125 mg) **(Limit Test)**	1575206	Propoxyphene Related Compound A (50 mg) (alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride)
1216000	Diphemanil Methylsulfate (500 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H(03/06)
1268820	Etoposide Related Compound A (25 mg) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) **DISCONTINUED**	1268852	Etoposide Resolution Mixture (30 mg)
1269006	Evans Blue (200 mg)	N/A	DISCONTINUED, Last Lot/Valid Use Date: G (04/04)
1277208	Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) (180 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (01/04)
1286209	4-Formylbenzenesulfonamide (50 mg)	1286209	Mafenide Related Compound A (50 mg) (4-Formylbenzenesulfonamide)
1294003	Glucagon (25 mg, 0.95 U/mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H (01/05)
1312003	Hyaluronidase (500 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H (06/05)
32720-4	3-Hydroxy-1-methylquinuclidinium Bromide (250 mg) **(Limit Test)**	1135021	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)
1329505	9-Hydroxypropantheline Bromide (50 mg)	1329505	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)
1330005	Hydroxypropyl Methylcellulose (250 mg)	1330005	Hypromellose (250 mg) (Hydroxypropyl Methylcellulose)
33010-7	Hydroxypropyl Methylcellulose Phthalate (100 mg)	1335304	Hypromellose Phthalate (100 mg)
1359007	Levallorphan Tartrate (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: G-1 (09/04)
1362001	Levo-alpha-acetylmethadol Hydrochloride **CII** (25 mg) (AS) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (08/03)
	Melting Point Standard - Acetanilide (500 mg; approximately 114 degrees)	1004001	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)
	Melting Point Standard - Caffeine (1 g; approximately 236 degrees)	1086006	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)
	Melting Point Standard - Phenacetin (500 mg; approximately 135 degrees)	1514008	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)
	Melting Point Standard - Sulfanilamide (1 g; approximately 165 degrees)	1633007	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)
	Melting Point Standard - Sulfapyridine (2 g; approximately 191 degrees)	1635002	Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees)
	Melting Point Standard - Vanillin (1 g; approximately 82 degrees)	1711009	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)
1384004	Mephentermine Sulfate (250 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (04/05)
1420006	3-Methoxytyrosine (50 mg)	1420006	Levodopa Related Compound B (50 mg) (3-Methoxytyrosine)
42420-0	2-Methylamino-5-chlorobenzophenone (25 mg) **(Limit Test)**	1185020	Diazepam Related Compound A (25 mg) (2-Methylamino-5-chlorobenzophenone)
42430-2	3-O-Methylcarbidopa (50 mg)	1095517	Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
1434000	Methylphenidate Hydrochloride Erythro Isomer **CII** (25 mg) **DISCONTINUED**; Last Lot/Valid Use Date: J0B294 (04/05); please order 1434011	1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)
1445222	Mitoxantrone Related Compound A Hydrochloride (30 mg) (8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride) **DISCONTINUED**; Please order 1445211	1445211	Mitoxantrone System Suitability Mixture (0.3 mg)
46600-7	5-Nitro-2-furfuraldazine (500mg)	1466007	Nitrofurazone Related Compound A (500mg) (5-Nitro-2-furfuraldazine)
46660-8	3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) **(Limit Test)**	1078336	Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid)
1477900	Octyl Methoxycinnamate (500 mg)	1477900	Octinoxate (500 mg) (Octyl Methoxycinnamate)
1477943	Octyl Salicylate (400 mg)	1477943	Octisalate (400 mg) (Octyl Salicylate)
1481500	Oxamniquine (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/05)
1481703	Oxamniquine Related Compound A (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/05)
1481805	Oxamniquine Related Compound B (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/05)
1489002	Oxyphenbutazone (1 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H(12/05)
1500229	Paroxetine Related Compound A (10 mg) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F1D058 (10/05)
49400-2	Pancreatin (2 g)	1494057 and/or 1494079	Pancreatin Amylase and Protease (2 g) and/or Pancreatin Lipase (2 g)
1527000	Phenprocoumon (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/04)
53180-1	Phenylcyclohexylglycolic Acid (100 mg) **(Limit Test)**	1485114	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)
53350-1	alpha-Phenyl-2-piperidineacetic Acid Hydrochloride (50 mg) **(Limit Test)**	1434022	Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride)
54500-1	Plastic, Negative Control	1546707	Polyethylene, High Density (3 strips)
1576720	Propylene Glycol Diacetate (250 mg) **DISCONTINUED**	N/A	**DISCONTINUED**, Last Lot/Valid Use Date: F (09/05)
61500-5	Sodium Taurocholate (20 g)	1071304	Bile Salts (10 g) (Sodium Taurocholate)
1640002	Sulfisoxazole Diolamine (500 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (02/07)
1653106	Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (11/04)
1667279	Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/04)
1672009	Toluenesulfonamides, ortho and para (200 mg of each supplied in a set) **DISCONTINUED**	1672010 and 1672020	o-Toluenesulfonamide (200 mg) and p-Toluensulfonamide (200 mg)
68800-9	3-(3,4,6-Trihydroxyphenyl)-alanine (50 mg) **(Limit Test)**	1361010	Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)-alanine)
1694001	Tripelennamine Citrate (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: G (02/07)
	Vitamin B1 Hydrochloride	1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)
	Vitamin B2	1603006	Riboflavin (500 mg) (Vitamin B2)
	Vitamin B3	1462006	Niacinamide (500 mg) (Vitamin B3)
	Vitamin B5	1087009	Calcium Pantothenate (200 mg) (Vitamin B5)
	Vitamin B6	1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)
	Vitamin B12	1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)
	Vitamim Bc	1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
	Vitamin C	1043003	Ascorbic Acid (1 g) (Vitamin C)
	Vitamin D2	1239005	Ergocalciferol (150 mg; 30 mg/ampule; 5 ampules) (Vitamin D2)
	Vitamin D3	1131009	Cholecalciferol (30 mg/ampul; 5 ampuls) (Vitamin D3)
	Vitamin E Alcohol	1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)
	Vitamin E Acetate	1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)
	Vitamin E Acid Succinate	1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)
	Vitamin K1	1538006	Phytonadione (500 mg) (Vitamin K1)
	Vitamin K3	1381006	Menadione (200 mg) (Vitamin K3)
	Vitamin M	1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
1005706	Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D002	$168
1036507	3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile (25 mg) (AS)	G2D383	$526
1017364	Aluminum Sulfate (2 g) (AS)	F0D342	$168
1019712	Amiloride Related Compound A (30 mg) (AS) (Methyl 3,5-diamino-6-chloropyrazine-2-carboxylate)	F0E287	$526
1029942	Ammonium Carbonate (2 g) (AS)	F0D102	$168
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	$168
1042000	Aprobarbital **CIII** (200 mg) (AS)	F-1	$224
1043105	Ascorbyl Palmitate (2 g) (AS)	F0D326	$168
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272	$224
1075600	Bismuth Subcarbonate (1 g) (AS)	F0D324	$168
1075622	Bismuth Subgallate (2 g) (AS)	F0D323	$168
1075644	Bismuth Subnitrate (1.5 g) (AS)	F0D388	$168
1076341	Boric Acid (1 g) (AS)	F0D036	$216
1082708	Butylated Hydroxytoluene (500 mg) (AS)	F0D122	$168
1086334	Calcium Acetate (1 g) (AS)	F0D156	$168
1086403	Calcium Carbonate (1 g) (AS)	F0D099	$168
1086436	Calcium Chloride (1 g) (AS)	F0D153	$168
1086855	Calcium Hydroxide (1 g) (AS)	F0D168	$168
1086935	Calcium Levulinate (1 g) (AS)	F0E142	$168
1087031	Tribasic Calcium Phosphate (1 g) (AS)	F0D394	$168
1087359	Calcium Stearate (2 g) (AS)	F0D255	$168
1087406	Calcium Sulfate (1 g) (AS)	F0D236	$168
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2	$526
1090003	Cannabinol **CI** (25 mg) (AS)		$224
1096531	Carboxymethylcellulose Calcium (1.5 g) (AS)	F0D336	$168
1096699	Carprofen (200 mg) (AS)	F0D335	$168
1098388	Microcrystalline Cellulose (1 g) (AS)	F0D362	$168
1098402	Powdered Cellulose (1 g) (AS)	F0D364	$168
1133503	Cholic Acid (2 g) (AS)	F3B159	$168
1134346	Ciprofloxacin Related Compound A (25 mg) (AS) (7-Chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid hydrochloride salt)	F0E333	$526
1148806	Corn Oil (1 g) (AS)	F0D181	$168
1150207	Cottonseed Oil (1 g) (AS)	F0D173	$168
1150513	Cromolyn Sodium Related Compound A (25 mg) (1,3-Bis-(2-acetyl-3-hydroxyphenoxy)-2-propanol) (AS)	F0E045	$526
1171251	2-Deoxy-D-Glucose (100 mg) (AS)	F0E006	$177
1183002	Diacetylmorphine Hydrochloride **CI** (25 mg) (AS) (Heroin Hydrochloride)	J	$224
1187091	Dibutyl Sebacate (1 mL) (AS)	F0D128	$168
1188301	Dichlorvos (150 mg) (2,2-dichlorovinyl dimethyl phosphate) (AS)	F0D141	$173
1210105	N-(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS)	F	$168
1235900	Enrofloxacin (200 mg) (AS)	F0E094	$168
1237509	Epitetracycline Hydrochloride (200 mg) (AS)	G0E261	$526
1251000	Estradiol Benzoate (250 mg) (AS)	H0C332	$168
1268965	Eugenol (500 mg) (AS)	F0D303	$168
1270355	Ferrous Sulfate (1.5 g) (AS)	F0D196	$168
1270446	Fexofenadine Related Compound C (15 mg) ((+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene) (AS)	F0E291	$526
1286606	L-Fucose (200 mg) (AS)	F0E007	$177
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224	$224
1338812	Indapamide Related Compound A (50 mg) (4-Chloro-N-(2-methyl-indol-1-yl)-3-sulfamoylbenzamide) (AS)	F0E052	$526
1350308	Isopropyl Alcohol (1.5 mL/ampule; 3 ampules) (AS)	F0D261	$168

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
1356643	Ketoprofen Related Compound A (25 mg) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) (AS)	H0E028	$526
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	$168
1371002	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) (AS) (LSD)	I	$584
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	$168
1374248	Magnesium Chloride (1 g) (AS)	F0D157	$168
1374260	Magnesium Hydroxide (1 g) (AS)	F0D158	$168
1374292	Magnesium Phosphate (2 g) (AS)	F0E107	$168
1374340	Magnesium Stearate (5 g) (AS)	F0D214	$168
1374361	Magnesium Sulfate (1 g) (AS)	F0D160	$168
1375127	Manganese Chloride (1 g) (AS)	F0D150	$168
1375149	Manganese Sulfate (1 g) (AS)	F0D151	$168
1379140	Meglumine (500 mg) (AS)	F0D385	$168
1381005	Melatonin (100 mg) (AS)	F0E027	$179
1396364	Methacholine Chloride (500 mg) (AS)	F0D222	$182
1410002	Methicillin Sodium (500 mg) (AS)	J0C333	$168
1424506	Methylcellulose (1 g) (AS)	G0B222	$168
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) (AS) (STP)	F	$224
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) (AS) (MDA)	F-1	$224
1437450	Methyl Salicylate (2 mL) (AS)	F0D070	$168
1446600	Monosodium Glutamate (1 g) (AS)	F0D387	$168
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G	$224
1478254	Olive Oil (1 g) (AS)	F0D175	$168
1478516	Omeprazole Related Compound A (15 mg) (Omeprazole Sulfone) (AS)	F0D363	$526
1491015	Oxytetracycline Hydrochloride (200 mg) (AS)	F0E258	$168
1492040	Palm Oil (1 g) (AS)	F0D179	$168
1500251	Paroxetine Related Compound D (10 mg) (AS) (cis-Paroxetine hydrochloride)	G0E096	$526
1500557	Peanut Oil (1 g) (AS)	F0D171	$168
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025	$224
1525707	Phenothiazine (500 mg) (AS)	F0D231	$168
1535802	Phosphoric Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D026	$168
1547346	Polyoxyl 2 Stearyl Ether (1 g) (AS)	F0D353	$168
1372606	Polyoxyl 10 Stearyl Ether (1 g)	F0D354	$168
1547925	Polysorbate 20 (2 g) (AS)	F0D130	$168
1547936	Polysorbate 40 (2 g) (AS)	F0D204	$168
1547947	Polysorbate 60 (2 g) (AS)	F0D131	$168
1547969	Polysorbate 80 (2 g) (AS)	F0D132	$168
1549807	Potassium Acetate (500 mg) (AS)	F0E083	$168
1548101	Potassium Benzoate (1 g) (AS)	F0D161	$168
1548134	Potassium Bicarbonate (1 g) (AS)	F0D074	$168
1549840	Potassium Bitartrate (3 g) (AS)	F0D384	$168
1548167	Potassium Carbonate (1 g) (AS)	F0D075	$168
1548190	Potassium Chloride (1 g) (AS)	F0D127	$168
1548225	Potassium Citrate (1 g) (AS)	F0D201	$168
1548280	Potassium Iodide (1 g) (AS)	F0D078	$168
1548349	Potassium Nitrate (5 g) (AS)	F0D325	$168
1551128	Dibasic Potassium Phosphate (5 g) (AS)	F0D281	$168
1551139	Monobasic Potassium Phosphate (5 g) (AS)	F0D313	$168
1551140	Potassium Sodium Tartrate (2 g) (AS)	F0D380	$168
1548407	Potassium Sorbate (1 g) (AS)	F0D264	$168

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
1572208	Propionic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D029	$168
1612404	Sesame Oil (1 mL/ampule; 2 ampules) (AS)	F0E134	$168
1613407	Sodium Acetate (1 g) (AS)	F0D083	$168
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	$168
1613757	Sodium Carbonate Anhydrous (1 g) (AS)	F0D100	$168
1613804	Sodium Chloride (1 g) (AS)	F0D269	$168
1613859	Sodium Citrate (1 g) (AS)	F0D172	$168
1614363	Sodium Lauryl Sulfate (1 g) (AS)	F0D381	$168
1614396	Sodium Metabisulfite (1 g) (AS)	F0D111	$168
1614454	Sodium Nitrite (1 g) (AS)	F0D117	$168
1614807	Sodium Sulfate Anhydrous (1 g) (AS)	F0D112	$168
1615107	Sodium Thiosulfate (1 g) (AS)	F0D178	$168
1615956	Sorbic Acid (1 g) (AS)	F0D129	$168
1619017	Spironolactone Related Compound A (100 mg) (Canrenone (3-Oxo-17-alpha-pregna-4,6-diene-21, 17-carbolactone)) (AS)	F0E184	$526
1643328	Tannic Acid (2 g) (AS)	F0D292	$168
1643340	Tartaric Acid (1 g) (AS)	F0D176	$168
1667585	Titanium Dioxide (1 g) (AS)	F0D079	$168
1708718	Valproic Acid Related Compound B (50 mg) ((2RS)-2-(1-methylethyl)pentanoic acid) (AS)	F0E201	$526
1724747	Zinc Oxide (2 g) (AS)	F0D170	$168
1724769	Zinc Sulfate (1 g) (AS)	F0D133	$168

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
AMINO ACIDS			
1012509	L-Alanine (200 mg)	G0E002	$168
1021000	Aminocaproic Acid (200 mg)	G0D101	$168
1042500	L-Arginine (200 mg)	G-1	$168
1042601	Arginine Hydrochloride (125 mg)	G0B060	$134
1043502	Asparagine Anhydrous (200 mg)	F0E013	$168
1043513	Asparagine Monohydrate (200 mg)	F0E012	$168
1161509	L-Cysteine Hydrochloride (200 mg)	H	$168
1294976	Glutamic Acid (200 mg)	F0C069	$168
1294808	Glutamine (100 mg)	F0B244	$168
1295800	Glycine (200 mg)	G0E099	$168
1308505	L-Histidine (200 mg)	G0A018	$168
1349502	L-Isoleucine (200 mg)	F-2	$168
1357001	L-Leucine (200 mg)	H0B237	$168
1359903	Levocarnitine (400 mg)	G0B197	$168
1359925	Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride)	F-1	$526
1371501	L-Lysine Acetate (200 mg)	F1C027	$168
1372005	L-Lysine Hydrochloride (200 mg)	H	$168
1411504	L-Methionine (200 mg)	G1D398	$168
1530503	L-Phenylalanine (200 mg)	H	$168
1568506	L-Proline (200 mg)	G0D146	$168
1612506	L-Serine (200 mg)	G	$168
1667202	L-Threonine (200 mg)	G	$168
1700501	L-Tryptophan (200 mg)	G2E237	$168
1705006	L-Tyrosine (500 mg)	K0C141	$168
1708503	L-Valine (200 mg)	F-2	$168
BOTANICALS			
BLACK COHOSH			
1076206	Powdered Black Cohosh Extract (1.5 g)	F0D086	$563
CAPSAICIN/CAPSICUM			
1091108	Capsaicin (100 mg)	G2D136	$168
1200600	Dihydrocapsaicin (25 mg)	G0C071	$281
CHAMOMILE			
1040708	Apigenin-7-Glucoside (30 mg)	F	$526
CHASTE TREE			
1012203	Agnuside (25 mg)	F0D397	$920
1096779	Casticin (25 mg)	F0D358	$957
1105009	Powdered Chaste Tree Extract (1.5 g)	F0C406	$563
RED CLOVER			
1286060	Formononetin (50 mg)	F0C196	$563
1599500	Powdered Red Clover Extract (500 mg)	F0C188	$281
CRANBERRY LIQUID			
1134368	Citric Acid (200 mg)	F2E269	$168
1181302	Dextrose (500 mg)	J-1	$134
1286504	Fructose (125 mg)	I-2	$134
1374601	Malic Acid (200 mg)	G0B158	$168
1594506	Quinic Acid (200 mg)	F	$168
1617000	Sorbitol (125 mg)	H1B139	$134
1623637	Sucrose (100 mg)	H1C223	$168

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
ELEUTHERO			
1234704	Powdered Eleuthero Extract (1.5 g)	F0C291	$563
1234668	Eleutheroside B (15 mg) (Syringin)	F0E056	$884
1234680	Eleutheroside E (15 mg) (Syringaresinol diglucoside)	F0E057	$884
ECHINACEA			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1231728	Powdered Echinacea Purpurea Extract (1 g)	F0D018	$563
1231706	Powdered Echinacea Angustifolia Extract (1 g)	F0D019	$563
1305507	2E, 4E-Hexadienoic Acid Isobutylamide (25 mg)	F0C353	$584
FEVERFEW			
1500400	Parthenolide (25 mg)	F	$168
1606503	Rutin (100 mg)	G0C355	$168
GARLIC			
1012145	Agigenin (25 mg)	F	$526
1012950	Alliin (25 mg)	F	$1,649
1115556	beta-Chlorogenin (20 mg)	F	$526
1294848	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F	$730
1411504	L-Methionine (200 mg)	G1D398	$168
GARLIC FLUID EXTRACT			
1013057	S-Allyl-L-Cysteine (25 mg)	F	$526
GINGER			
1091108	Capsaicin (100 mg)	G2D136	$168
1291504	Powdered Ginger (500 mg)	F	$281
GINKGO			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1592409	Quercetin (500 mg)	G0D407	$168
1606503	Rutin (100 mg)	G0C355	$168
AMERICAN GINSENG			
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289	$563
ASIAN GINSENG			
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289	$563
GOLDENSEAL			
1065210	Berberine Chloride (50 mg)	F0E185	$281
1313210	Hydrastine (10 mg)	F0E204	$281
HAWTHORN LEAF WITH FLOWER			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1335202	Hyperoside (50 mg)	F	$925
1592409	Quercetin (500 mg)	G0D407	$168
1606503	Rutin (100 mg)	G0C355	$168
1717708	Vitexin (30 mg)	F0C142	$563
KAVA			
1355709	Powdered Kava Extract (1 g)	F0C161	$281
KAWAIN			
1355753	Kawain (200 mg)	F0C160	$225
LICORICE			
1295888	Glycyrrhizic Acid (25 mg)	F0C006	$526
MILK THISTLE			
1443850	Powdered Milk Thistle Extract (250 mg)	F0B321	$281
1612630	Silybin (50 mg)	G0D392	$168

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
1612641	Silydianin (20 mg)	F	$168
PYGEUM			
1612947	Beta-Sitosterol (300 mg)	F0D217	$563
ST. JOHN S WORT			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1335202	Hyperoside (50 mg)	F	$925
1485001	Oxybenzone (150 mg)	H0B263	$168
1606503	Rutin (100 mg)	G0C355	$168
SAW PALMETTO			
1424233	Methyl Caprate (300 mg)	G0D087	$168
1424244	Methyl Caproate (300 mg)	F	$168
1424255	Methyl Caprylate (300 mg)	G0D064	$168
1430305	Methyl Laurate (500 mg)	G0C356	$168
1430327	Methyl Linoleate (5 x 50 mg)	G0D107	$168
1430349	Methyl Linolenate (5 x 50 mg)	F	$168
1431501	Methyl Myristate (300 mg)	G0C357	$168
1431556	Methyl Oleate (500 mg)	G0C148	$168
1431603	Methyl Palmitate (300 mg)	G0E329	$168
1431625	Methyl Palmitoleate (300 mg)	F	$168
1437508	Methyl Stearate (300 mg)	G0E290	$168
1612947	Beta-Sitosterol (300 mg)	F0D217	$563
STINGING NETTLE			
1043819	Aspartic Acid (100 mg)	F0B087	$168
1294976	Glutamic Acid (200 mg)	F0C069	$168
1610090	Scopoletin (20 mg)	F0C329	$168
1612947	Beta-Sitosterol (300 mg)	F0D217	$563
VALERIAN			
1707908	Valerenic Acid (15 mg)	H0D126	$753
MISCELLANEOUS DIETARY SUPPLEMENTS			
1133536	Choline Bitartrate (200 mg)	F0C057	$168
1133547	Choline Chloride (200 mg)	F0C058	$168
1133570	Chondroitin Sulfate Sodium (300 mg)	G0E236	$168
1133638	Chromium Picolinate (100 mg)	F	$168
1150353	Creatinine (100 mg)	F	$168
1294207	Glucosamine Hydrochloride (200 mg)	F0C363	$168
1381005	Melatonin (100 mg) (AS)	F0E027	$179
1611955	Selenomethionine (100 mg)	F0B006	$168
1705301	Ubidecarenone (200 mg)	G0E154	$270
1705323	Ubidecarenone Related Compound A (15 mg) (Coenzyme Q9)	F0E210	$526
1705312	Ubidecarenone for System Suitability (25 mg)	F0B194	$526
VITAMINS-MINERALS			
1043003	Ascorbic Acid (1 g) (Vitamin C)	Q0B012	$168
1071508	Biotin (200 mg)	I0D114	$168
1086356	Calcium Ascorbate (200 mg)	F-1	$168
1087009	Calcium Pantothenate (200 mg) (Vitamin B5)	O0C331	$168
1131009	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157	$172
1131803	Delta-4,6-cholestadienol (30 mg)	F	$526
1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N	$168
1179504	Dexpanthenol (500 mg)	J0C293	$173

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1239005	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275	$182
1241007	Ergosterol (50 mg)	H	$168
1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P	$168
1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176	$168
1370804	Lutein (1 mL)	F0D291	$919
1381006	Menadione (200 mg) (Vitamin K3)	H-3	$168
1461003	Niacin (200 mg)	I0E295	$168
1462006	Niacinamide (500 mg) (Vitamin B3)	N0E024	$168
1494501	Panthenol, Racemic (200 mg)	G	$168
1494807	Pantolactone (500 mg)	F	$526
1538006	Phytonadione (500 mg) (Vitamin K1)	N0B303	$168
1550001	Potassium Gluconate (200 mg)	H0C064	$168
1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P	$168
1603006	Riboflavin (500 mg) (Vitamin B2)	N0C021	$168
1613509	Sodium Ascorbate (200 mg)	G2C067	$168
1614002	Sodium Fluoride (1 g)	I0E033	$168
1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O	$168
1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M	$168
1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K	$168
1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)	G0D077	$168
1716002	Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil)		$168
1717504	Vitamin D Assay System Suitability (1.5 g)	F-1	$168

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1012906	Alfentanil Hydrochloride **CII** (500 mg)	F0B016	$224
1014005	Alphaprodine Hydrochloride **CII** (250 mg)	F	$224
1015008	Alprazolam **CIV** (200 mg)	H1C133	$224
1030001	Amobarbital **CII** (200 mg)	F-2	$224
1036008	Anileridine Hydrochloride **CII** (250 mg)	F	$224
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272	$224
1078700	Buprenorphine Hydrochloride **CIII** (50 mg)	G0E026	$224
1078711	Buprenorphine Related Compound A **CII** (50 mg) (21-[3-(1-propenyl)]-7alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine)	F1C076	$526
1079000	Butabarbital **CIII** (200 mg)	H0C007	$224
1081002	Butalbital **CIII** (200 mg)	H0C054	$224
1082504	Butorphanol Tartrate **CIV** (500 mg)	J	$224
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2	$526
1090003	Cannabinol **CI** (25 mg) (AS)		$224
1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I	$605
1109000	Chlordiazepoxide **CIV** (200 mg)	I0B063	$224
1110009	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4	$224
1140305	Clonazepam **CIV** (200 mg)	H0E003	$224
1140509	Clorazepate Dipotassium **CIV** (125 mg)	G0B027	$224
1143008	Cocaine Hydrochloride **CII** (250 mg)	I0B074	$224
1143802	Codeine N-Oxide **CI** (50 mg)	G0A034	$224
1144000	Codeine Phosphate **CII** (100 mg)	J0C200	$224
1145003	Codeine Sulfate **CII** (250 mg)	H-2	$224
1180004	Dextroamphetamine Sulfate **CII** (500 mg)	I0C311	$234
1183002	Diacetylmorphine Hydrochloride (Heroin Hydrochloride) **CI** (25 mg) (AS)	J	$224
1185008	Diazepam **CIV** (100 mg)	I1C364	$224
1187207	Dichloralphenazone **CIV** (200 mg)	F0B010	$224
1194009	Diethylpropion Hydrochloride **CIV** (200 mg)	H	$224
1200804	Dihydrocodeine Bitartrate **CII** (200 mg)	I0D205	$224
1219008	Diphenoxylate Hydrochloride **CII** (200 mg)	I1D339	$224
1258305	Ethchlorvynol **CIV** (0.7 ml)	F0B011	$224
1270005	Fentanyl Citrate **CII** (100 mg)	K0C264	$260
1280009	Fluoxymesterone **CIII** (200 mg)	G-2	$224
1285002	Flurazepam Hydrochloride **CIV** (200 mg)	J0C365	$224
1295006	Glutethimide **CII** (500 mg)	F	$224
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224	$224
1307003	Hexobarbital **CIII** (500 mg)	F	$224
1315001	Hydrocodone Bitartrate **CII** (250 mg)	L0E176	$224
1315012	Hydrocodone Bitartrate Related Compound A **CII** (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl)	F0C214	$555
1323000	Hydromorphone Hydrochloride **CII** (50 mg)	J0C372	$224
1356009	Ketamine Hydrochloride **CIII** (250 mg)	H0E091	$224
1359506	Levmetamfetamine **CII** (75 mg)	F1C113	$224
1364007	Levorphanol Tartrate **CII** (500 mg)	I0D138	$224
1370305	Lorazepam **CIV** (200 mg)	I1D404	$224
1371002	Lysergic Acid Diethylamide Tartrate (LSD) **CI** (10 mg) (AS)	I	$584
1375309	Mazindol **CIV** (350 mg)	H	$224
1383001	Meperidine Hydrochloride **CII** (200 mg)	I	$224
1386000	Mephobarbital **CIV** (250 mg)	G	$224
1389008	Meprobamate **CIV** (200 mg)	G-1	$224

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1398009	Methadone Hydrochloride **CII** (200 mg)	I0B163	$224
1399001	Methamphetamine Hydrochloride **CII** (125 mg)	I	$224
1404000	Methaqualone **CI** (500 mg)	F-1	$224
1405002	Metharbital **CIII** (200 mg)	F-2	$224
1413000	Methohexital **CIV** (500 mg)	G0D252	$224
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) **CI** (25 mg) (AS)	F	$224
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) **CI** (25 mg) (AS)	F-1	$224
1433008	Methylphenidate Hydrochloride **CII** (125 mg)	I1C241	$179
1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)	F0C368	$605
1438001	Methyltestosterone **CIII** (200 mg)	J1E324	$224
1445404	Modafinil **CIV** (200 mg)	F0D351	$270
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G	$224
1448005	Morphine Sulfate **CII** (500 mg)	N0E161	$359
1452002	Nalorphine Hydrochloride **CIII** (250 mg)	I	$224
1453526	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone hydrochloride)	F	$526
1454008	Nandrolone **CIII** (50 mg)	F4D144	$605
1455000	Nandrolone Decanoate **CIII** (250 mg)	J0D218	$224
1456003	Nandrolone Phenpropionate **CIII** (250 mg)	H	$224
1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)	H1B035	$605
1473002	Noroxymorphone Hydrochloride **CII** (50 mg)	H1C177	$605
1482003	Oxandrolone **CIII** (50 mg)	H0E223	$224
1483006	Oxazepam **CIV** (200 mg)	H0D259	$224
1485191	Oxycodone **CII** (200 mg)	I1D206	$224
1487007	Oxymetholone **CIII** (200 mg)	G1B247	$224
1488000	Oxymorphone **CII** (500 mg)	H0B214	$224
1505007	Pentazocine **CIV** (500 mg)	I0C418	$224
1507002	Pentobarbital **CII** (200 mg)	I0D359	$224
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025	$224
1516502	Phendimetrazine Tartrate **CIII** (350 mg)	G	$224
1523009	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2	$224
1524001	Phenobarbital **CIV** (200 mg)	J	$224
1528501	Phentermine Hydrochloride **CIV** (200 mg)	H0B309	$224
1554501	Prazepam **CIV** (500 mg)	G0C066	$224
1574000	Propoxyphene Hydrochloride **CII** (1 g)	L0C285	$224
1575002	Propoxyphene Napsylate **CII** (1 g)	H1C323	$224
1592205	Quazepam **CIV** (200 mg)	F	$224
1611004	Secobarbital **CII** (200 mg)	H	$224
1620005	Stanozolol **CIII** (200 mg)	F-3	$224
1623648	Sufentanil Citrate **CII** (25 mg)	H1E105	$238
1643000	Talbutal **CIII** (250 mg)	F	$224
1643408	Temazepam **CIV** (200 mg)	H0C205	$224
1645006	Testolactone **CIII** (125 mg)	F-1	$179
1646009	Testosterone **CIII** (125 mg)	I1B253	$179
1647001	Testosterone Cypionate **CIII** (200 mg)	H0D162	$224
1648004	Testosterone Enanthate **CIII** (200 mg)	K0D253	$224
1649007	Testosterone Propionate **CIII** (200 mg)	L1C005	$224
1656308	Thiamylal **CIII** (200 mg)	F	$224
1661002	Thiopental **CIII** (250 mg)	I1D198	$224
1673806	Trenbolone **CIII** (50 mg)	F0D389	$179

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Cat. No.	Description	Curr. Lot	Price
1673828	Trenbolone Acetate **CIII** (200 mg)	F0D390	$179
1680506	Triazolam **CIV** (200 mg)	H0B041	$224

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Reference Standards; USP–NF (*Print or Electronic*); *Pharmacopeial Forum; USP Dictionary; Spanish USP-NF (Print); Chromatographic Reagents*

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Reference Standards; USP–NF (*Print or Electronic*); *Pharmacopeial Forum; USP Dictionary*

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Reference Standards; USP–NF (*Print or Electronic*); *Pharmacopeial Forum; USP Dictionary*

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Reference Standards; USP–NF (*Print or Electronic*); *Pharmacopeial Forum; USP Dictionary; Chromatographic Reagents*

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Fax: (27) 11-466-4611
E-mail: info@industrialanalytical.co.za
http://www.industrialanalytical.co.za
Reference Standards; USP–NF (*Print or Electronic*); *Pharmacopeial Forum; USP Dictionary; Chromatographic Reagents*

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Reference Standards

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National Technical Information Service
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Springfield, VA 22161
USA
Tel: 703-605-6400
Fax: 703-605-6715
USP–NF (*Print or Electronic*)

Notice to the USP Executive Secretariat of Intent to Comment

Date: _____

Mail to: Executive Secretariat, *USP-NF*
12601 Twinbrook Parkway
Rockville, MD 20852

I am unable to comment at present, but please be informed of my intent to comment at a later date, on the topics as indicated below.

Note: Please include a brief summary of intended comments to help USP make a decision on the reverse. Submitters should comment not later than the next comment deadline.

Monograph/General Chapter Title	With reference to the proposal(s) in *Pharmacopeial Forum*			Estimated date USP can expect comments
	PF Vol.	No.	Pages	

Submitter information (please type or print):

Name: _____

Company: _____

Address: _____

_____

_____

_____

Phone: _____

Fax: _____

E-mail: _____

**Note—specifying the date(s) by which you expect to submit comments to the Executive Secretariat will not necessarily result in a deferment of the implementation of the proposal to which you refer above.*

CHROMATOGRAPHIC REAGENTS USED IN *USP–NF* AND *PHARMACOPEIAL FORUM*

This is a update based on the proposals published in this issue of *PF*.

CHROMATOGRAPHIC REAGENTS USED IN *USP–NF* AND *PHARMACOPEIAL FORUM*

This is a update based on the proposals published in this issue of *PF*.

Chromatographic Reagents Used in *USP-NF* and *Pharmacopeial Forum*
May–June 2006

AMLODIPINE BESYLATE (DSD Mgh #3570)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Nova-Pak C18	Assay and Related compounds	Alternative column. 3.9 mm × 15 cm, 4 µm, manufacturer Waters.
32(3)	L1	Symmetry C-18	Assay and Related compounds	3.9 mm x 15 cm, 5 µm, manufacturer Waters.

BEMOTRIZINOL (DSD Mgh #1131)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Hypersil BDS C-18	Assay and Related compounds	3 mm × 12.5 cm, 3 µm, manufacturer Thermo Electron.

CAPECITABINE (DSD Mgh #12330)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Chromatographic purity	4.6 mm × 25 cm, 5 µm, manufacturer GL Sciences.

CAPECITABINE TABLETS (DSD Mgh #12335)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Chromatographic purity	4.6 mm × 25 cm, 5 µm, manufacturer GL Sciences.

CLARITHROMYCIN EXTENDED-RELEASE TABLETS (DSD Mgh #17997)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L7	LiChrospher 60 RP-Select B	Dissolution	Dissolution, Test 4. 4.0 mm × 12.5 cm, 5 µm, manufacturer Merck KGaA.

CONJUGATED ESTROGENS TABLETS (DSD Mgh #30900)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Bio-Sil ODS	Dissolution	Dissolution, Test 4, Test 5, Test 6. 4.6 mm × 3.0 cm, 3 µm, manufacturer BioRad.

GLIPIZIDE (DSD Mgh #35030)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L43	Discovery HS F5	Assay and Related compounds	Alternative column. 4.6 mm × 25 cm, 5 µm, manufacturer Supelco.
32(3)	L43	Curosil PFP	Assay and Related compounds	4.6 mm × 25 cm, 5 µm, manufacturer Phenomenex.

GLIPIZIDE AND METFORMIN HYDROCHLORIDE TABLETS (DSD Mgh #847)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Symmetry C-18	Dissolution	4.6 mm × 15 cm, 5 µm, manufacturer Waters.

GLYCERYL MONOSTEARATE (DSD Mgh #35490)

PF	LGS#	Reagent Brand	Type of Test	Comments
0(0)	L21	PLgel	Assay for	Assay for monoglycerides. 7.5 mm × 60 cm, 5 µm, 100 Å, manufacturer Phenomenex.

MELOXICAM ORAL SUSPENSION (DSD Mgh #2140)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Kromasil C18	Assay and Chromatographic purity	4 mm × 12.5 cm, manufacturer EKA Nobel.

METHYLSULFONYLMETHANE (DSD Mgh #53000)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(2)	G2	Zebron ZB-1	Assay and Chromatographic purity	0.53 mm × 30 m, 5 µm, manufacturer Phenomenex.

METHYLSULFONYLMETHANE TABLETS (DSD Mgh #2187)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(2)	G2	Zebron ZB-1	Assay	0.53 mm × 30 m, 5 µm, manufacturer Phenomenex.

MODAFINIL (DSD Mgh #54521)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Related compounds	Related compounds, Test 2. 4.6 mm × 25 cm, 5 µm, manufacturer GL Sciences.

NEVIRAPINE ORAL SUSPENSION (DSD Mgh #56488)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L10	Zorbax SB-CN	Assay and Related compounds	Guard column. 4.6 mm × 12.5 mm, 5 µm; analytical column. 4.6 mm × 15 cm, 3.5 µm, manufacturer Agilent.
32(4)	L1	Symmetry C-18	Dissolution	Guard column. 3.9 mm × 20 mm; analytical column. 3.9 mm × 15 cm, 5 µm, manufacturer Waters.

ORLISTAT (DSD Mgh #58790)

PF	LGS#	Reagent Brand	Type of Test	Comments
31(3)	L1	Aminoquant	Impurity test	Impurity, Test 5. 2.1 mm × 20 cm, manufacturer Agilent.
32(3)	G27	DB-5	Limit of	Limit of related compound B. 32 mm × 30 m, 0.25 µm, manufacturer J&W Scientific.
32(3)	L1	Nova-Pak C18	Assay and Impurity Test	Test 3. 3.9 mm × 15 cm, 4 µm, manufacturer Waters.

PAROXETINE HYDROCHLORIDE (DSD Mgh #61180)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L13	Adsorbosphere TMS	Assay	4.6 mm × 25 cm, 5 µm, manufacturer Grace Davison–Alltech.

PERMETHRIN (DSD Mgh #62530)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Related compounds	4.6 mm × 15 cm, 5 µm, manufacturer GL Sciences.

PERMETHRIN CREAM (DSD Mgh #62535)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Related compounds	4.6 mm × 15 cm, 5 µm, manufacturer GL Sciences.

PRAVASTATIN SODIUM TABLETS (DSD Mgh #68368)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Nova-Pak C18	Assay and Related compounds	Alternative column. 3.9 mm × 7.5 cm, 4 µm, manufacturer Waters.
32(3)	L1	Spherisob ODS-2	Assay and Related compounds	4.6 mm × 5 cm, 3 or 5 µm, endcapped, manufacturer Waters.

RISPERIDONE TABLETS (DSD Mgh #73744)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Zorbax SB-C18	Dissolution and Uniformity of dosage units	4.6 mm × 15 cm, 5 µm, manufacturer Agilent.
32(3)	L1	Zorbax SB-C18	Assay and Related compounds	4.6 mm × 15 cm, 5 µm, manufacturer Agilent.

SPIRONOLACTONE (DSD Mgh #77860)

PF	LGS#	Reagent Brand	Type of Test	Comments
0(0)	L1	TSKgel ODS-80Tm	Assay	4.6 mm × 15 cm, manufacturer Tosoh Corp.

Chromatographic Reagents Used in *USP-NF* and *Pharmacopeial Forum*
May–June 2006

AMLODIPINE BESYLATE (DSD Mgh #3570)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Nova-Pak C18	Assay and Related compounds	Alternative column. 3.9 mm × 15 cm, 4 µm, manufacturer Waters.
32(3)	L1	Symmetry C-18	Assay and Related compounds	3.9 mm x 15 cm, 5 µm, manufacturer Waters.

BEMOTRIZINOL (DSD Mgh #1131)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Hypersil BDS C-18	Assay and Related compounds	3 mm × 12.5 cm, 3 µm, manufacturer Thermo Electron.

CAPECITABINE (DSD Mgh #12330)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Chromatographic purity	4.6 mm × 25 cm, 5 µm, manufacturer GL Sciences.

CAPECITABINE TABLETS (DSD Mgh #12335)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Chromatographic purity	4.6 mm × 25 cm, 5 µm, manufacturer GL Sciences.

CLARITHROMYCIN EXTENDED-RELEASE TABLETS (DSD Mgh #17997)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L7	LiChrospher 60 RP-Select B	Dissolution	Dissolution, Test 4. 4.0 mm × 12.5 cm, 5 µm, manufacturer Merck KGaA.

CONJUGATED ESTROGENS TABLETS (DSD Mgh #30900)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Bio-Sil ODS	Dissolution	Dissolution, Test 4, Test 5, Test 6. 4.6 mm × 3.0 cm, 3 µm, manufacturer BioRad.

GLIPIZIDE (DSD Mgh #35030)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L43	Discovery HS F5	Assay and Related compounds	Alternative column. 4.6 mm × 25 cm, 5 µm, manufacturer Supelco.
32(3)	L43	Curosil PFP	Assay and Related compounds	4.6 mm × 25 cm, 5 µm, manufacturer Phenomenex.

GLIPIZIDE AND METFORMIN HYDROCHLORIDE TABLETS (DSD Mgh #847)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Symmetry C-18	Dissolution	4.6 mm × 15 cm, 5 µm, manufacturer Waters.

GLYCERYL MONOSTEARATE (DSD Mgh #35490)

PF	LGS#	Reagent Brand	Type of Test	Comments
0(0)	L21	PLgel	Assay for	Assay for monoglycerides. 7.5 mm × 60 cm, 5 µm, 100 Å, manufacturer Phenomenex.

MELOXICAM ORAL SUSPENSION (DSD Mgh #2140)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Kromasil C18	Assay and Chromatographic purity	4 mm × 12.5 cm, manufacturer EKA Nobel.

METHYLSULFONYLMETHANE (DSD Mgh #53000)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(2)	G2	Zebron ZB-1	Assay and Chromatographic purity	0.53 mm × 30 m, 5 µm, manufacturer Phenomenex.

METHYLSULFONYLMETHANE TABLETS (DSD Mgh #2187)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(2)	G2	Zebron ZB-1	Assay	0.53 mm × 30 m, 5 µm, manufacturer Phenomenex.

MODAFINIL (DSD Mgh #54521)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Related compounds	Related compounds, Test 2. 4.6 mm × 25 cm, 5 µm, manufacturer GL Sciences.

NEVIRAPINE ORAL SUSPENSION (DSD Mgh #56488)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L10	Zorbax SB-CN	Assay and Related compounds	Guard column. 4.6 mm × 12.5 mm, 5 µm; analytical column. 4.6 mm × 15 cm, 3.5 µm, manufacturer Agilent.
32(4)	L1	Symmetry C-18	Dissolution	Guard column. 3.9 mm × 20 mm; analytical column. 3.9 mm × 15 cm, 5 µm, manufacturer Waters.

ORLISTAT (DSD Mgh #58790)

PF	LGS#	Reagent Brand	Type of Test	Comments
31(3)	L1	Aminoquant	Impurity test	Impurity, Test 5. 2.1 mm × 20 cm, manufacturer Agilent.
32(3)	G27	DB-5	Limit of	Limit of related compound B. 32 mm × 30 m, 0.25 µm, manufacturer J&W Scientific.
32(3)	L1	Nova-Pak C18	Assay and Impurity Test	Test 3. 3.9 mm × 15 cm, 4 µm, manufacturer Waters.

PAROXETINE HYDROCHLORIDE (DSD Mgh #61180)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L13	Adsorbosphere TMS	Assay	4.6 mm × 25 cm, 5 µm, manufacturer Grace Davison–Alltech.

PERMETHRIN (DSD Mgh #62530)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Related compounds	4.6 mm × 15 cm, 5 µm, manufacturer GL Sciences.

PERMETHRIN CREAM (DSD Mgh #62535)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Inertsil ODS-2	Assay and Related compounds	4.6 mm × 15 cm, 5 µm, manufacturer GL Sciences.

PRAVASTATIN SODIUM TABLETS (DSD Mgh #68368)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Nova-Pak C18	Assay and Related compounds	Alternative column. 3.9 mm × 7.5 cm, 4 µm, manufacturer Waters.
32(3)	L1	Spherisob ODS-2	Assay and Related compounds	4.6 mm × 5 cm, 3 or 5 µm, endcapped, manufacturer Waters.

RISPERIDONE TABLETS (DSD Mgh #73744)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(3)	L1	Zorbax SB-C18	Dissolution and Uniformity of dosage units	4.6 mm × 15 cm, 5 µm, manufacturer Agilent.
32(3)	L1	Zorbax SB-C18	Assay and Related compounds	4.6 mm × 15 cm, 5 µm, manufacturer Agilent.

SPIRONOLACTONE (DSD Mgh #77860)

PF	LGS#	Reagent Brand	Type of Test	Comments
0(0)	L1	TSKgel ODS-80Tm	Assay	4.6 mm × 15 cm, manufacturer Tosoh Corp.

Table of Contents*

PHARMACOPEIAL FORUM VOL. 32 NO. 4 **JULY–AUG. 2006**

* The *USP–NF* (*USP 30–NF 25*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

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

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

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

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

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Fax: (301) 816-8148.

STANDARDS DEVELOPMENT

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

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

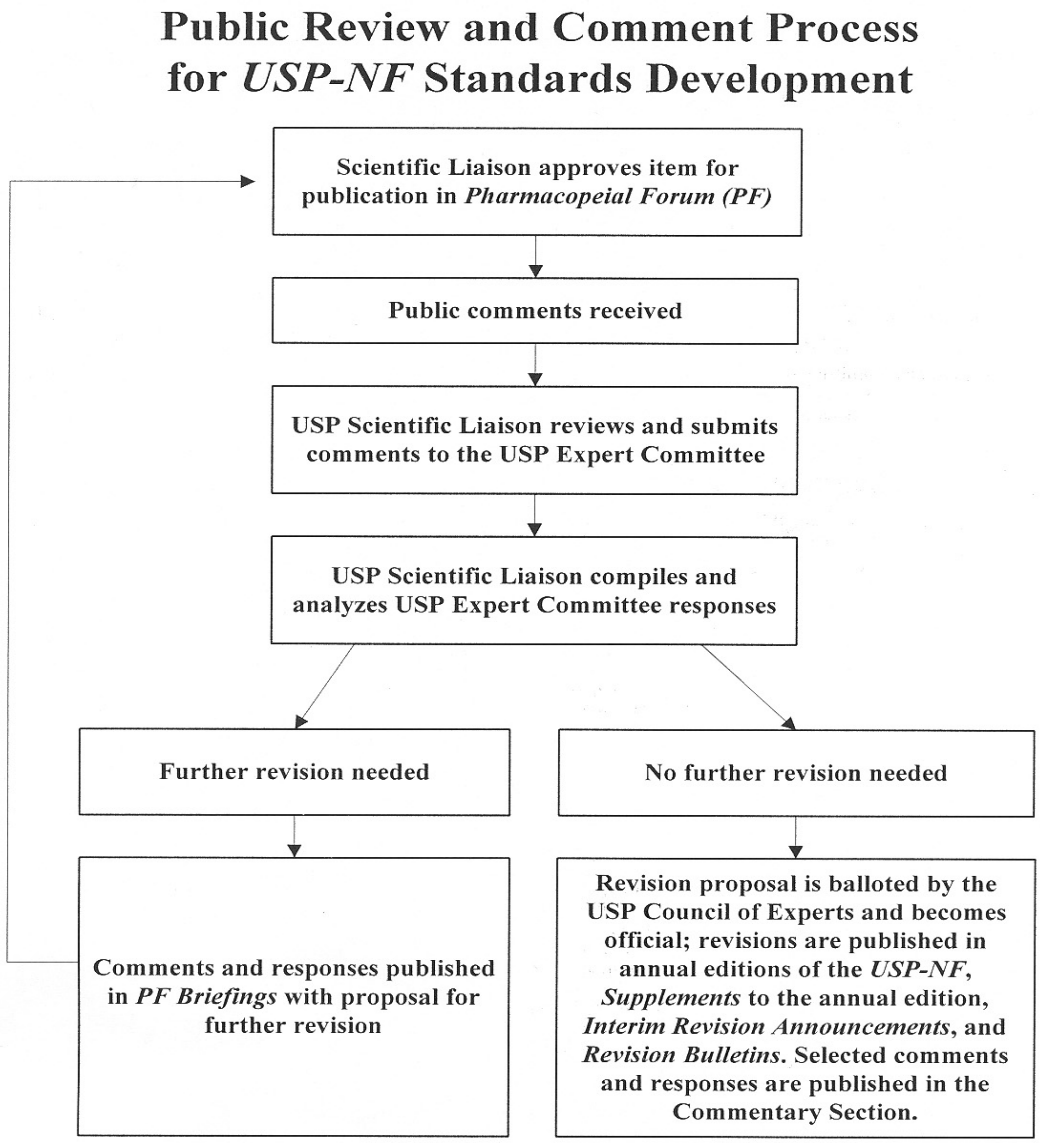
PF includes the following:

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

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

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

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



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@usp.org).

HOW TO USE *PF*

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

The content of the different sections of *PF* is briefly described below. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a *Request for Revision* is available in the *Guideline for Submitting Requests for Revision to the USP–NF* on the USP website (www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP–NF*

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

Other Sections

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

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

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

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

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

Index
Cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

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

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

EXPERT COMMITTEE DESIGNATIONS*

2005–2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell, Gene, and Tissue Therapies
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding
RMI	Radiopharmaceuticals and Medical Imaging Agents
RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics
VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005–2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

STAFF	E-MAIL	PHONE	ASSIGNMENT
Clydewyn M. Anthony, Ph.D., Scientist	cma@usp.org	(301) 816-8139	Monograph Development—Cough, Cold, and Analgesics (MD-CCA)
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Daniel K. Bempong, Ph.D., Senior Scientist	dkb@usp.org	(301) 816-8143	Pulmonary and Steroids (MD-PS)
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William E. Brown, Senior Scientist	web@usp.org	(301) 816-8380	Biopharmaceutics (BPC); Pharmaceutical Dosage Forms (PDF)
Evelyn Bryant, Manager, Editorial Services	eb@usp.org	(301) 816-8302	
Damian A. Cairatti, Senior Scientific Associate	dac@usp.org	(301) 816-8307	USP–NF Spanish Edition; Dietary Supplements—Bioavailability (DS-BA); Dietary Supplements—General Chapters (DS-GC)
Larry N. Callahan, Ph.D., Scientist	lnc@usp.org	(301) 816-8385	B&B Proteins and Polysaccharides (BB PP)
Todd L. Cecil, Ph.D., Vice President, Standards Development	tlc@usp.org	(301) 816-8234	
Diane Cousins, R.Ph., Vice President, Patient Safety	ddc@usp.org	(301) 816-8215	
Behnam Davani, Ph.D., Senior Scientist	bd@usp.org	(301) 816-8394	Monograph Development—Antivirals and Antimicrobials (MD-AA)
Ian F. DeVeau, Ph.D., Director, Veterinary Drugs and Radiopharmaceuticals	ifd@usp.org	(301) 816-8178	Veterinary Drugs (VET); Veterinary Medicine Information (VMI)
Shawn F. Dressman, Ph.D., Director, Reference Standards Evaluation	sfd@usp.org	(301) 816-8261	USP Reference Standards
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L. Valentin Feyns, Ph.D., Scientific Fellow	lvf@usp.org	(301) 816-8121	Reference Standards (RS)
Gabriel I. Giancaspro, Ph.D., Director, Dietary Supplements	gig@usp.org	(301) 816-8343	Dietary Supplements—Information (DSI)
Brian D. Gilbert, Ph.D., Scientist	bg@usp.org	(301) 816-8223	Monograph Development—Antibiotics (MD-ANT)
Elena Gonikberg, Ph.D., Senior Scientist	eg@usp.org	(301) 816-8251	Monograph Development—Gastrointestinal, Renal, and Endocrine (MD-GRE)
Antonio Hernandez-Cardoso, Scientist, Latin American Specialist	ahc@usp.org	(301) 816-8308	USP Spanish Edition; General Chapters (GC)

STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
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Christina H. Lee, Ph.D., Senior Scientific Associate	chl@usp.org	(301) 816-8335	Compounding Pharmacy (CRX)
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Anju K. Malhotra, Manager, Scientific Administration	akm@usp.org	(301) 816-8346	
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Feiwen Mao, Senior Scientific Associate	fm@usp.org	(301) 816-8320	Monograph Development—Ophthalmology, Oncology, and Dermatology (MD-OOD)
Margareth R. Marques, Ph.D., Senior Scientist and Latin American Liaison	mrm@usp.org	(301) 816-8106	Biopharmaceutics (BPC); Pharmaceutical Dosage Forms (PDF); Reagents
Marcia D. Mayfield, Manager, Monograph Development	mxm@usp.org	(301) 816-8358	
Kevin Moore, Ph.D., Scientist	ktm@usp.org	(301)816-8369	Harmonization; Monograph Improvement
Tina S. Morris, Ph.D., Director, Biologics and Biotechnology	tsm@usp.org	(301) 816-8397	B&B Vaccines and Virology (BB-VV)
Alan W. Nichols, MBA, Director, Reference Standards Production	awn@usp.org	(301) 816-8321	USP Reference Standards
Claudia C. Okeke, Ph.D., Scientific Fellow, Patient Safety	cco@usp.org	(301) 816-8243	Compounding Pharmacy Sterile Compounding (SCC)
Horacio Pappa, Ph.D., Scientist and Latin American Liaison	hp@usp.org	(301) 816-8319	General Chapters (GC); Statistics (STAT)
W. Larry Paul, Ph.D., Scientific Fellow	wlp@usp.org	(301) 816-8331	Nomenclature (NOM)
Denise Penn, R.Ph., Drug Information Specialist	dsp@usp.org	(301) 816-8392	Drug Information
Deborah G. Perfetto, Pharm.D., Director, Information Programs	dgp@usp.org	(301) 816-8317	
David A. Porter, Ph.D., Director, General Chapters	dap@usp.org	(301) 816-8225	
Sujatha Ramakrishna, Ph.D., Scientist	syk@usp.org	(301) 816-8349	Monograph Development—Cardiovascular (MD-CV)
Ravi Ravichandran, Ph.D., Senior Scientist	rr@usp.org	(301) 816-8330	Monograph Development—Psychiatrics and Psychoactives (MD-PP)

STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
Gary E. Ritchie, M.S., Scientific Fellow for PAT	ger@usp.org	(301) 816-8353	General Chapters (GC); Pharmaceutical Waters (PW); Statistics (STAT)
Karen A. Russo, Ph.D., Director, Small Molecules and Monograph Acquisition	kar@usp.org	(301) 816-8379	Monograph Acquisition and Infrastructure
Stefan P. Schuber, Ph.D., Director, Scientific Reports	sps@usp.org	(301) 816-8551	
Maged H. M. Sharaf, Ph.D., Senior Scientist	mhs@usp.org	(301) 816-8318	Dietary Supplements—Botanicals (DSB); Dietary Supplements—General Chapters (DS-GC)
Catherine M. Sheehan, Director, Excipients	cxs@usp.org	(301) 816-8262	Excipient Monographs 1 (EM1); Excipient General Chapters (EGC)
Anita Y. Szajek, Ph.D., Senior Scientist	aey@usp.org	(301) 816-8325	B&B Blood and Blood Products (BB BBP); B&B Cell, Gene, and Tissue Therapies (BB CGT)
Radhakrishna S. Tirumalai, Ph.D., Scientist	rst@usp.org	(301) 816-8339	General Toxicity and Medical Device Biocompatability (GTMDB); Microbiology and Sterility Assurance (MSA)
Beryl Voigt, Director, Executive Secretariat	bev@usp.org	(301) 816-8155	
Hong Wang, Ph.D., Senior Scientific Associate	hw@usp.org	(301) 816-8351	Excipient Monographs 2 (EM2); Excipient General Chapters (EGC)
Andrzej Wilk, Ph.D., Scientist	aw@usp.org	(301) 816-8305	Radiopharmaceuticals and Medical Imaging Agents (RMI); Radiopharmaceutical Information (RI)
Kahkashan Zaidi, Ph.D., Senior Scientist	kxz@usp.org	(301) 816-8269	Aerosols (AER); General Chapters (GC)

POLICIES AND ANNOUNCEMENTS

This section includes information about general scientific and policy issues that may have an impact on *USP–NF* standards and processes and announcements about issues being considered by USP. This section also includes publication and comment schedules.

CHANGES ADOPTED FOR THE *RULES AND PROCEDURES OF THE 2005–2010 COUNCIL OF EXPERTS.* The 2005–2010 USP Council of Experts has voted to approve changes to the *Rules and Procedures of the 2005–2010 Council of Experts,* which were originally adopted on a provisional basis in April 2005. Pursuant to USP's Bylaws, the revised *Rules and Procedures* will be made available to USP's Convention membership for comment and will become effective following review and approval by USP's Board of Trustees and formal adoption by the Council of Experts.

Details about the changes of the revised *Rules and Procedures* are captured in a USP Statement titled "Recent Modifications to the USP Standards-Setting Process," which is posted on USP's website (http://www.usp.org/USPNF/notices/). The changes to the Rules include provisions that:

- Reinforce the ability of an Expert Committee to finalize and approve revisions to the *USP–NF* without the need to republish the proposed revisions in the *Pharmacopeial Forum (PF);*
- Allow the use of USP's website and other vehicles in addition to the *PF* to communicate proposed revisions to the *USP–NF;*
- Require USP to publish summaries of the public comments it receives on proposed revisions to the *USP–NF* and Expert Committee responses to such comments;
- Increase to six months the time between publication of revisions to the *USP–NF* and the date on which such revisions generally become official;
- More closely synchronize the official date of revisions to the *USP–NF* with the date on which any new official USP reference standards called for in such revisions are released;
- Clarify the requirements and process for establishing standards in an expedited fashion through *Interim Revision Announcements* and Revision Bulletins;
- Facilitate the development of monographs for articles pending approval at FDA, so that such monographs can be made available and can immediately become official upon FDA approval;
- Allow for the development of monographs for medicines legally marketed outside of the U.S. that are used to treat neglected diseases; and
- Enable FDA representatives to more fully participate in USP's Expert Committee meetings.

Please direct any comments or questions on this topic to Susan de Mars, Chief Legal Officer (301-816-8296 or sdm@usp.org).

IMPLEMENTATION PERIOD FOR UPCOMING OFFICIAL REVISIONS TO THE USP–NF EXTENDED. To provide additional time to adopt revisions made to the compendia, USP is pleased to announce that effective beginning with the publication of *USP 30–NF 25,* implementation periods for revisions to official text in *United States Pharmacopeia–National Formulary (USP–NF)* and its *Supplements* are being extended. This change responds to stakeholder requests (see the *Pharmacopeial Forum (PF)* 31(2) *Stimuli* article, "The USP Revision Process: Recommendations for Enhancements"). As a result of this change, users will have six months from the publication date to implement new official texts as opposed to the previous 60-day period. The complete revised Publication Schedule for *USP 30–NF 25* reflecting this new six month implementation period is outlined below.

Publication Schedule for *USP 30–NF 25*

***USP–NF* Publication**	**Publication Date**	**Official Date**
USP–NF (Book)	November 2006	May 1, 2007
Supplement One	February 2007	August 1, 2007
Supplement Two	June 2007	December 1, 2007

Users may implement the newly official texts prior to the official date and the use becomes mandatory on the official date.

Please direct any comments or questions on this topic to Beryl Voigt, Director, Executive Secretariat (301-816-8155 or execsec@usp.org).

COORDINATION OF *PF* SUBMISSIONS AND NEW USP REFERENCE STANDARDS. USP recently announced a new process in which revisions and new monographs will not be published as official standards until the required USP Reference Standards are available for purchase [see *Policies and Announcements, PF* 32(3)]. We are pleased to announce another process change to better synchronize the availability of USP Reference Standards and the adoption of new documentary standards in the *USP–NF.* Effective March 28, 2006, any revision proposal involving the use of a first-time USP Reference Standard will be scheduled for publication in the *PF* only after a suitable reference standard bulk candidate has been received by USP. The timing of this new process affects regular revisions (not new monographs/general chapters) submitted to *PF* 32(4) and all revisions and new monographs/general chapters beginning with *PF* 32(5). While we acknowledge that this may cause a brief delay in publication of some proposed revisions and new monographs, we believe this process change is a benefit to USP customers and will ultimately lead to better public standards. It is anticipated that there may be some exceptions to this new process on a case-by-case basis.

Please direct any comments or questions on this topic to Beryl Voigt, Director, Executive Secretariat (301-816-8155 or execsec@usp.org).

IMMEDIATE IRA COMMENTARY

RESIDUAL SOLVENTS: GENERAL NOTICES AND GENERAL CHAPTER ⟨467⟩—IMPLEMENTATION DATE DELAYED—The Executive Committee of the Council of Experts has voted to delay the implementation date for the new requirements related to USP General Chapter ⟨467⟩ from January 1, 2007 to July 1, 2007. This decision affects two sections of the *USP–NF: General Notices* and the General Chapter. This decision is presented in the 4th IRA in this issue of *Pharmacopeial Forum,* which states: "The implementation date of the section on *Residual Solvents* in the *General Notices* and the change in the title of General Chapter ⟨467⟩ from *Organic Volatile Impurities* to *Residual Solvents* will be delayed from January 1, 2007 to July 1, 2007." Additionally, the section in ⟨467⟩ titled *Other Analytical Procedures,* originally slated to be deleted at the time when the title changes, will be kept in the chapter until the new implementation date.

Users should also recall that references to "*Residual Solvents* ⟨467⟩: meet the requirements" were retracted from *USP–NF* monographs according to the Notice of Retraction issued by USP on January 1, 2006. Specifications for *Organic Volatile Impurities* ⟨467⟩ in *USP–NF* monographs will remain official until **July 1, 2007.**

After July 1, 2007, the change in the title of General Chapter ⟨467⟩ and the *General Notices* statement on *Residual Solvents* will be effective, and references to *Organic Volatile Impurities* will be deleted from monographs.

Please direct any comments or questions to Horacio Pappa, Ph.D., Senior Scientist (301-816-8319 or hp@usp.org).

IMMEDIATE IRA FOR *TABLETS CONTAINING AT LEAST THREE OF THE FOLLOWING—ACETAMINOPHEN AND SALTS OF CHLORPHENIRAMINE, DEXTROMETHORPHAN, AND PSEUDOEPHEDRINE*—The *Dissolution* test for *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine* is being revised to add an additional *Dissolution* procedure *(Test 2)* to provide appropriate standards for a product already on the market.

Please direct any comments or questions to Margareth Marques, Ph.D., Senior Scientist (301-816-8106 or mrm@usp.org) or Clydewyn Anthony, Ph.D., Scientist (301-816-8139 or cma@usp.org).

IMMEDIATE IRA FOR *NITROFURANTOIN CAPSULES*—The *Nitrofurantoin Capsules* test for *Dissolution* is being revised to include an additional *Dissolution* procedure *(Test 3)* to provide appropriate standards for an FDA-approved product.

Please direct any comments or questions to Margareth Marques, Ph.D., Senior Scientist (301-816-8106 or mrm@usp.org) or Behnam Davani, Ph.D., M.B.A., Senior Scientist (301-816-8394 or bd@usp.org).

IMMEDIATE IRA FOR *ZINC SULFATE TABLETS*—The *Zinc Sulfate Tablets* tests for *Identification* are being revised to describe the preparation of several solutions used in the procedures. The test for *Dissolution* is also being replaced with a test for *Disintegration* because of the performance characteristics of this product. Immediate revisions to this monograph are necessary to support the efforts by the United Nations International Children's Emergency Fund (UNICEF), the United States Agency for International Development (USAID), and the World Health Organization (WHO). Although the product is not approved by the FDA, USP is giving this monograph special consideration to support efforts by the aforementioned organizations to ensure the availability of quality public standards for this product marketed outside the United States.

Please direct any comments or questions to Margareth Marques, Ph.D., Senior Scientist (301-816-8106 or mrm@usp.org) or Horacio Pappa, Ph.D., Senior Scientist (301-816-8319 or hp@usp.org) or Lawrence Evans, Ph.D., Scientist (301-816-8389 or le@usp.org).

USP INFORMATION EXPERT COMMITTEE MEMBERS ELECTED. USP is pleased to announce that Expert Committee members have been elected to 14 of the 16 Information Expert Committees. A complete list of newly elected members is available at http://www.usp.org/aboutUSP/governance/expertList.html.

USP ANNUAL SCIENTIFIC MEETING 2006. USP will host its third Annual Scientific Meeting, September 26–29, 2006 at the Marriott Denver City Center, Denver, Colorado. This year's topics include:

- Track I: Biologics and Biotechnology
- Track II: Reference Standards
- Track III: Dietary Supplements
- Track IV: Excipients and Harmonization
- Track V: USP—Working for You
- Track VI: Impurities in Drug Substances and Products
- One Day Track: Chromatography
- Special Topic: International Activities

Many members of USP's Council of Experts, Expert Committees are presenting at the various track sessions. USP anticipates that the collegial exchange of comments during session discussions will provide the Expert Committees with a better understanding of the varied perspectives of USP's many audiences. This year's Annual Scientific Meeting also will feature an expanded exhibit program and a spouse/guest program.

For more information and to register, go to www.usp.org/conferences, call (301) 816-8134, or e-mail conferences@usp.org.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, other scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2006 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

Calendar of Forthcoming Pharmacopeial Education Courses as of July 1, 2006

Date	Name of Course	Location	Price
15-Aug-06	Basic Statistics and their Applications to the *USP–NF*	PRChem, Puerto Rico	*
16-Aug-06	Effectively Using the *USP–NF*—Sessions I and II	PRChem, Puerto Rico	*
23-Aug-06	Effectively Using the *USP–NF*—Session I	USP Headquarters, Rockville, MD	$895
24-Aug-06	Effectively Using the *USP–NF*—Session II	USP Headquarters, Rockville, MD	$895 $1,695 both days
26-Sep-06	Effectively Using the *USP–NF*—Sessions I and II	Denver, CO (USP Annual Scientific Meeting)	$595
26-Sep-06	Fundamentals of Microbiological Testing	Denver, CO (USP Annual Scientific Meeting)	$595
3-4 Oct-06	Fundamentals of Dissolution—Lecture and Laboratory	North Brunswick, NJ	$1,695
10-11 Oct-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for German)	Basel, Switzerland	**
12-13 Oct-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for French)	Basel, Switzerland	**
18-Oct-06	Effectively Using the *USP–NF*—Sessions I and II	Brussels, Belgium	$595
19-Oct-06	Analytical Method Validation	Brussels, Belgium	$595
8-9 Nov-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for Italian)	Milan, Italy	**
14-15 Nov-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for Italian)	Rome, Italy	**

* Registration handled by:
Colegio de Quimicos de Puerto Rico
Programa Educacion Continuada
52 Hatillo Street
San Juan, PR 00918
Tel: 787-763-6070 or 787-763-6076
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Email: sales@sotax.ch

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

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

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

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

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

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

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

***PHARMACOPEIAL FORUM* PUBLIC REVIEW AND COMMENT PERIOD DEADLINES.** The full year's listing of comment period deadlines and the targeted official publications appears below. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts*, USP has implement a 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing.

The listing of comment period deadlines and the targeted official publications appears below.

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Publication Date	Official Date
PF 32(2)	June 15, 2006	*USP 30–NF 25 1st Supplement*	February 2007	August 2007
PF 32(3)	August 15, 2006			
PF 32(4)	October 16, 2006	*USP 30–NF 25 2nd Supplement*	June 2007	December 2007
PF 32(5)	December 15, 2006			
PF 32(6)	February 15, 2007	*USP 31–NF 26*	November 2007	May 2008
PF 33(1)	April 16, 2007			
PF 33(2)	June 15, 2007	*USP 31–NF 26 1st Supplement*	February 2008	April 2008
PF 33(3)	August 15, 2007			

* ***Section 9.04(b) of the Rules and Procedures of the 2005–2010 Council of Experts***
A period of at least ninety (90) days from the date of publication will be allowed for public review and comment. The time allowed for public comments shall be noted in the publication in the PF. For good cause shown, the Chairperson may alter the time specified.

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, official revisions are published in *PF* in the *Interim Revision Announcement;* these revisions are also incorporated in the upcoming *Supplement.* The official publication in which an *IRA* is incorporated will depend upon publication deadlines. The 5th *IRA* and the 6th *IRA* will not appear until *Supplement 1*. See table below. The electronic version of *USP–NF* is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement.* The new table below outlines the publications and their release and official dates, and the book or supplement which supersedes them.

Publication Schedules

Publication	Release Date	Official Date	Superseded by
1st *IRA* [*PF* 32(1)]	Jan. 1, 2006	Feb. 1, 2006	*2nd Supplement*
2nd *IRA* [*PF* 32(2)]	Mar. 1, 2006	Apr. 1, 2006	*2nd Supplement*
3rd *IRA* [*PF* 32(3)]	May 1, 2006	June 1, 2006	*USP 30–NF 25*
2nd Supplement	June 1, 2006	Aug. 1, 2006	*USP 30–NF 25*
4th *IRA* [*PF* 32(4)]	July 1, 2006	Aug. 1, 2006	*USP 30–NF 25*
5th *IRA* [*PF* 32(5)]	Sept. 1, 2006*	Oct. 1, 2006*	*1st Supplement USP 30–NF 25*
6th *IRA* [*PF* 32(6)]	Nov. 1, 2006*	Dec. 1, 2006*	*1st Supplement USP 30–NF 25*
USP 30–NF 25	Nov. 1, 2006*	May 1, 2007*	*1st Supplement USP 30–NF 25*
1st *IRA* [*PF* 33(1)]	Jan. 1, 2007*	Feb. 1, 2007*	*2nd Supplement USP 30–NF 25*
2nd *IRA* [*PF* 33(2)]	Mar. 1, 2007*	Apr. 1, 2007*	*2nd Supplement USP 30–NF 25*

* Tentative

PRIORITY NEW MONOGRAPH ITEMS. USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monographs are marked received upon receipt of monograph proposal. Received monographs are removed from this list upon publication in *Pharmacopeial Forum.* (This list has been updated as of April 21, 2006.) For additional information, contact Karen A. Russo, Ph.D., kar@usp.org. Monograph sponsors should consult USP's *Guideline for Submitting Requests for Revision to the USP–NF.*

Noncomplex Actives (Drug Substances)

Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Amlodipine Besylate ***(Received)***	Anagrelide Hydrochloride ***(Received)***	Arsenic Trioxide
Azelaic Acid	Balsalazide Disodium	Bentoquatam
Bepridil Hydrochloride	Bivalirudin	Cabergoline
Calcipotriene	Calcium Trisodium Pentetate	Calfactant
Candesartan Cilexetil	Carmustine ***(Received)***	Carvedilol ***(Received)***
Cefdinir ***(Received)***	Cefditoren Pivoxil	Ceftibuten
Cetrorelix	Cevimeline	Chloroxine
Colfosceril	Cytarabine Liposome	Dalfopristin
Dapirazole Hydrochloride	Desirudin	Desonide ***(Received)***
Dexrazoxane	Difloxacin Hydrochloride	Docosanol
Entacapone	Epoprostenol Sodium ***(Received)***	Erythromycin Phosphate
Erythromycin Thiocyanate	Esmolol	Esomeprazole Magnesium ***(Received)***
Estazolam	Estradiol Benzoate	Estramustine Phosphate Sodium
Ethanolamine Oleate	Etomidate	Etoposide Phosphate
Exemestane	Felbamate	Flavoxate Hydrochloride Fluoromethane F 18
Fluoromethane F 18	Foscarnet Sodium	Fosfomycin Tromethamine
Gadobenate Dimeglumine	Gadopentetic Acid	Galantamine Hydrobromide ***(Received)***
Gallium Nitrate	Ganirelix	Glyceryl Aminobenzoate
Granisetron	Halobetasol Propionate	Haloperidol Decanoate ***(Received)***
Hydrocodone Polistirex	Ibandronate Sodium	Imipramine Pamoate
Imiquimod	Irinotecan	Isosulfan Blue
Itraconazole	Lamotrigine ***(Received)***	Latanoprost
Lawsone	Levetriacepam	Levobetaxolol
Levomethadyl Acetate	Lomustine	Lopinavir

Noncomplex Actives (Drug Substances) *(Continued)*

Metipranolol Hydrochloride	Midazolam Hydrochloride	Mifepristone
Miglitol	Misoprostol ***(Received)***	Mivacurium
Moexipril	Nalbuphine Hydrochloride	Nalmefene Hydrochloride
Nateglinide ***(Received)***	Nedocromil Sodium	Nicardipine Hydrochloride
Nilutamide	Nisoldipine	Olopatadine
Olsalazine Sodium	Orbifloxacin ***(Received)***	Orlistat ***(Received)***
Oxcarbazepine ***(Received)***	Pantoprazole Sodium ***(Received)***	Pemoline
Pentamidine Isethionate	Piperonyl Butoxide	Pirbuterol Acetate
Poractant Alpha		Proguanil
Quetiapine Fumarate	Rose Bengal	Salmeterol Xinafoate
Sertraline Hydrochloride ***(Received)***	Sodium Phenylbutyrate	Sterile Methotrexate Sodium
Streptozocin	Sulfacytine	Tacrolimus
Terbinafine Hydrochloride	Terconazole	Tiludronate Disodium
Tiopronin	Tranexamic Acid	Trimipramine Maleate ***(Received)***
Trovafloxacin Mesylate	Voriconazole	Zinc Tridosium Pentetate

Noncomplex Actives (Drug Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate, and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol for Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Suppository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Aminopterin Sodium Tablets	Amlodipine and Benazepril Hydrochloride Capsules
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Bivalirudin Injection
Brompheniramine Maleate, Dextromethorphan Hydrobromide, and Pseudoephedrine Hydrochloride Oral Solution	Budesonide Inhalation Aerosol	Bupivacaine and Lidocaine Hydrochlorides Injection
Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules	Butalbital and Acetaminophen Tablets
Calcipotriene Cream	Calcipotriene Ointment	Calcipotriene Topical Solution
		Cabergoline Tablets
Calcitriol Capsules	Calcitriol Oral Solution	Calcium Acetate Capsules
Calcium Trisodium Pentetate Injection	Calfactant Intratracheal Suspension	Carbidopa and Levodopa Extended-Release Tablets ***(Received)***
Carbidopa and Levodopa Tablets for Oral Suspension	Carbidopa, Levodopa, and Entacapone Tablets	Carmustine for Injection ***(Received)***
Carmustine Implant	Carvedilol Tablets ***(Received)***	Cefdinir Tablets
Cefditoren Pivoxil Tablets	Ceftibuten Capsules	Ceftibuten for Oral Suspension
Ceftiofur Hydrochloride Oral Suspension	Cetirizine Hydrochloride Oral Solution	Cetirizine Hydrochloride Tablets ***(Received)***
Cetrorelix Injection	Cevimeline Hydrochloride Capsules	Chloroxine Cream
Chlorpromazine Hydrochloride Extended-Release Capsules	Choline and Magnesium Salicylates Oral Solution	Choline and Magnesium Salicylates Tablets
Choline Salicylate Oral Solution	Ciclopirox Shampoo	Ciclopirox Topical Gel
Ciclopirox Topical Solution	Cilostazol Tablets ***(Received)***	Cimetidine Oral Solution

Noncomplex Actives (Drug Products) *(Continued)*

Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	Ciprofloxacin Otic Solution	Citalopram Hydrobromide Oral Solution
Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation	Cladribine Injection	Clemastine Fumarate Syrup
Clobetasol Propionate Gel	Clonazepam Orally-Disintegrating Tablets	Clorazepate Dipotassium Capsules
Clorazepate Dipotassium Extended-Release Tablets	Clotrimazole and Betamethasone Dipropionate Lotion	Colestipol Hydrochloride Tablets
Colfosceril and Tyloxapol Suspension	Compound Undecylenic Acid Cream	Compound Undecylenic Acid Topical Powder
Conjugated Estrogens and Medroxyprogesterone Acetate Tablets	Cromolyn Sodium Nasal Solution	Cyclosporine Modified Capsules
Cyclosporine Modified Oral Solution	Cyclosporine Ointment	Cyclosporine Topical Solution
Cysteamine Bitartrate Capsules	Cytarabine Liposome Injection	Dalfopristin and Quinupristin Injection
Dantrolene Sodium Capsules ***(Received)***	Dantrolene Sodium for Injection ***(Received)***	Dantrolene Sodium Oral Suspension
Dapiprazole for Ophthalmic Solution	Desirudin for Injection	Desonide Cream
Dexrazoxane for Injection	Dextroamphetamine Sulfate Extended-Release Capsules	Dextromethorphan Polistirex Extended-Release Oral Suspension
Diazepam Injectable Emulsion	Diclofenac Sodium Ophthalmic Solution	Diethylpropion Hydrochloride Extended-Release Tablets
Difenoxin and Atropine Tablets	Difloxacin Hydrochloride Tablets	Dihydroergotamine Mesylate Metered Spray
Diltiazem Malate Extended-Release Tablets	Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets
Divalproex Sodium Delayed-Release Capsules	Dorzolamide and Timolol Ophthalmic Solution	Dorzolamide Ophthalmic Solution
Doxacurium Chloride Injection	Doxepin Hydrochloride Cream	Doxycycline Oral Gel
Econazole Nitrate Cream	Edrophonium Chloride and Atropine Sulfate Injection	Enalapril Maleate and Diltiazem Malate Extended-Release Tablets
Enalapril Maleate and Felodipine Extended-Release Tablets	Enalaprilat Injection	Entacapone Tablets
Ephedrine Sulfate and Guaifenesin Tablets	Epoprostenol for Injection	Epoprostenol Injection
Esmolol Hydrochloride Injection	Esomeprazole Magnesium Capsules	Estazolam Tablets
Estramustine Phosphate Sodium Capsules	Ethanolamine Oleate Injection	Etidronate Disodium Injection Concentrate
Etomidate Injection	Exemestane Tablets	Famotidine Orally Disintegrating Tablets
Felbamate Oral Suspension	Felbamate Tablets	Fentanyl Lozenges
Fentanyl Transdermal System ***(Received)***	Ferrous Fumarate and Docusate Sodium Extended- Release Capsules	Flavoxate Hydrochloride Tablets
Fluconazole Injection ***(Received)***	Fluconazole Tablets	Flunisolide Inhalation Aerosol
Flunisolide Nasal Spray	Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution
Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***	Fluticasone Propionate Inhalation Powder
Fluticasone Propionate Ointment ***(Received)***	Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection
Fosfomycin for Oral Solution	Gabapentin Oral Solution	Gabapentin Tablets ***(Received)***
Gadobenate Dimeglumine Injection	Galantamine Hydrobromide Tablets ***(Received)***	Gallium Nitrate Injection
Ganciclovir Capsules	Ganirelix Acetate Injection	Gatifloxacin Injection
Gatifloxacin Tablets	Gentamicin Sulfate Oral Solution	Gentamicin Sulfate Soluble Powder
Glimepiride Tablets ***(Received)***	Glipizide Extended-Release Tablets	Granisetron Injection
Granisetron Tablets	Guaifenesin and Salts Of Dextromethorphan and Pseudoephedrine Oral Solution	Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets
Guanidine Hydrochloride	Guanidine Hydrochloride Tablets	Halobetasol Propionate Cream
Halobetasol Propionate Ointment	Haloperidol Decanoate Injection	Haloperidol Lactate Injection
Haloperidol Lactate Oral Concentrate	Hydralazine Hydrochloride and Hydrochlorothiazide Capsules	Hydrochlorothiazide Capsules
Hydrochlorothiazide Oral Solution Concentrate	Hydrocodone Bitartrate and Acetaminophen Oral Solution	Hydrocodone Bitartrate and Aspirin Tablets
Hydrocodone Bitartrate and Guaifenesin Oral Solution	Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrocodone Bitartrate and Homatropine Methylbromide Tablets
Hydrocortisone Acetate Dental Paste	Hydrocortisone Acetate Rectal Foam Aerosol	Hydrocortisone Butyrate Lotion
Hydroflumethiazide and Reserpine Tablets	Hydromorphone Hydrochloride Oral Solution	Hydroquinone Lotion

Noncomplex Actives (Drug Products) *(Continued)*

Ibandronate Sodium Tablets	Ibuprofen Capsules	Idarubicin Hydrochloride Injection
Imipramine Pamoate Capsules	Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol
Ipratropium Bromide Inhalation Solution	Irinotecan Hydrochloride Injection	Isosulfan Blue Injection
Isradipine Extended-Release Tablets	Itraconazole Injection	Itraconazole Oral Solution
Ketoconazole Cream	Ketoconazole Shampoo	Ketoprofen Capsules
Ketoprofen Extended-Release Capsules	Ketoprofen Tablets	Ketotifen Fumarate
Ketotifen Fumarate Ophthalmic Solution	Lactic Acid Lotion	Lamivudine Tablets
Latanoprost Ophthalmic Solution	Leucovorin Calcium for Injection	Levetriacepam Tablets
Levobetaxolol Ophthalmic Suspension	Levocabastine Ophthalmic Suspension	Levofloxacin Solution
Levomethadyl Acetate Hydrochloride Oral Concentrate	Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder	Liothyronine Injection
Lisinopril and Hydrochlorothiazide Tablets	Lomustine Capsules	Lopinavir and Ritonavir Solution
Lopinavir Capsules	Lopinavir Solution	Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***
Loratadine Orally-Disintegrating Tablets	Losartan Potassium Tablets	Mefloquine Hydrochloride Tablets
Melphalan for Injection	Mesalamine Suppositories	Mesoridazine Besylate Concentrate
Metaraminol Bitartrate Injection	Methacholine Chloride for Inhalation Solution	Methadone Hydrochloride Oral Concentrate
Methocarbamol and Aspirin Tablets	Methoxsalen Softgels	Methyclothiazide and Deserpidine Tablets
Methylphenidate Hydochloride Chewable Tablets	Metipranolol Ophthalmic Solution	Metronidazole Capsules
Metronidazole Cream	Metronidazole Extended-Release Tablets	Metronidazole Hydrochloride for Injection
Metronidazole Lotion	Miconazole Nitrate Topical Aerosol	Midazolam Hydrochloride Injection ***(Received)***
Mifepristone Tablets	Miglitol Tablets	Milrinone Injection
Misoprostol Tablets ***(Received)***	Mivacurium In Dextrose Injection	Mivacurium Injection
Moexipril Hydrochloride and Hydrochloro thiazide Tablets	Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution
Morphine Sulfate for Injection Concentrate	Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate
Morphine Sulfate Tablets	Mycophenolate Mofetil Capsules	Mycophenolate Mofetil Oral Solution
Mycophenolate Mofetil Tablets	Nalbuphine Hydrochloride Injection	Nalmefene Hydrochloride Injection
Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution		Naproxen Extended-Release Tablets
Nateglinide Tablets	Nedocromil Sodium Inhalation Aerosol	Neomycin Sulfate Oral Powder
Nevirapine Oral Suspension ***(Received)***	Nevirapine Tablets ***(Received)***	Nicardipine Hydrochloride Capsules
Nilutamide Tablets	Nimodipine Capsules	Nisoldipine Extended-Release Tablets
Nitroglycerin Solution in Acrylic Adhesive	Nizatidine Tablets	Ofloxacin In Dextrose Injection
Ofloxacin Injection	Ofloxacin Tablets ***(Received)***	Olopatadine Ophthalmic Solution
Olsalazine Sodium Capsules	Ondansetron Tablets	Orbifloxacin Tablets
Orlistat Capsules ***(Received)***	Orphenadrine Citrate Extended-Release Tablets	Orphenadrine Citrate, Aspirin, and Caffeine Tablets
Oxcarbazepine Suspension	Oxcarbazepine Tablets	Oxiconazole Cream
Pancuronium Bromide Injection ***(Received)***	Pantoprazole Sodium for Injection	Pantoprazole Sodium Tablets
Paroxetine Hydrochloride Extended-Release Tablets	Paroxetine Oral Suspension	Pemirolast Potassium Ophthalmic Solution
Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution	Pentaerythritol Tetranitrate Extended-Release Capsules
Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation	Pentamidine Isethionate for Injection
Pentazocine Hydrochloride and Acetaminophen Tablets	Phendimetrazine Tartrate Extended-Release Capsules	Phenobarbital Capsules
Phentermine Resin Complex	Phentermine Resin Complex Capsules	Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules
Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pilocarpine Hydrochloride Ophthalmic Gel	Pilocarpine Hydrochloride Ophthalmic Ointment

Noncomplex Actives (Drug Products) *(Continued)*

Pilocarpine Hydrochloride Tablets	Piperonyl Butoxide and Pyrethrins Aerosol Foam	Pirbuterol Acetate Inhalation Aerosol
Poractant Alpha Supension	Porfimer Sodium for Injection	Povacrylate Solution
Povacrylate-Iodine Topical Solution	Povidone-Iodine Gauze	Povidone-Iodine Swabsticks
Povidone-Iodine Topical Aerosol Foam	Povidone-Iodine Vaginal Suppositories	Pramipexole Dihydrochloride Tablets
Prazosin Hydrochloride and Polythiazide Capsules	Prednisolone Sodium Phosphate Oral Solution	Prochlorperazine Maleate Extended-Release Capsules
Progesterone Capsules	Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup	Promethazine and Phenylephrine Hydrochlorides Syrup
Promethazine Hydrochloride and Codeine Phosphate Oral Solution	Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup	Propafenone Hydrochloride Tablets
Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets	Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution
Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution
	Pyrilamine Maleate Injection	
Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	Quinidine Sulfate Injection	Ramipril Capsules
Ranitidine Capsules	Rauwolfia Serpentina and Endroflumethiazide Tablets	Reserpine and Polythiazide Tablets
Rimantadine Hydrochloride Oral Solution	Risperidone Oral Solution	Risperidone Orally Disintegrating Tablets
Risperidone Tablets ***(Received)***	Rivastigmine Tartrate Capsules	Rivastigmine Tartrate Oral Solution
Rocuronium Bromide Injection	Ropinirole Hydrochloride Tablets	Rose Bengal Ophthalmic Solution
Rosiglitazone Maleate Tablets	Salicylic Acid and Sulfur Cleansing Lotion	Salicylic Acid and Sulfur Lotion
Salicylic Acid and Sulfur Shampoo	Salicylic Acid Cream	Salicylic Acid Ointment
Salmeterol Inhalation Aerosol	Salmeterol Xinafoate Inhalation Powder	Scopolamine Transdermal System
Selegiline Hydrochloride Capsules	Serpacwa Topical Cream	Sertraline Hydrochloride Oral Solution
Sibutramine Hydrochloride Capsules	Sodium Bicarbonate and Sodium Citrate for Oral Solution	Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension
Sodium Chlorophyllin Copper Complex Tablets	Sodium Iodide Injection	Sodium Phenylbutyrate Oral Powder
Sodium Phenylbutyrate Tablets	Sodium Phosphates for Oral Suspension	Sodium Phosphates Tablets
Sodium Salicylate and Sulfur Shampoo	Sterile Talc Aerosol	Streptozocin for Injection
Sucralfate Oral Suspension	Sulconazole Nitrate Cream	Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension
Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sulfacytine Tablets	Sulfanilamide Vaginal Cream
Sulfasalazine Oral Suspension	Sulisobenzone Lotion	Sumatriptan Injection
Sumatriptan Tablets	Tacrolimus Capsules	Tacrolimus Injection
Tacrolimus Ointment	Tamsulosin Hydrochloride Capsules	Technetium Tc 99m Teboroxime Injection
Tenofovir Disoproxil Fumarate Tablets	Terbinafine Hydrochloride Cream	Terbinafine Tablets
Terbinafine Topical Solution	Terconazole Vaginal Cream	Terconazole Vaginal Suppositories
Testosterone Transdermal System	Tetracycline Hydrochloride Periodontal Fiber	Theophylline Extended-Release Tablets
Tioconazole Vaginal Ointment	Tiopronin Tablets	Tolnaftate Topical Aerosol Solution
Topiramate Capsules	Topiramate Tablets	Torsemide Injection
Torsemide Tablets	Trandolapril and Verapamil Hydrochloride Extended-Release Tablets	Trandolapril Tablets
Tranexamic Acid Injection	Tranylcypromine Sulfate	Tranylcypromine Sulfate Tablets
Tretinoin Capsules	Tretinoin Microsphere Gel	Triamcinolone Acetonide Nasal Suspension
Trifluridine Ophthalmic Solution	Trimetrexate for Injection	Trimipramine Maleate Capsules
Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup	Trolamine Salicylate Cream	Trolamine Salicylate Gel
Trolamine Salicylate Topical Emulsion	Trovafloxacin Injection	Trovafloxacin Mesylate for Injection
Undecylenic Acid Topical Foam Aerosol	Unoprostone Isopropyl Ophthalmic Solution	Urea Cream
Vecuronium Bromide for Injection	Venlafaxine Extended-Release Capsules	Venlafaxine Tablets

Noncomplex Actives (Drug Products) *(Continued)*

Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules	Voriconazole Injection
Voriconazole Oral Suspension	Voriconazole Tablets	Yttrium Y-90 Chloride Solution
Yttrium Y-90 Glass Microspheres	Yttrium Y-90 Microspheres Injection	Zidovudine and Lamivudine Tablets ***(Received)***
Zinc Acetate Capsules	Zinc Tridosium Pentetate Injection	Ziprasidone Hydrochloride Capsules
Zoledronic Acid for Injection		

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	Aconitic Acid (Achilleic Acid)
Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal	Aliphatic Polyesters
Allantoin-Sodium Pyrrolidone Carboxylate	Aluminum Ammonium Sulfate	Aluminum Ammonium Sulfate
Aluminum Lactate	Aluminum Oxide	Aluminum Potassium Sulfate
Aluminum Silicate	Aluminum Sodium Sulfate	Aluminum Stearate
Ammonium Bicarbonate	Ammonium Calcium Alginate	Ammonium Phosphate
Beeswax, Synthetic	Benzododecinium Bromide	Benzyl Chloride
Benzyl Nicotinate	Beta Naphthol	Brominated Vegetable Oil
Butadiene-Styrene Rubber	Butylalcohol Monostearate	Butylated Hydromethylphenol
Butylene Glycol	Butylphthalyl Butylglycolate	Calcium Acid Pyrophosphate
Calcium Alginate	Calcium Alginate and Ammonium Alginate	Calcium Bromide
Calcium Chloride Solution	Calcium Glycerophosphate ***(Received)***	Calcium Phosphate Monobasic
Calcium Propionate	Calcium Pyrophosphate	Calcium Sorbate
Calcium Stearoyl Lactylate	Caldiamide Sodium	Calteridol Calcium
Canola Oil	Capric Acid	Caprylic/Capric Diglyceril Diglyceryl Succinate
Carbon	Carboxymethyl Starch	Carboxymethylamylopectin Sodium
Carboxymethylcellulose Potassium	Cetostearyl Isononanoate	Chlorodifluoroethane
Cholic Acid	Cinnamaldehyde	Cocamide Diethanolamine
Cocamide Oxide	Cocoyl Caprylocaprate	Crystal Gum
Cutina	Cystine	Dammar Gum
Decanoic Acid	Decyl Oleate	Dehydroacetic Acid
Desoxycholic Acid	Dextrin Palmitate	Dextrins Modified
Diacetyl Tartaric Acid Esters Of Mono- and Diglycerides	Dicetyl Phosphate	Dichlorofluoromethane
Diethyl Sebacate	Difluoroethane	Diglycol Stearate
Diisobutyl Adipate	Diisopropyl Adipate	Diisopropylbenzothiazyl-2-Sulfenamide
Dilauryl Thiodipropionate	Dimethyl Dicarbonate	Dimyristoyl Lecithin
Dimyristoyl Phosphatidylglycerol	Dipropylene Glycol	Disodium Edisylate
Disodium Guanylate	Disodium Inosinate	Disodium Monooleamide Sulfasuccinate
D-Mannose	Docusate Sodium/Sodium Benzoate	Erythorbic Acid
Erythrosine	Ethoxylated Mono- and Diglycerides	Ethoxyquin
Ethyl Hexanediol	Ethyl Linoleate	Ethyl Maltol
Ethylene Dichloride	Ethylurea	Ferric Ammonium Citrate
Ferric Citrate	Ferric Oxide, Brown	Ferric Phosphate
Ferric Pyrophosphate	Ferrous Citrate	Ferrous Glycinate
Ferrous Lactate	Fluorochlorohydrocarbons	Formic Acid
Furcelleran	Gamma-Cyclodextrin	Gentistic Acid
Geraniol	Glutamic Acid Hydrochloride	Gluten
Glycerol Ester Of Gum Rosin (Ester Gum)	Glyceryl Laurate	Glyceryl Palmitate
Glyceryl Ricinoleate	Glyceryl Tristearate	Glycine Hydrochloride
Glycofurol	Glycol Stearate	Heptafluoropropane
Heptylparaben	Hexadecyl Isostearate	Hexane
Hexanetriol(-1,2,6-)	Hydrocarbon Gel	Hydrogenated Starch Hydrolysate
Hydroxyethylmethylcellulose	Hydroxylated Lecithin	Hydroxypropyl Beta Cyclodextrin
Indigotine	Inositol	Iron Carbonyl
Iron Subcarbonate	Isobutylated- Isoprene Copolymer	Isooctylacrylate
Isopropyl Isostearate	Isopropyl Stearate	Isostearic Acid
Isostearyl Alcohol	Lactobionic Acid	Lactose Ferrin, Bovine

Excipients *(Continued)*

Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol	Lactylic Esters Of Fatty Acids	Lanolin (Wool Fat), Hydrogenated
Lanolin Alcohols, Acetylated	Lanolin Hydrous	L-Ascorbyl Stearate
Lauramine Oxide	Lauric Myristic Diethanolamide	Lauric Acid
Lauric Diethanolamide	Lavender Oil	L-Cysteine Monohydrochloride
Lecithin, Hydroxylated	L-Glutamic Acid	Linoleic Acid
L-Leucine	Macrogol Sorbitan Tristearate	Macrogolglycerol Cocoates
Macrogolglycerol Triisostearate	Magnesium Aluminum Silicate Hydrate	Magnesium Aspartame Dihydrate
Magnesium Aspartate	Magnesium Phosphate Tribasic	Magnesium Phosphate, Diabasic, Trihydrate
Magnesium Tartrate	Malt Syrup	Maltitol Syrup
Maltol Isobutyrate	Manganese Chloride	Manganese Citrate
Manganese Glycerophosphate	Manganese Hypophosphite	Medical Antifoam Emulsion C
Medronate Disodium	Medronic Acid	Methyl Chloride
Methylchloroisothiazolinone	Methylisothiazolinone	Microcrystalline Cellulose, Silicified ***(Received)***
Mineral Spirits	Monoisostearyl Glyceryl Ester	Monopotassium Glutamate Monohydrate
Monosodium Citrate	Mullein Leaf	Myristyl Gamma-Picolinium Chloride
Myristyl Lactate	*N,N*-Bis(2-hydroxyethyl)stearamide	*N*-Acetyl-L- Methionine
Naphtha	*N*-Methylpyrrolidone ***(Received)***	Non-Pareil Seeds
Nutmeg Oil	Octanoic Acid	Oxystearin
Palm Kernel Oil ***(Received)***	Palm Oil	Pentasodium Triphosphate
Pentetate Calcium Trisodium	Pentetate Pentasodium	Phenprobamate
Phenylmercuric Acetate	Phenylmercuric Nitrate	Pine Oil
Polacrilin	Polydextrose ***(Received)***	Polydextrose Solution
Polyglycerol Esters Of Fatty Acids	Polyglycerol Polyricinoleic Acid	Polyoxyethylene Castor Oil—(USP has 35)
Polyoxyl Stearate—(USP has 40)	Polypropylene Oleate	Polypropylene Stearyl Ether
Polysorbate 65	Polyvinylacetal	Polyvinylacetal Diethylanoacetate
Polyvinylpolypyrrolidone	Polyvinylpyrrolidone Ethylcellulose	Potassium Acid Tartrate
Potassium Bromate	Potassium Carbonate Solution	Potassium Dichloroisocyanurate
Potassium Gibberellate	Potassium Glycerophosphate	Potassium Iodate
Potassium Nitrite	Potassium Phosphate	Potassium Phosphate Tribasic
Potassium Polymetaphosphate	Potassium Pyrophosphate	Potassium Stearate
Potassium Sulfate	Potassium Sulfite	Potassium Tripolyphosphate
Propyl Propionate	Propylene Glycol Diacetate	Propylene Glycol Mono- and Diesters
Purified Polyoxyl 35 Castor Oil ***(Received)***	Rapeseed Oil, Hydrogenated ***(Received)***	Rapeseed Oil, Superglycerinated ***(Received)***
Rice Bran Wax	Rosin	Silicone
Sodium Acid Pyrophosphate	Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic
Sodium Aluminum Phosphate Basic	Sodium Aspartate	Sodium Bisulfate
Sodium Bisulfite	Sodium Carbonate Hydrate	Sodium Carboxymethyl Betaglucan
Sodium Caseinate	Sodium Chlorate	Sodium Citrate, Dibasic
Sodium Citrate, Monobasic	Sodium Dehydroacetate	Sodium Diacetate
Sodium Erythorbate	Sodium Ferric Pyrophosphate	Sodium Ferrocyanide
Sodium Hypophosphite	Sodium Laureth Sulfate	Sodium Lauroyl Sarcosinate
Sodium Lauryl Sulfoacetate	Sodium Magnesium Aluminosilicate	Sodium Magnesium Silicate
Sodium Malate	Sodium Metaphosphate, Insoluble	Sodium Metasilicate
Sodium Methylate	Sodium Polyphosphates Glassy	Sodium Potassium Tripolyphosphate
Sodium Pyrophosphate	Sodium Pyrrolidone Carboxylate	Sodium Sesquicarbonate
Sodium Sesquinoleate	Sodium Stearoyl Lactylate	Sodium Thiomalate
Sodium Trimetaphosphate	Sodium Trioleate	Sodium Tripolyphosphate
Soy Polysaccharides	Stannous Chloride	Stannous Tartrate
Starch, Pregelatinized Corn	Starch, Pregelatinized Tapioca	Stearalkonium Chloride
Stearyl Citrate	Stearyl Monoglyceridyl Citrate	Succinylated Monoglycerides
Sucrose Acetate Isobutyrate	Sucrose Fatty Acid Esters	Sucrose Stearate
Sugar Fruit Fine	Sulfobutyl Ether Beta Cyclodextran	Tallow
Tallow Glycerides	Tallow Oil	Tetrafluoroethane
Thioglycerol	Thyme Oil	Tribehenin
Tricetеareth-4 Phosphate	Trichloroethylene	Trimyristin

Excipients *(Continued)*

Trolamine Lauryl Sulfate	Vegetable Oil	Wheat Flour
Wheat Germ Oil	Wheat Gluten	Whey

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

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

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

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ■new text■, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ■■, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement,* and ■2S (*USP29*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 29*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in future *Supplements,* and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

FOURTH INTERIM REVISION ANNOUNCEMENT to *USP 29* and to *NF 24*

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

John W. Mauger, *Chair*
USP Board of Trustees

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

Roger L. Williams, M.D., *Chief Standards Officer, Acting*

Official August 1, 2006 **Released July 1, 2006**

All inquiries and comments regarding *USP 29* text and *NF 24* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were not available when the associated monograph was made official, have since become available. The respective official date of each *USP 29* or *NF 24* standard, test, or assay requiring the use of the following USP Reference Standards is indicated in parentheses after the name of the Reference Standard.

USP Budesonide RS (September 1, 2006)
USP Escin RS (January 1, 2007)
USP Fluticasone Propionate RS (November 1, 2006)
USP Fluticasone Propionate Resolution Mixture RS (September 1, 2006)
USP Fluticasone Propionate System Suitability Mixture RS (September 1, 2006)
USP Fluvastatin Related Compound B RS (November 1, 2006)
USP Polyisobutylene RS (November 1, 2006)
USP Ropivocaine Hydrochloride RS (November 1, 2006)
USP Ropivacaine Related Compound A RS (September 1, 2006)
USP Ropivacaine Related Compound B RS (September 1, 2006)
USP Sulisobenzone RS (January 1, 2007)
USP Tinidazole Related Compound B RS (September 1, 2006)

Unavailable First-Time Official USP Reference Standards

The official dates of any *USP 29* or *NF 24* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards. This listing was updated as of May 5, 2006.

USP Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Aprotinin RS
USP Aprotinin System Suitability RS
USP Cetrimonium Bromide RS
USP Citalopram Hydrobromide RS
USP Cladribine RS
USP Cladribine Related Compound A RS
USP Copolymer Polypropylene RS
USP Decoquinate RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Eucatropine Hydrochloride RS
USP Fludeoxyglucose Related Compound B RS
USP Fluvastatin Sodium RS
USP Fluvastatin Related Compound A RS
USP Gabapentin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Distearate RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Hexacosanol RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Lamivudine Resolution Mixture B RS
USP Alpha Lipoic Acid RS
USP Maritime Pine Extract RS
USP Mecamylamine Related Compound A RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Naratriptan Resolution Mixture RS
USP Near Infrared Calibrator RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Paricalcitol Solution RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Polyoxyl 10 Oleyl Ether RS
USP Potassium Perchlorate RS
USP Pygeum Extract RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Powdered St. John's Wort Extract RS
USP Saccharin Sodium RS
USP Sargramostim RS
USP Sincalide RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tizanidine Hydrochloride RS
USP Tizanidine Related Compound A RS
USP Tizanidine Related Compound B RS
USP Tizanidine Related Compound C RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS

GENERAL NOTICES AND REQUIREMENTS

Change to read:

TESTS AND ASSAYS

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

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

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

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

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

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

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

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

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

Other Impurities—Official substances may be obtained from more than one process, and thus may contain impurities not considered during preparation of monograph assays or tests. Wherever a monograph includes a chromatographic assay or purity test based on chromatography, other than a test for organic volatile impurities, and that monograph does not detect such an impurity, solvents excepted, the impurity shall have its amount and identity, where both are known, stated under the heading *Other Impurity(ies)* by the labeling (certificate of analysis) of the official substance.

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

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

Residual Solvents—The requirements are stated in •*Residual Solvents*•$_{4}$ ⟨467⟩ together with information in *Impurities in Official Articles* ⟨1086⟩. Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in •*Residual Solvents*•$_{4}$ ⟨467⟩, using the general methods presented therein or other suitable methods. (Official •July•$_{4}$ 1, 2007)

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

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

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

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

In the performance of assay or test procedures, not fewer than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least

equivalent accuracy. To minimize environmental impact or contact with hazardous materials, apparatus and chemicals specified in Pharmacopeial procedures also may be proportionally changed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Water and Loss on Drying—Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading *Water.* Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading *Loss on drying.* However, *Loss on drying* is most often given as the heading where the loss in weight is known to represent residual volatile constituents, including organic solvents as well as water.

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

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

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

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

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

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

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

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

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

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

MONOGRAPHS (USP)

Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine

Change to read:

Labeling—The label for each article encompassed by this monograph bears a name composed of the active ingredients. The label states the name and quantity of each active ingredient and indicates its function (or purpose) in the article.•When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.•4

Change to read:

Dissolution, *Procedure for a Pooled Sample* ⟨711⟩—

•TEST 1—•4

Medium: ■pH 5.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*);■1S (*USP29*) 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Test preparation—Mix 9.0 mL of a filtered portion of the solution under test with 1.0 mL of 1% phosphoric acid solution.

Procedure—Determine the amounts of pseudoephedrine hydrochloride or pseudoephedrine sulfate (as appropriate), acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide dissolved, employing the procedures set forth in the *Assay for pseudoephedrine hydrochloride* or *Assay for pseudoephedrine sulfate, Assay for acetaminophen, Assay for chlorpheniramine maleate,* and *Assay for dextromethorphan hydrobromide,* respectively, making any necessary volumetric adjustments.

Tolerances—Not less than 75% *(Q)* of the labeled amounts of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) or pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$], acetaminophen ($C_8H_9NO_2$), chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), and dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$) are dissolved in 45 minutes.

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: water; 900 mL.

Apparatus, Time, Test preparation, Procedure, and *Tolerances*—Proceed as directed for *Test 1.*•4

Amoxicillin Tablets

Change to read:

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Determine the amount of $C_{16}H_{19}N_3O_5S$ dissolved by employing the following method.

pH 5.0 Buffer—Dissolve 27.2 g of monobasic potassium phosphate in 3 L of water, adjust with a 45% (w/w) solution of potassium hydroxide to a pH of 5.0 ± 0.1, dilute with water to obtain 4 L of solution, and mix.

Mobile phase—Prepare a mixture of *pH 5.0 Buffer* and acetonitrile (3900 : 100), and pass through a filter having a 0.5-µm or finer porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Amoxicillin RS in *pH 5.0 Buffer* to obtain a solution having a known concentration of about 0.05 mg per mL. Use this solution within 6 hours.

Test solution—Pass a portion of the solution under test through a filter having a 0.5-µm or finer porosity. Quantitatively dilute an accurately measured volume of the filtrate with water to obtain a solution having an estimated concentration of about 0.045 mg of amoxicillin per mL. Use this solution within 6 hours.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector, a 3.9-mm × 30-cm analytical column that contains packing L1, and a 2-mm × 2-cm guard column that contains packing L2. The analytical column is maintained at a constant temperature of about 40 ± 1°. The flow rate is about 0.7 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is between 1.1 and 2.8; the column efficiency is not less than 1700 theoretical plates; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of amoxicillin ($C_{16}H_{19}N_3O_5S$) dissolved by the formula:

$$0.9DCP(r_U/r_S)$$

in which D is the dilution factor used in preparing the *Test solution;* C is the concentration, in mg per mL, of USP Amoxicillin RS in the *Standard solution;* P is the stated content, in µg of amoxicillin ($C_{16}H_{19}N_3O_5S$) per mg, of USP Amoxicillin RS; and r_U and r_S are the amoxicillin peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 30 minutes.

FOR PRODUCTS LABELED AS CHEWABLE TABLETS—Proceed as directed above.

•FOR CHEWABLE TABLETS LABELED TO CONTAIN 200 MG OR 400 MG—•4

Time: 20 minutes.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 20 minutes.

•FOR CHEWABLE TABLETS LABELED TO CONTAIN 125 MG OR 250 MG—

Time: 90 minutes.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{16}H_{19}N_3O_5S$ is dissolved in 90 minutes.•4

FOR VETERINARY PRODUCTS—Proceed as directed above, except to use *Apparatus 2* at 100 rpm.

Fluoxetine Delayed-Release Capsules

Change to read:

Chromatographic purity—

Ion-pair solution—Dissolve about 6.5 g of sodium 1-octanesulfonate and 2.9 g of anhydrous sodium acetate in 1 L of water, and adjust with glacial acetic acid to a pH of 5.0.

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

Degraded fluoxetine solution—Dissolve a quantity of USP Fluoxetine Hydrochloride RS in 1.0 N sulfuric acid to obtain a solution containing about 2.2 mg per mL. Heat to 85° for 3 hours, and cool to room temperature.

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Fluoxetine related compound solution—Dissolve a quantity of USP Fluoxetine Related Compound C RS in *Mobile phase* to obtain a solution containing about 0.5 mg per mL.

System suitability solution—Transfer about 13.5 mg of USP Fluoxetine Hydrochloride RS to a 100-mL volumetric flask, add 2 mL of *Degraded fluoxetine solution* and 2 mL of *Fluoxetine related compound solution,* and dissolve in and dilute with *Mobile phase* to volume. Transfer 10.0 mL of this solution to a 250-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Detector sensitivity solution—•Transfer 2 mL of the *System suitability solution* to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume.•[4]

Test solution—Weigh and finely powder not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of fluoxetine, to a 250-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Filter before injection.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L7. The column temperature is maintained at 30°. The flow rate is about 1 mL per minute. Inject the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.49 for α,α,α-trifluoro-*p*-cresol, 0.70 for fluoxetine related compound C, and 1.0 for fluoxetine; the resolution, *R,* between α,α,α-trifluoro-*p*-cresol and fluoxetine related compound C is not less than 2.0; and the resolution, *R,* between fluoxetine related compound C and fluoxetine is not less than 6.0. Chromatograph the *Detector sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the fluoxetine peak is not less than 10.

Procedure—Inject a volume (about 50 µL) of the *Test solution* into the chromatograph, record the chromatogram for at least three times the retention time of the fluoxetine peak, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.2% of any individual impurity is found, and not more than 0.7% of total impurities is found.

Nifedipine Extended-Release Tablets

Change to read:

Dissolution ⟨711⟩—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1.*

Medium: water; 50 mL.

Apparatus 7 (see *Drug Release* ⟨724⟩): 15 to 30 cycles per minute. Do not use the reciprocating disk, but use a 25-cm Plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue. The solution containers are 25-mm test tubes, 150 to 200 mm in length, and the water bath is maintained at 37 ± 0.5°. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.

Times: 4, 8, 12, 16, 20, and 24 hours.

Diluting solution: a mixture of methanol and water (1 : 1).

Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of methanol, dilute with water to volume, and mix to obtain a Standard stock solution. Quantitatively dilute this Standard stock solution with *Diluting solution* to obtain solutions having suitable known concentrations.

Test solution—Use portions of the solution under test, passed through a 0.4-µm filter, suitably diluted with methanol, and stepwise, if necessary, with *Diluting solution* to obtain a final mixture consisting of equal parts of methanol and water.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in the *Test solution* at each 4-hour interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm, in 0.5-cm cells. [NOTE—For the 4-hour time period, determine the absorbance at 456 nm, and use this determination to correct for excipient interference.]

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved*
4	between 5% and 17%
8	—
12	between 43% and 80%
16	—
20	—
24	not less than 80%

* The amount dissolved is expressed in terms of the labeled Tablet strength rather than in terms of the labeled total contents.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Buffer concentrate—Transfer 330.9 g of dibasic sodium phosphate and 38 g of citric acid to a 1-L volumetric flask, add water to dissolve, add 10 mL of phosphoric acid, dilute with water to volume, and mix.

Medium—Mix 125.0 mL of *Buffer concentrate* and 1 L of 10% sodium lauryl sulfate solution, and dilute to 10 L. Adjust if necessary to a pH of 6.8; 900 mL.

Apparatus 2: 50 rpm, with sinkers (see *Figure 1*).

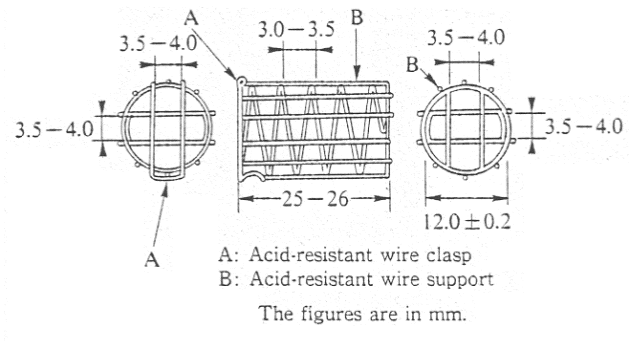


Figure 1 (printed with permission of the Japanese Pharmacopoeia)

Times: 3, 6, and 12 hours.

Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol to obtain a solution having a known concentration of about 1.11 mg per mL. Dilute quantitatively and stepwise with *Medium* to obtain a solution having a known concentration of 0.1 mg per mL.

Chromatographic system—The liquid chromatograph is equipped with a 350-nm detector and a 4.0-mm × 125-mm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column is maintained at about 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of filtered portions of the *Standard solution* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved.

Tolerances—The percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) released in vivo and dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
3	between 10% and 30%
6	between 40% and 65%
12	not less than 80%

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

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Apparatus 2: 100 rpm.

Time: 1 hour.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm, using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 30% and 55%
8	not less than 60%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Medium* for *Phase 2*.] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Medium* as the blank.

Apparatus 2: 100 rpm.

Time: 25 minutes.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm, using filtered portions of the solution under test, in comparison with the *Standard solution,* using *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 40% and 70%
8	not less than 70%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

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

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL for Tablets labeled to contain 60 mg, and about 0.034 mg of USP Nifedipine RS per mL for Tablets labeled to contain 30 mg. [NOTE—If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.]

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution,* using the *Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released at the times specified, conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 12% and 35%
4	between 44% and 67%
12	not less than 80%

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 10% and 30%
4	between 40% and 63%
12	not less than 80%

(Official April 1, 2006)

•TEST 5—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 5*.

Medium: water; 50 mL.

Apparatus 7 (see *Drug Release* ⟨724⟩)—Use a 25-cm Plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue; 30 dips per minute. The solution containers are 25-mm test tubes, 150 to 200 mm in length, and the water bath is maintained at 37 ± 0.5°.

Times: 4, 12, and 24 hours.

Diluting solution 1—Prepare a mixture of methanol and acetonitrile (1 : 1).

Diluting solution 2—Prepare a mixture of *Diluting solution 1* and water (1 : 1).

Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Diluting solution 1,* dilute with water to volume, and mix. Quantitatively dilute this solution with *Diluting solution 2* to obtain solutions having known concentrations of 0.01 mg per mL, 0.05 mg per mL, and 0.20 mg per mL that are used at 4, 12, and 24 hours sampling, respectively.

Procedure—[NOTE—For the 4-hour time period, filter the solution under test, and determine the absorbance at 456 nm. Use this absorbance value to correct for excipient interference at the other time points.] Determine the amount of nifedipine released at each interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted, if necessary, with *Diluting solution 1* and water to obtain a final mixture of water, methanol, and acetonitrile (2 : 1 : 1), in comparison with the appropriate *Standard solution,* using 0.5-cm cells, and *Diluting solution 2* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine, released in vivo and dissolved at the times specified, conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
4	not more than 14%
12	between 39% and 75%
24	not less than 75%

•4

Sterile Water for Inhalation

Change to read:

Oxidizable substances—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Inhalation in containers having a fill volume of less than 50 mL, add 0.4 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Sterile Water for Injection

Change to read:

Oxidizable substances—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Injection in containers having a fill volume of less than 50 mL, add 0.4 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Sterile Water for Irrigation

Change to read:

Oxidizable substances—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Irrigation in containers having a fill volume of less than 50 mL, add 0.4 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Sterile Purified Water

Change to read:

Oxidizable substances—To 100 mL, add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Purified Water in containers having a fill volume of less than 50 mL, add 0.4 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and pass through a sintered-glass filter: the pink color does not completely disappear.

Water for Hemodialysis

Change to read:

Oxidizable substances—To 100 mL, add 10 mL of 2 N sulfuric acid, and heat to boiling. Add ▲0.2 mL▲*USP29* of •0.02 $M_{•4}$ potassium permanganate, and boil for 5 minutes. The pink color does not completely disappear; or alternatively follow the test method for *Total Organic Carbon* ⟨643⟩.

Interim Revision Announcement

Zinc Sulfate Tablets

Change to read:

Identification—

Test solution—•Dissolve a portion of powdered Tablets in water to obtain a solution containing about 0.05 g of zinc sulfate per mL.

Glycerin solution: a mixture of glycerin and water (85 : 15).

Sodium sulfide solution—Dissolve 12 g of sodium sulfide with heating in a 45-mL mixture of *Glycerin solution* and water (29 : 10), allow to cool, and dilute with the same mixture of solvents to 100 mL. The solution should be colorless.

Hydrochloric acid solution—Transfer 20 g of hydrochloric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

Barium chloride solution—Transfer 61 g of barium chloride to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Sodium hydroxide solution—Transfer 42 g of sodium hydroxide to a 100-mL volumetric flask, dilute with water to volume, and mix.

Ammonium chloride solution—Transfer 107 g of ammonium chloride to a 1000-mL volumetric flask, dilute with water to volume, and mix.•4

A: •To 5 mL of the *Test solution* add 1 mL of *Hydrochloric acid solution* and 1 mL of *Barium chloride solution.* A white precipitate is formed.•4

B: •To 5 mL of the *Test solution* add 0.2 mL of *Sodium hydroxide solution.* A white precipitate is formed. Add an additional 2 mL of *Sodium hydroxide solution* and the precipitate dissolves. Add 10 mL of *Ammonium chloride solution* and the solution remains clear. Add 0.1 mL of *Sodium sulfide solution* and a white precipitate is formed•4

Delete the following:

•**Dissolution—**

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

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

Time: 20 seconds.

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

Tolerances—The disintegration of the Tablets is complete in 20 seconds, and the resistivity stabilizes at about 255 to 260 µS in 20 seconds.•4

Add the following:

•**Disintegration** ⟨701⟩**:** 60 seconds.•4

Interim Revision Announcement

DIETARY SUPPLEMENTS—MONOGRAPHS

Valerian

Change to read:

USP Reference standards ⟨11⟩—•4 *USP Valerenic Acid RS.*

Change to read:

Identification—

A: Transfer about 0.2 g of freshly powdered Valerian to a test tube, add 5 mL of methylene chloride, shake several times, and allow to stand for 5 minutes. Filter, wash the filter with 2 mL of methylene chloride, and combine the filtrate and washings in one container. Heat the combined filtrate and washings on a water bath for the minimum time required to evaporate the solvent, and dissolve the residue in 0.2 mL of methylene chloride.•4 To about 0.1 mL of this solution, add 3 mL of a mixture of equal volumes of glacial acetic acid and 25% hydrochloric acid, and shake several times: a blue color develops within 15 minutes.
•4

•**B:**•4 The retention time of the valerenic acid peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *Standard solution*, as obtained in the test for *Content of valerenic acid.*

Powdered Valerian

Change to read:

USP Reference standards ⟨11⟩—•4 *USP Valerenic Acid RS.*

ERRATA

Following is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP 29–NF 24*. If necessary, this list will be updated with every issue of *PF*. This information will also be available as a cumulative table in future *Supplements* and will appear in its corrected form in a future annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff is available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
664	*Dextroamphetamine Sulfate Tablets*	*Identification A*	Line 4: Change "into a 250-mL separator, add 5 mL of 2.5 N sodium hydroxide, and mix." to: into a 250-mL separator, add 5 mL of 2.5 N sodium hydroxide, mix, and extract with 60 mL of ether.
		Isomeric purity	Line 15: Change "With the aqueous phase in the separator, preventing it from" to: Add to the aqueous phase in the separator 2.5 g of sodium bicarbonate. Preventing it from
3273	*Ammonium Sulfate*	*Limit of phosphate*	Line 6 under *Procedure:* Change "made with 2.0 mL of the *Standard Phosphate Solution*" to: made with 0.2 mL of the *Standard Phosphate Solution*
Supplement 1			
3580	*Saccharin Sodium*	*Organic volatile impurities*	Line 1: Change "*Method I*" to: *Method IV*

Interim Revision Announcement

IN-PROCESS REVISION

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

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

BRIEFING

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

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

•new text•

if slated for an *Interim Revision Announcement to USP 29–NF 24* (*IRA*);

▲new text▲*USP30*

if slated for *USP 30–NF 25*; and

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, ■2S (*USP 29*) indicates that the proposed revision is slated for the *Second Supplement to USP 29*, and ▲*USP30* and ▲*NF25* indicate that the revisions are proposed for *USP 30* and *NF 25*, respectively.

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

MONOGRAPHS (USP)

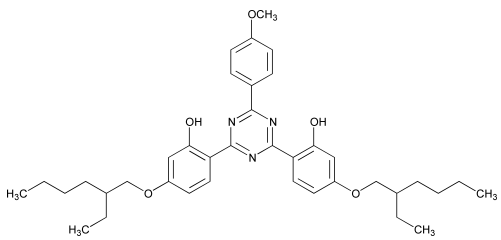
BRIEFING

Bemotrizinol. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on validated methods, is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Hypersil BDS brand of L1 column. The typical retention time for bemotrizinol is about 13 minutes.

(MD-OOD: C. Anthony) RTS—C41734

Add the following:

■Bemotrizinol



$C_{38}H_{49}N_3O_5$ 627.80

Phenol, 2,2′-[6-(4-methoxyphenyl)-1,3,5-triazine-2,4-diyl]-bis[5-[(2-ethylhexyl)oxy]].

2,2′-[6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis[5-[(2-ethylhexyl)oxy]phenol] [*CAS-187393-00-6*].

» Bemotrizinol contains not less than 96.5 percent and not more than 100.0 percent of $C_{38}H_{49}N_3O_5$, calculated on the as-is basis.

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

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

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Spectral range: 210 to 750 nm.

Solution: 10 mg per mL.

Medium: 1,4-dioxane.

Ratio: A_{308}/A_{342} is about 0.9.

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

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

Limit of residual solvents—

Sample cartridge—Transfer 50 mg of Bemotrizinol to a previously weighed thermodesorption glass tube, and reweigh. Determine the weight of Bemotrizinol using the weight by difference method. Place two glass wool plugs into each end of the tube to hold the packed sample in the tube.

Standard solution—Dissolve 10 µL of acetone, 5 µL of 2-butanol, and 2 µL of *N,N*-dimethylformamide in 10 mL of methanol.

Reference cartridge—Weigh an empty thermodesorption glass tube. Add enough S9 support (60- to 80-mesh) to obtain 100 mg. Place two glass wool plugs into each end of the tube. With a syringe, inject 3 µL of the *Standard solution* into the cartridge, corresponding to 2.37 µg of acetone, 1.22 µg of 2-butanol, and 0.57 µg of *N,N*-dimethylformamide. After purging with nitrogen for 1.5 minutes (15 mL per minute), transfer the cartridge to the thermodesorption device.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a thermodesorption device, a cryo-trap injector cooled by liquid nitrogen, and a flame-ionization detector, and contains a 0.53-mm × 30-m column coated with a 3-µm film of liquid phase G43. The carrier gas is nitrogen, flowing at a rate of 64 cm per second. The chromatograph is programmed as follows. Initially the temperature of the thermodesorption unit is set at 30°, then the temperature is increased at a rate of 60° per minute to

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150°, and maintained at 150° for 8 minutes. The initial temperature of the cryo-trap is set at –150°, then the temperature is increased at a rate of 12° per second (after sample transfer) to 300° and maintained at 300° for 2 minutes. Initially the temperature of the column is maintained at 40° for 2 minutes, then the temperature is increased at a rate of 8° per minute to 120°, and then the temperature is increased at a rate of 20° per minute to 250° and maintained at 250° for 5 minutes. The transfer line from the cryo-trap to the column is maintained at 300°, and the detector is maintained at 260°. Chromatograph the *Reference cartridge* and the *Sample cartridge*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5% for each of the solvents.

Procedure—Attach the *Sample cartridge* and the *Reference cartridge* to the cryo-trap injector, and allow the analyte to thermodesorb. Increase the temperature of the cryo-trap injector to facilitate the rapid transfer of analyte to the column, record the chromatograms, and measure the responses for the major peaks. Calculate the concentration of each residual solvent in the portion of Bemotrizinol taken by the formula:

$$1000(W_S / W_U)(r_U / r_S)$$

in which W_S is the weight, in µg, of the individual solvent spiked on the *Reference cartridge;* W_U is the weight of Bemotrizinol, in mg, spiked on the *Sample cartridge;* r_U is the peak response obtained from the *Sample cartridge;* and r_S is the peak response of the solvent obtained from the *Reference cartridge:* not more than 50 ppm of acetone is found; not more than 50 ppm of 2-butanol is found; and not more than 10 ppm of *N,N*-dimethylformamide is found.

Related compounds—

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

Test solution—Transfer about 500 mg of Bemotrizinol, accurately weighed, to a 100-mL volumetric flask, dissolve by sonication in 80 mL of 1,4-dioxane, dilute with 1,4-dioxane to volume, and mix. Transfer 5 mL of the solution to a 25-mL volumetric flask, and dilute with *Diluent* to volume to obtain a solution having a concentration of about 1.0 mg per mL.

Standard stock solution—Transfer about 25 mg of USP Bemotrizinol RS, accurately weighed, to a 100-mL volumetric flask. Dissolve by sonication for 5 minutes in 60 mL of 1,4-dioxane. Cool to room temperature, dilute with 1,4-dioxane to volume, and mix.

Standard solution—Pipet 2.0 mL of the *Standard stock solution* into a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix to obtain a solution having a known concentration of 10 µg per mL.

Sensitivity check solution—Pipet 2.0 mL of the *Standard stock solution* into a 100-mL volumetric flask, dilute with 1,4-dioxane to volume, and mix. Pipet 5.0 mL of this solution into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix to obtain a solution having a concentration of 0.25 µg per mL.

Procedure—Separately inject a volume (about 20 µL) of the *Test solution,* the *Standard solution,* and the *Sensitivity check solution* into the chromatograph; record the chromatograms; measure the peak responses of bemotrizinol in the *Standard solution,* the *Test solution,* and the *Sensitivity check solution;* and measure the response of any impurity peak in the *Test solution* with a response greater than that obtained for bemotrizinol in the *Sensitivity check solution.* Calculate the percentage of each impurity in the portion of Bemotrizinol taken by the formula:

$$50(C/FW)(r_i / r_S)$$

in which C is the concentration, in µg per mL, of USP Bemotrizinol RS in the *Standard solution;* F is the relative response factor; W is the weight, in mg, of Bemotrizinol taken; r_i is the peak response for each individual impurity in

the *Test solution* with a response equal to or greater than the bemotrizinol peak obtained from the *Sensitivity check solution;* and r_S is the response of the bemotrizinol peak obtained from the *Test solution*.

Assay—

Diluent—Prepare a mixture containing 1,4-dioxane and water (80 : 20).

Buffer—Transfer 600 mg of ammonium formate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust with formic acid to a pH of 4.6.

Solution A—Use the *Buffer,* filtered and degassed.

Solution B—Use 1,4-dioxane.

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

Standard preparation—Transfer about 50 mg of USP Bemotrizinol RS, accurately weighed, to a 50-mL volumetric flask. Dissolve by sonication in 40 mL of 1,4-dioxane. Cool to room temperature, dilute with 1,4-dioxane to volume, and mix. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Assay preparation—Transfer about 50 mg of Bemotrizinol, accurately weighed, to a 50-mL volumetric flask. Dissolve by sonication in 40 mL of 1,4-dioxane. Cool to room temperature, dilute with 1,4-dioxane to volume, and mix. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 332-nm detector and a 3.0-mm × 12.5-cm column that contains packing L1. The flow rate is about 0.3 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Impurity	Relative Retention Time	Response Factor (*F*)	Limit (%)
2-[2-Hydroxy, 4-(2-ethylhexyloxy)phenyl], 4-(resorcin-4-yl), 6-(4-methoxyphenyl) 1,3,5-triazine	0.26	1.11	< 1.0
2-Hydroxy, 4-(2-ethylhexyloxy)benzophenone	0.30	0.4	< 1.0
Impurity A	0.35	1.11	< 1.0
2-[4-(2-Ethylhexyloxy), 2-hydroxyphenyl], 4,6-bis-(4-methoxyphenyl) 1,3,5-triazine	0.39	1.11	< 1.0
2-[2,4-Bis-(2-ethylhexyloxy)phenyl], 4-[2-hydroxy, 4-(2-ethylhexyloxy)phenyl], 6-[4-methoxyphenyl] 1,3,5-triazine	1.46	0.77	< 1.0
Impurity B	1.62	0.77	< 1.0
2,4,6-Tris-[2-hydroxy, 4-(2-ethylhexyloxy)phenyl] 1,3,5-triazine	1.66	0.67	< 1.0
2,4-Bis-[2-hydroxy, 4-(2-ethylhexyloxy)phenyl], 6-[4-2-ethyl-hexyloxy)phenyl] 1,3,5-triazine	1.69	0.83	< 1.0
Any other unknown impurity	—	1.0	< 1.0
Total impurities	—	—	< 2.5

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	20	80	isocratic
5–25	20→0	80→100	linear gradient
25–27	0	100	isocratic
27–27.1	0→20	100→80	linear gradient
38	20	80	isocratic

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections of the *Standard preparation* is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{38}H_{49}N_3O_5$ in the portion of Bemotrizinol taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Bemotrizinol RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

BRIEFING

Bupropion Hydrochloride Extended-Release Tablets, *USP 29* page 322 and page 312 of *PF* 32(2) [Mar.–Apr. 2006]. In *Dissolution Test 4,* it is proposed to correct the cell path length and the tolerances at the 8-hour time point.

(BPC: M. Marques) RTS—C44872

Change to read:

Drug release ⟨724⟩—

■FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—■1S (*USP30*)

TEST 1—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, and 8 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	between 25% and 45%
4	between 60% and 85%
8	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Medium: 0.1 N hydrochloric acid, pH 1.5

■(prepared by transferring about 50 mL of concentrated hydrochloric acid to 6000 mL of water, adding about 18 g of sodium hydroxide, mixing, and adjusting with either diluted sodium hydroxide or hydrochloric acid to a pH of 1.5 ± 0.05.);■1S (*USP30*)
900 mL,

■deaerated.■1S (*USP30*)

Apparatus 1: 50 rpm.

Times: 1, 2, 4, and 6 hours.

Determine the percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing the following method.

Buffer solution—Dissolve 3.45 g of monobasic sodium phosphate monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 2.80 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration similar to the one expected in the *Test solution.*

Test solution—Use portions of the solution under test, and pass through a 0.45-µm nylon filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 298-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	between 25% and 50%
2	between 40% and 65%
4	between 65% and 90%
6	not less than 80%

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

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* except to use the wavelength at about 250 nm.

Times: 1, 2, 4, and 6 hours.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	between 30% and 55%
2	between 50% and 75%
4	between 70% and 90%
6	not less than 80%

■FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

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

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 1: 75 rpm.

Times: 2, 4, 8, and 16 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 252 nm, using a ~~1.0-cm~~■1.0-mm■2S (*USP30*) cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
2	not more than 20%
4	between 20% and 45%
8	between 65% and ~~85%~~■90%■2S (*USP30*)
16	not less than 80%

■1S (*USP30*)

Change to read:

Dissolution ⟨711⟩—

■FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—■1S (*USP30*)

TEST 1—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Times: 1, 4, and 8 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 298 nm, using a 1.0-cm cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	between 25% and 45%
4	between 60% and 85%
8	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 0.1 N hydrochloric acid, pH 1.5

■(prepared by transferring about 50 mL of concentrated hydrochloric acid to 6000 mL of water, adding about 18 g of sodium hydroxide, mixing, and adjusting with either diluted sodium hydroxide or hydrochloric acid to a pH of 1.5 ± 0.05.);■1S (*USP30*)

900 mL,

■deaerated.■1S (*USP30*)

Apparatus 1: 50 rpm.

Times: 1, 2, 4, and 6 hours.

Determine the percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing the following method.

Buffer solution—Dissolve 3.45 g of sodium phosphate monobasic monohydrate in 996 mL of water, add 4.0 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 2.80 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and methanol (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration similar to the one expected in the *Test solution.*

Test solution—Use portions of the solution under test, and pass through a 0.45-µm nylon filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 298-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of bupropion hydrochloride dissolved at each time point.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	between 25% and 50%
2	between 40% and 65%
4	between 65% and 90%
6	not less than 80%

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

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* except using the wavelength at about 250 nm.

Times: 1, 2, 4, and 6 hours.

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 30% and 55%
2	between 50% and 75%
4	between 70% and 90%
6	not less than 80%

■FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

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

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 1: 75 rpm.

Times: 2, 4, 8, and 16 hours.

Procedure—Determine the amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 252 nm, using a ~~1.0-cm~~■1.0-mm■2S (*USP30*) cell, on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Bupropion Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{13}H_{18}ClNO \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	not more than 20%
4	between 20% and 45%
8	between 65% and ~~85%~~■90%■2S (*USP30*)
16	not less than 80%

■1S (*USP30*)

(Official April 1, 2006)

BRIEFING

Butorphanol Tartrate Nasal Solution, page 1346 of *PF* 31(5) [Sept.–Oct. 2005]. On the basis of comments received, it is proposed to make the following revisions. The test for *Microbial limits* is revised. The test for *Delivered dose uniformity over the entire contents* is deleted, because this test is appropriate only for metered-dose inhalers, not for nasal sprays. The preparation of the *Mobile phase* is revised in both the test for *Related compounds* and the *Assay,* to make it more acceptable for the proposed methods. The column length specification for the *Chromatographic system* in the *Assay* is changed. Minor editorial changes have also been made.

(MD-CCA: C. Anthony) RTS—C45970

Add the following:

■Butorphanol Tartrate Nasal Solution

» Butorphanol Tartrate Nasal Solution is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. It contains the equivalent of not less than 90.0 percent and not more than 110.0 percent of the labeled amount of butorphanol tartrate ($C_{21}H_{29}NO_2 \cdot C_4H_6O_6$).

Packaging and storage—Preserve in tight containers at controlled room temperature. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Butorphanol Tartrate RS.*

Identification—

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

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

Test solution—Prepare a composite solution by pooling the contents of three containers of Nasal Solution into a suitable vessel. Transfer 1.0 mL of pooled sample to a 10-mL volumetric flask, and dilute with methanol to volume.

Standard solution—Dissolve an accurately weighed quantity of USP Butorphanol Tartrate RS in methanol to obtain a solution having a known concentration of about 1.0 mg per mL.

Developing solvent system—Prepare a mixture of chloroform, methanol, benzene, and ammonium hydroxide (17 : 5 : 4 : 1). Mix thoroughly. *[Caution—Prepare in a hood while wearing appropriate safety gloves, lab coat, and protective eyewear.]*

Spray reagent—Prepare a 1 in 10 solution of chloroplatinic acid in water. To 0.5 mL of this solution, add 33 mL of water and 1 g of potassium iodide. Prepare fresh daily.

Procedure—Proceed as directed in the chapter, except to spray the plate with *Spray reagent.* The typical R_F value is about 0.7 for butorphanol tartrate.

Osmolality ⟨785⟩**:** between 252 and 292 mOsmol per kg.

Microbial limits ⟨61⟩~~— The total aerobic count is not more than 100 cfu per mL, and the total combined molds and yeasts count is not more than 100 cfu per mL. It meets the requirements of the tests for absence of *Coliforms, Staphylococcus aureus,* and *Pseudomonas aeruginosa.*~~ The total aerobic microbial count does not exceed 1000 cfu per g or mL, and the total combined molds and yeasts count does not exceed 100 cfu per g or mL. It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa.*

pH ⟨791⟩**:** between 4.0 and 6.0.

~~**Delivered dose uniformity over the entire contents:** meets the requirements for *Metered-Dose Inhalers* under *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩.~~

Related compounds—

Phosphate buffer (0.025 M)—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of phosphate buffer, acetonitrile, and triethylamine ~~(85 : 15 : 5)~~ (85 : 15 : 5.1). Mix thoroughly, and adjust with 85.0% phosphoric acid to a pH of 3.0 ± 0.1. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Butorphanol Tartrate RS in water, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.005 mg per mL.

Sensitivity solution—Transfer 2.5 mL of the *Standard solution* to a 50-mL volumetric flask, dilute with water to volume, and mix. Do not filter.

Test solution—Prepare a composite solution by pooling a minimum of four containers of Nasal Solution into a suitable glass vessel. Transfer the equivalent of 50 mg of butorphanol tartrate to a 50-mL volumetric flask. Dilute with water to volume, and mix. Do not filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector, ~~and a 4.6 × 250 mm~~ a 4.6-mm × 25-cm column that contains 5-µm packing L11, and a ~~4.6 × 10 mm~~ 4.6-mm × 1-cm guard column packed with 5-µm packing L11. The column temperature is maintained at 40°. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for six replicate injections is not more than 10.0%. Chromatograph the *Sensitivity solution,* and record the peak responses as directed for *Procedure:* the peak height for butorphanol tartrate is greater than or equal to three times the baseline noise.

Procedure—Separately inject equal volumes (about 60 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the butorphanol tartrate peak in the *Standard*

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solution and for all known and unknown related compounds in the *Test solution.* The chromatographic run time is about 40 minutes. Calculate the percentage of each related compound (see *Table 1*) and each unknown impurity in the portion of Nasal Solution taken by the formula:

$$5000(C/VLA)(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Butorphanol Tartrate RS in the *Standard solution; V* is the volume of sample taken; *LA* is the labeled amount, in mg per mL, of butorphanol tartrate in the sample; r_i is the peak response of each known or unknown related compound in the *Test solution;* and r_S is the peak response of butorphanol tartrate in the *Standard solution:* the impurities meet the requirements specified in *Table 1.*

Table 1

Compound	Relative Retention Time	Limit (%)
3,14-Dihydroxymorphinan	0.3	0.3
Δ6-Butorphanol	0.7	0.5
Butorphanol tartrate	1.0	—
Unknown impurity	—	0.3
Total impurities	—	1.0

Assay—

Phosphate buffer (0.025 M)—Transfer 3.4 g of monobasic potassium phosphate into a 1000-mL volumetric flask. Dilute with water to volume, and filter. ~~Mix, and adjust with phosphoric acid to a pH of 3.0 ± 0.1.~~

Mobile phase—Prepare a filtered and degassed mixture of phosphate buffer, acetonitrile, and triethylamine (85 : 15 : 2). Mix thoroughly, and adjust with 85.0% phosphoric acid to a pH of 3.0 ± 0.1. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Butorphanol Tartrate RS in *Mobile phase* to obtain a solution having a known concentration of 0.2 mg per mL. Mix, and filter, discarding the first 2 mL of the filtrate. The *Standard preparation* is stable for at least 108 hours.

Assay preparation—Prepare a composite solution by pooling a minimum of four containers of Nasal Solution into a suitable glass vessel. Transfer the equivalent of 20 mg of butorphanol tartrate to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, mix, and filter, discarding the first 2 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector, a ~~4.6 × 250 mm~~ 4.6-mm × 15-cm column that contains 5-µm packing L11, and a ~~4.6 × 10 mm~~ 4.6-mm × 1-cm guard column that contains 5-µm packing L11. The column temperature is maintained at 30°. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the butorphanol tartrate peak is not more than 2.0; and the relative standard deviation for five replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the butorphanol tartrate peak. Calculate the quantity, in mg, of butorphanol tartrate ($C_{21}H_{29}NO_2 \cdot C_4H_6O_6$) in the portion of Nasal Solution taken by the formula:

$$100C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Butorphanol Tartrate RS in the *Standard preparation;* and r_U and r_S are the peak responses for butorphanol tartrate obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

In-Process Revision

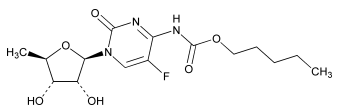
BRIEFING

Capecitabine; Capecitabine Tablets. Because there are no existing *USP* monographs for this drug substance and dosage form, new monographs, based on validation data received, are being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the Metachem Technologies Inertsil ODS-2 brand of L1 column. The typical retention time for capecitabine is about 22 minutes.

(MD-OOD: F. Mao) RTS—C43499

Add the following:

■Capecitabine



$C_{15}H_{22}FN_3O_6$ 359.35

Carbamic acid, [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinyl]-, pentyl ester.

Pentyl 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinecarbamate [*154361-50-9*].

» Capecitabine contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{22}FN_3O_6$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve in tight containers. Store at controlled room temperature.

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

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen: 2 mg of sample in 300 mg of potassium bromide.

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

Water, *Method Ic* ⟨921⟩**:** not more than 0.3%.

Specific rotation ⟨781S⟩**:** between +96.0° and +100.0°.

Test solution: 10 mg per mL, on the anhydrous and solvent-free basis, in methanol, at 20°.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** not more than 20 ppm.

Related compounds—

Diluent, Solution A, Solution B, Peak identification solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

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

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Capecitabine taken by the formula:

$$100(1/F)(C_S/C_U)(r_I/r_S)$$

in which F is the relative response factor for each impurity obtained from *Table 1;* C_S is the concentration, in mg per mL, of USP Capecitabine RS in the *Standard solution;* C_U is the concentration, in mg per mL, of capecitabine in the *Test solution;* r_I is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for capecitabine obtained from the *Standard solution.* The limits are given in *Table 1.*

Assay—

Diluent—Prepare a mixture of water, methanol, and acetonitrile (60 : 35 : 5).

In-Process Revision

Table 1

Compound	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
Capecitabine related compound A	0.18	1.05	≤0.3
Capecitabine related compound B	0.19	0.81	≤0.3
2′,3′-Di-*O*-acetyl-5′-deoxy-5-fluorocytidine	0.36	0.89	≤0.1
5′-Deoxy-5-fluoro-N4-(2-methyl-1-butyloxycarbonyl) cytidine + 5′-Deoxy-5-fluoro-N4-(3-methyl-1-butyloxycarbonyl)cytidine	0.95	1.01	≤0.5
Capecitabine	1.00	1.00	—
[1-[5-Deoxy-3-*O*-(5-deoxy-*β*-D-ribofuranosyl)-*β*-D-ribofuranosyl]-5-fluoro-2-oxo–1,2-dihydropyrimidin-4-yl]-carbamic acid pentyl-ester	1.06	1.00	≤0.3
[1-[5-Deoxy-2-*O*-(5-deoxy-*β*-D-ribofuranosyl)-*β*-D-ribofuranosyl]-5-fluoro-2-oxo–1,2-dihydropyrimidin-4-yl]-carbamic acid pentyl ester	1.09	1.00	≤0.2
Capecitabine related compound C	1.11	0.91	≤0.3
[1-[5-Deoxy-3-*O*-(5-deoxy-α-D-ribofuranosyl)-*β*-D-ribofuranosyl]-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]-carbamic acid pentyl ester	1.20	1.00	≤0.3
2′,3′-Di-*O*-acetyl-5′-deoxy-5-fluoro-N4-(pentyloxy-carbonyl)cytidine	1.37	0.85	≤0.1
Individual unspecified impurity	—	1.00	≤0.1
Total unspecified impurities	—	—	≤0.5
Total impurities	—	—	≤1.5

Diluted acetic acid—Prepare a 0.1% (v/v) mixture of acetic acid in water.

Solution A—Prepare a mixture of *Diluted acetic acid,* methanol, and acetonitrile (60 : 35 : 5).

Solution B—Prepare a mixture of methanol, *Diluted acetic acid,* and acetonitrile (80 : 15 : 5).

Standard preparation—Dissolve an accurately weighed quantity of USP Capecitabine RS in *Diluent*, and sonicate if necessary, to obtain a solution having a known concentration of about 0.6 mg per mL.

Peak identification solution—Dissolve suitable quantities of USP Capecitabine RS, USP Capecitabine Related Compound A RS, USP Capecitabine Related Compound B RS, and USP Capecitabine Related Compound C RS in

Diluent, and sonicate if necessary, to obtain a solution having known concentrations of about 0.06 mg each per mL. Quantitatively dilute this solution with *Diluent* to obtain a solution having known concentrations of about 0.6 µg of each per mL.

Assay preparation—Dissolve an accurately weighed quantity of Capecitabine in *Diluent,* and sonicate if necessary, to obtain a solution having a known concentration of about 0.6 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 250-nm detector, a refrigerated autosampler at 5°, and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	100	0	isocratic
5–20	100→49	0→51	linear gradient
20–30	49	51	isocratic
30–31	49→100	51→0	linear gradient
31–40	100	0	equilibration

Chromatograph the *Diluent,* followed by the *Peak identification solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between USP Capecitabine Related Compound A RS and USP Capecitabine Related Compound B RS is not less than 1.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor of the capecitabine peak is not greater than 1.5, and the relative standard deviation for replicate injections of the capecitabine peak is not more than 2.0%. [NOTE—For the purpose of peak identification, the approximate relative retention times are given in *Table 1*. The relative retention times are measured with respect to capecitabine.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the capecitabine peaks. Calculate the quantity, in percentage, of $C_{15}H_{22}FN_3O_6$ in the portion of Capecitabine taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Capecitabine RS in the *Standard preparation;* C_U is the concentration of capecitabine in the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP30*)

BRIEFING

Capecitabine Tablets—See briefing under *Capecitabine*.

(MD-OOD: F. Mao; BPC: M. Marques) RTS—C43862; C44035

Add the following:

■Capecitabine Tablets

» Capecitabine Tablets contain not less than 93.0 percent and not more than 105.0 percent of the labeled amount of capecitabine ($C_{15}H_{22}FN_3O_6$).

Packaging and storage—Preserve in tight containers. Store at controlled room temperature.

In-Process Revision

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

Identification—

A: *Infrared Absorption* ⟨197K⟩—Bands in the region of 1500–1760 cm^{-1} obtained for the test sample correspond to the bands obtained for USP Capecitabine RS.

Test specimen—Grind one Tablet to a fine powder with a mortar and pestle. Mix 1 mg of this sample with 300 mg of potassium bromide.

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

Dissolution ⟨711⟩—

Medium: water; 900 mL, degassed.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Standard solution—For Tablets labeled to contain 150 mg: Transfer 17 mg, accurately weighed, of USP Capecitabine RS to a 100-mL volumetric flask, dissolve in and dilute with *Medium* to volume, and mix. For Tablets labeled to contain 500 mg: Transfer 28 mg, accurately weighed, of USP Capecitabine RS to a 50-mL volumetric flask, dissolve in and dilute with *Medium* to volume, and mix.

Test solution—Pass a portion of the solution under test through a 0.45-µm fiberglass filter.

Procedure—Determine the amount of capecitabine ($C_{15}H_{22}FN_3O_6$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about 304 nm (for Tablets labeled to contain 150 mg) and at about 325 nm (for Tablets labeled to contain 500 mg) on portions of the *Test solution*, suitably diluted with *Medium*, if necessary, in comparison with the appropriate *Standard solution*, using a 1-mm quartz cell. Calculate the amount, in percentage, of $C_{15}H_{22}FN_3O_6$ dissolved by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of capecitabine ($C_{15}H_{22}FN_3O_6$) in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{22}FN_3O_6$ is dissolved in 30 minutes.

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

Related compounds—

Diluent, Solution A, Solution B, Peak identification solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

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

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(1/F)(C_S/C_U)(r_I/r_S)$$

in which F is the relative response factor for each impurity obtained from *Table 1;* C_S is the concentration, in mg per mL, of USP Capecitabine RS in the *Standard solution;* C_U is the concentration, in mg per mL, of capecitabine in the *Test solution;* r_I is the peak response for each impurity obtained from the *Test solution,* and r_S is the peak response for capecitabine obtained from the *Standard solution*. The limits are given in *Table 1.*

Table 1

Compound	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Capecitabine related compound A	0.18	1.05	≤ 1.0
Capecitabine related compound B	0.19	0.81	≤ 1.0
Capecitabine	1.00	1.00	—
Capecitabine related compound C	1.11	0.91	≤ 0.5
Individual unspecified impurity	—	1.00	≤ 0.1
Total unspecified impurities	—	—	≤ 0.5
Total impurities	—	—	≤ 2.0

Assay—

Diluent—Prepare a mixture of water, methanol, and acetonitrile (60 : 35 : 5).

Diluted acetic acid—Prepare a 0.1% (v/v) mixture of acetic acid in water.

Solution A—Prepare a mixture of *Diluted acetic acid,* methanol, and acetonitrile (60 : 35 : 5).

Solution B—Prepare a mixture of methanol, *Diluted acetic acid,* and acetonitrile (80 : 15 : 5).

Standard preparation—Dissolve an accurately weighed quantity of USP Capecitabine RS in *Diluent,* and sonicate if necessary, to obtain a solution having a known concentration of about 0.6 mg per mL.

Peak identification solution—Dissolve suitable quantities of USP Capecitabine RS, USP Capecitabine Related Compound A RS, USP Capecitabine Related Compound B RS, and USP Capecitabine Related Compound C RS in *Diluent,* and sonicate if necessary, to obtain a solution having known concentrations of about 0.06 mg of each per mL. Quantitatively dilute this solution with *Diluent* to obtain a solution having known concentrations of about 0.6 µg of each per mL.

Assay preparation—Grind not fewer than 20 Tablets to a fine powder. Dissolve an accurately weighed quantity of powdered Tablets, dilute quantitatively with *Diluent,* and sonicate if necessary, to obtain a solution having a known concentration of about 0.6 mg per mL. Pass through a PVDF 0.45-µm membrane filter, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 250-nm detector, a refrigerated autosampler maintained at 5°, and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–5	100	0	isocratic
5–20	100→49	0→51	linear gradient
20–30	49	51	isocratic
30–31	49→100	51→0	linear gradient
31–40	100	0	equilibration

Chromatograph the *Diluent* and the *Peak identification solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between capecitabine related compound A and capecitabine related compound B is not less than 1.0. Chromatograph the *Standard preparation;* and record the peak responses as directed for *Procedure:* the tailing factor of the capecitabine peak is not greater than 1.5; and the relative standard deviation for replicate injections of the capecitabine peak is not more than 2.0%. [NOTE—For the purpose of peak identification the approximate relative retention times are given in *Table 1.* The relative retention times are measured with respect to capecitabine.]

In-Process Revision

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the capecitabine peaks. Calculate the quantity, in percentage, of $C_{15}H_{22}FN_3O_6$ in the portion of Tablets taken by the formula:

$$100\ (C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Capecitabine RS in the *Standard preparation;* C_U is the concentration of capecitabine in the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

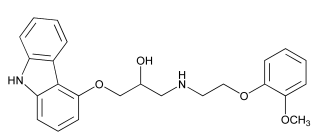
BRIEFING

Carvedilol. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the test for *Related compounds* and in the *Assay* is based on analyses performed with the YMC Pro brand of L7 column. The typical retention time for the carvedilol peak is about 5 minutes.

(MD-CV: S. Ramakrishna) RTS—C44223

Add the following:

■Carvedilol



$C_{24}H_{26}N_2O_4$ 406.47

2-Propanol, 1-(9*H*-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (±)-.

(±)-1-Carbazol-4-yloxy)-3-[[2-(*o*-methoxyphenoxy)ethyl]amino]-2-propanol [*72956-09-3*].

» Carvedilol contains not less than 99.0 percent and not more than 101.0 percent of $C_{24}H_{26}N_2O_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at 25°; excursions permitted between 15° and 30°.

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

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Loss on drying ⟨731⟩**—**Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

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

Residue on ignition ⟨281⟩**:** not more than 0.1%, using a 1-g specimen.

Related compounds—

Buffer and *Mobile phase*—Proceed as directed in the *Assay.*

System suitability solution—Dissolve accurately weighed quantities of USP Carvedilol RS and USP Carvedilol Related Compound C RS in *Mobile phase* to obtain a solution having known concentrations of about 0.05 mg per mL of each USP Reference Standard.

Standard solution—Dissolve accurately weighed quantities of each of USP Carvedilol RS, USP Carvedilol Related Compound A RS, USP Carvedilol Related Compound B RS, USP Carvedilol Related Compound C RS, USP Carvedilol

In-Process Revision

Related Compound D RS, and USP Carvedilol Related Compound E RS, in *Mobile phase,* to obtain a solution having known concentrations of about 0.001 mg per mL of each of USP Carvedilol RS and USP Carvedilol Related Compounds A, B, D, and E RS, and 0.2 µg per mL of USP Carvedilol Related Compound C RS.

Test solution—Prepare a solution of Carvedilol in *Mobile phase* having a concentration of about 1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a dual wavelength detector (use 220 nm for quantitating carvedilol related compound E and 240 nm for carvedilol and all other related compounds) and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute, and the run time is 60 minutes. The column temperature is maintained at 55°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between carvedilol and carvedilol related compound C is not less than 17.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of carvedilol related compounds A, B, C, D, and E in Carvedilol taken by the formula:

$$100(C_S / C_U)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of each of the known impurities in the *Standard solution;* C_U is the concentration, in mg per mL, of Carvedilol in the *Test solution;* r_i is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of each impurity obtained from the *Standard solution*. To calculate the percentage of other impurities in the formula, use the concentration of USP Carvedilol RS for C_S.

Name	Relative Retention Time	Limit (%)
Carvedilol related compound A[1]	0.52	0.1
Carvedilol related compound B[2]	8.5	0.1
Carvedilol	1.0	—
Carvedilol related compound C[3]	—	0.02
Carvedilol related compound D[4]	5.0	0.1
Carvedilol related compound E[5]	0.35	0.1
Any other individual impurity	—	0.1

[1] 1-[[9-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]-9*H*-carbazol-4-yl]oxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol.
[2] 1,1′-[[2-(2-methoxyphenoxy)ethyl]nitrilo]bis[3-(9*H*-carbazol-4-yloxy)propan-2-ol].
[3] (2*RS*)-1-[benzyl[2-(2-methoxyphenoxyethyl]amino]-3-(9*H*-cabazol-4-yloxy)propan-2-ol.
[4] 4-(2,3-Epoxypropoxy)carbazole.
[5] 2-(2-Methoxyphenoxy)ethylamine.

In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.5% of total impurities is found. [NOTE—Disregard any impurity less than 0.01% calculated using the *Standard solution.*]

Assay—

Buffer—Dissolve 2.72 g of monobasic potassium phosphate, accurately weighed, in 1000 mL of water, and adjust with dilute phosphoric acid to a pH of 2.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (69 : 31). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

In-Process Revision

System suitability solution—Dissolve accurately weighed quantities of USP Carvedilol RS and USP Carvedilol Related Compound A RS in *Mobile phase* to obtain a solution having known concentrations of about 0.05 mg per mL of each USP Reference Standard.

Standard preparation—Dissolve an accurately weighed quantity of USP Carvedilol RS in *Mobile phase* to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Transfer an accurately weighed quantity of about 20 mg of Carvedilol to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. In a standardized volumetric flask transfer 10 mL of this solution, and further dilute with *Mobile phase* to 50 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute, and the run time is about 60 minutes. The column temperature is maintained at 55°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between carvedilol and carvedilol related compound A is not less than 4.0; the tailing factor for carvedilol is not more than 1.5; and the relative standard deviation is not more than 2%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate on the dried basis the quantity, in mg, of $C_{24}H_{26}N_2O_4$ in the portion of Carvedilol taken by the formula:

$$500C_S(r_S/r_U)$$

in which C_S is the concentration, in mg per mL, of USP Carvedilol RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP30*)

BRIEFING

Ciprofloxacin Injection, *USP 29* page 518 and page 326 of *PF* 32(2) [Mar.–Apr. 2006]. On the basis of supporting data and comments received, the bacterial endotoxin limit is revised according to the FDA guideline indicating that if the pediatric dose per kg is higher than the adult dose, then it shall be the dose used in the formula to calculate the endotoxin limit.

(MD-AA: B. Davani; MSA: R. Tirumalai) RTS—C44476

Change to read:

Bacterial endotoxins ⟨85⟩—It contains not more than ~~0.88~~

■0.50■2S (*USP30*)
USP Endotoxin Unit per mg of ciprofloxacin.

Change to read:

Limit of ciprofloxacin ethylenediamine analog—
Mobile phase

■*Resolution solution, Assay preparation,* ■1S (*USP30*) and *Chromatographic system*—~~Proceed~~

■Prepare■1S (*USP30*) as directed in the *Assay.* ~~under *Ciprofloxacin.*~~

■■1S (*USP30*) ~~*Standard preparation, Resolution solution,* and *Assay preparation*—Proceed as directed in the *Assay* under *Ciprofloxacin.*~~

■■1S (*USP30*) *Procedure*—Proceed as directed for *Procedure* in the *Assay.* ~~under *Ciprofloxacin.*~~

■■1S (*USP30*) Calculate the percentage of ciprofloxacin ethylenediamine analog from the chromatogram obtained from the *Assay preparation* ~~in the *Assay* under *Ciprofloxacin*~~

■■1S (*USP30*) by the formula:

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

in which 0.7 is the correction factor for ciprofloxacin ethylenediamine analog; and r_A and r_C are the responses of the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak, respectively. It contains not more than 0.5% of ciprofloxacin ethylenediamine analog.

In-Process Revision

Change to read:

Assay—

~~*Mobile phase* and *Chromatographic system*—Proceed as directed in the *Assay* under *Ciprofloxacin*.~~

■*Mobile phase*—Prepare a filtered and degassed mixture of 0.025 M phosphoric acid, previously adjusted with triethylamine to a pH of 3.0 ± 0.1, and acetonitrile (87 : 13). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).■1S *(USP30)*

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Ciprofloxacin Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about ~~0.3 mg~~

■0.5 mg■1S *(USP30)* per mL.

Resolution solution—~~Dissolve a quantity of USP Ciprofloxacin Ethylenediamine Analog RS in *Standard preparation* to obtain a solution having a concentration of about 0.25 mg per mL.~~

■Prepare a 0.025 mg per mL solution of USP Ciprofloxacin Ethylenediamine Analog RS in *Mobile phase.* Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with *Standard preparation* to volume, and mix.■1S *(USP30)*

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 25 mg of ciprofloxacin, to a ~~100-mL~~

■50-mL■1S *(USP30)* volumetric flask, dilute with *Mobile phase* to volume, and mix.

■*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 25-cm column that contains packing L1 and is maintained at a temperature of 30 ± 1°. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak is not less than 6. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency, determined from the ciprofloxacin peak, is not less than 2500 theoretical plates; the tailing factor for the ciprofloxacin peak is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.5%. [NOTE—For the purpose of identification, the relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin.]■1S *(USP30)*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of ciprofloxacin in each mL of the Injection taken by the formula:

~~(331.34/367.81)(100*C*/*V*)(r_U/r_S)~~

■(331.34/367.81)(50*C*/*V*)(r_U/r_S)■1S *(USP30)*

in which 331.34 and 367.81 are the molecular weights of ciprofloxacin and anhydrous ciprofloxacin hydrochloride, respectively; *C* is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Standard preparation,* calculated on the anhydrous basis; *V* is the volume, in mL, of Injection taken to prepare the *Assay preparation;* and r_U and r_S are the ciprofloxacin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Citalopram Hydrobromide, page 3562 of the *First Supplement* and page 742 of *PF* 31(3) [May–June 2005]. On the basis of comments received, the following changes are proposed.

1. The total impurity limit in the test for *Related compounds* is raised from 0.2% to 0.5%.
2. A specific requirement in the *Labeling* section is added to reflect the flexibility in the monograph.
3. Five new Reference Standards have been added, to be used in *Test 2.* Of these, USP Citalopram Related Compound G RS is the chloro analog, and USP Citalopram Related Compound H RS is the bromo analog.
4. A note for clarification has been added at the beginning of the test for *Related compounds.*
5. In the tests for *Related compounds, Test 2* for impurities has been added. The test has been validated with the Waters Symmetry brand C18 column. Under the chromatographic conditions, the typical retention time of citalopram is about 13 minutes; that of the chloro analog is 29 minutes; and that of the bromo analog is 30 minutes.

(MD-PP: R. Ravichandran) RTS—C43102

Add the following:

■**Labeling—**If a test for *Related compounds* other than *Test 1* is used, then the labeling states with which *Related compounds* test the article complies.■2S *(USP30)*

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Change to read:

USP Reference standards ⟨11⟩— ~~*USP Citalopram Hydrobromide RS. USP Citalopram Hydrobromide Related Compound D RS.*~~

■*USP Citalopram Hydrobromide RS. USP Citalopram Related Compound A RS. USP Citalopram Related Compound C RS. USP Citalopram Related Compound D RS. USP Citalopram Related Compound G RS. USP Citalopram Related Compound H RS.*■2S (*USP30*)

Add the following:

■**Related compounds—**

NOTE—On the basis of the synthetic route used, perform either *Test 1* or *Test 2*. However, if the chloro and bromo analogs are potential related compounds in the synthetic route used, *Test 2* is recommended.

TEST 1—

Buffer, Mobile phase, Diluent, and *Chromatographic system*—Proceed as directed in the *Assay.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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

Working standard solution—Dilute the *Standard solution* with *Mobile phase,* quantitatively and stepwise if necessary, to obtain a solution having a concentration of 0.625 µg per mL of citalopram hydrobromide.

System suitability solution—Dissolve an accurately weighed quantity of USP Citalopram Hydrobromide RS and USP Citalopram Related Compound D RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.001 mg per mL.

Sensitivity solution—Dilute 5.0 mL of the *Working standard solution* with *Diluent* to 50 mL to obtain a solution having 0.0625 µg of citalopram hydrobromide per mL.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—Inject the *Diluent* as directed for *Procedure* to verify that there are no interfering peaks. Chromatograph the *Sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is at least 3. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between citalopram related compound D and citalopram is not less than 1.8; the tailing factor for the citalopram hydrobromide peak is not less than 0.8 and not more than 1.5; and the relative standard deviation for replicate injections, based on the citalopram peak, is not more than 5%.

NOTE—For the purpose of identification, the approximate relative retention times are 0.90 for citalopram related compound D and 1.0 for citalopram hydrobromide.

Procedure—Separately inject equal volumes (about 20 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms for about 40 minutes, and measure the responses for the major peaks. Calculate the percentage of related compounds in the portion of Citalopram Hydrobromide taken by the formula:

$$100(C_S / C_T)(r_i / r_S)(324.39/405.30)(1/F)$$

in which C_S and C_T are the concentrations, in mg per mL, of Citalopram Hydrobromide in the *Working standard solution* and the *Test solution,* respectively; r_i is the peak response for each impurity obtained from the *Test solution;* r_S is the peak response for the citalopram peak, obtained from the *Working standard solution;* 324.39 and 405.30 are the molecular weights for citalopram and citalopram hydrobromide, respectively; and F is the relative response factor for each impurity relative to citalopram (free base), as presented in *Table 1.*

TEST 2—

Buffer—Dissolve about 2.7 g of monobasic potassium phosphate in 1000 mL of water, add 1 mL of *N,N*-dimethyloctylamine, stir, and adjust with phosphoric acid to a pH of 3.0.

Diluent—Prepare a mixture of *Buffer* and acetonitrile (70 : 30).

Solution A—Prepare a mixture of *Buffer,* methanol, and tetrahydrofuran (70 : 24 : 6).

Table 1

Related Compound	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
1-(3-Dimethylaminopropyl)-1-(4′-fluorophenyl)-5-(4-dimethyl-aminobutyryl)-1,3-dihydrobenzofuran	0.13	0.34	NMT* 0.1
Citalopram related compound A	0.18	0.77	NMT 0.1
4-[4-Dimethylamino-1-(4′-fluorophenyl)-1-hydroxy-1-butyl]-3-hydroxymethyl benzonitrile	0.26	0.99	NMT 0.1
Citalopram related compound B	0.40	0.98	NMT 0.1
Citalopram related compound C	0.67	0.69	NMT 0.1
Citalopram related compound D	0.90	1.04	NMT 0.1
Citalopram hydrobromide	1.0	1.0	—
Citalopram related compound E	1.29	0.91	NMT 0.1
~~Unkown~~ Individual unknown impurity	—	1.0	NMT 0.1 each
~~Total known and unknown~~ Total impurities	—	—	~~NMT 0.2%~~ NMT 0.5%

* NMT = not more than.

Solution B—Prepare a mixture of acetonitrile and *Buffer* (80 : 20).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed in *Table 2* for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities of USP Citalopram Hydrobromide RS, USP Citalopram Related Compound A RS, USP Citalopram Related Compound C RS, USP Citalopram Related Compound D RS, USP Citalopram Related Compound G RS, and USP Citalopram Related Compound H RS in *Diluent* to obtain a final solution having a concentration of 1.5 µg per mL of each compound.

Test solution—Dissolve an accurately weighed quantity of Citalopram Hydrobromide in a suitable volume of *Diluent* to obtain a solution having a final concentration of 1.5 mg per mL of citalopram hydrobromide.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 224-nm detector and a 4.6-mm × 25-cm column that contains 3-µm packing L1. The flow rate is about 0.8 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as shown in *Table 2.*

Table 2

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–18	100	0	isocratic
18–40	100→10	0→90	linear gradient
40–45	10	90	isocratic
45–46	10→100	90→10	linear gradient
46–55	100	0	re-equilibration

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between citalopram and citalopram related compound D is not less than 2.0, and that between citalopram related

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compound G and citalopram related compound H is not less than 4.0; and the relative standard deviation for the citalopram peak in replicate injections is not more than 2.0%.

NOTE—For the purpose of identification, the approximate relative retention times of citalopram related compounds are provided in *Table 3*.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each citalopram related compound in the portion of Citalopram Hydrobromide taken by the formula:

$$100(C_S / C_T)(r_i / r_S)(324.39/405.30)$$

in which C_S is the concentration, in mg per mL, of each citalopram related compound in the *Standard solution;* C_T is the concentration of citalopram hydrobromide in the *Test solution;* r_i is the peak area of each impurity obtained from the *Test solution;* r_S is the peak area of each corresponding impurity obtained from the *Standard solution;* and 324.39 and 405.30 are the molecular weights of citalopram free base and citalopram hydrobromide, respectively.

Table 3

Related Compound	Relative Retention Time	Limit (%)
Citalopram related compound A	0.40	NMT* 0.10
Citalopram related compound C	0.88	NMT 0.10
Citalopram	1.0	—
Citalopram related compound D	1.09	NMT 0.10
Citalopram related compound G	2.20	NMT 0.10
Citalopram related compound H	2.30	NMT 0.10
Individual unspecified impurity	—	NMT 0.10
Total specified and unspecified impurities	—	NMT 0.50

*NMT = not more than.

■2S (*USP30*)

BRIEFING

Dantrolene Sodium Capsules. Because there is no existing *USP* monograph for this dosage form, a new monograph, based on validation data received, is being proposed. The proposed liquid chromatographic procedures in the test for *Related compounds* and the *Assay* are based on analyses performed with the Waters Symmetry C18 brand of L1 packing. The typical retention time for dantrolene related compound B is about 2.3 minutes, and that for dantrolene is about 3.3 minutes.

(MD-PP: R. Ravichandran; BPC: M. Marques) RTS—C42655

Add the following:

■Dantrolene Sodium Capsules

» Dantrolene Sodium Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of dantrolene sodium ($C_{14}H_9N_4NaO_5 \cdot 3½H_2O$).

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

USP Reference standards ⟨11⟩—*USP Dantrolene RS. USP Dantrolene Related Compound B RS. USP Dantrolene Sodium RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Dissolution ⟨711⟩—

Medium: 0.5% methylbenzethonium chloride in water, pH 6.8; 900 mL, deaerated.

Apparatus 1: 100 rpm.

Time: 40 minutes.

Determine the amount of $C_{14}H_9N_4NaO_5 \cdot 3½H_2O$ dissolved by employing the following method.

Standard solution 1 (for capsules labeled to contain 100 mg)—Accurately weigh 25 mg of USP Dantrolene RS into a 250-mL volumetric flask. Dissolve in 5.0 mL of dimethylformamide. Add 200 mL of *Medium* and 10.0 mL of 0.1 N potassium hydroxide. Mix, dilute with *Medium* to volume, and mix. Pass through a 0.45-µm polytetrafluoroethylene (PTFE) filter, previously wetted with a few drops of isopropyl alcohol, discarding the first 5 mL.

Standard solution 2 (for capsules labeled to contain 50 mg)—Transfer 25.0 mL of *Standard solution 1* to a 50-mL volumetric flask containing 0.5 mL of 0.1 N potassium hydroxide. Dilute with *Medium* to volume, and mix. Pass through a 0.45-µm PTFE filter, previously wetted with a few drops of isopropyl alcohol, discarding the first 5 mL.

Standard solution 3 (for capsules labeled to contain 25 mg)—Transfer 25.0 mL of *Standard solution 1* to a 100-mL volumetric flask containing 1.0 mL of 0.1 N potassium hydroxide. Dilute with *Medium* to volume, and mix. Pass through a 0.45-µm PTFE filter, previously wetted with a few drops of isopropyl alcohol, discarding the first 5 mL.

Test solution—Withdraw 10 mL of the solution under test. Pass through a 0.45-µm PTFE filter, previously wetted with a few drops of isopropyl alcohol. Discard the first 5 mL. Collect the filtered solution in a tube that contains 1 drop of 1 N potassium hydroxide, and mix.

System suitability—[NOTE—All absorbance values should be obtained on solutions within 2 hours of their preparation.] Using a 0.1-cm cell, measure the absorbance of *Medium,* using water as the blank, and measure the absorbance of each of the three *Standard solutions* using *Medium* as the blank, at the wavelength of maximum absorbance at about 395 nm. The system is considered suitable for use if the following criteria are met: the absorbance of *Medium* is less than 10% of the absorbance of *Standard solution 1;* the absorbance of *Standard solution 2* is between 0.3 and 0.5; and the ratio of the absorbance of *Standard solution 1* to that of *Standard solution 3* is 4.00 ± 0.10.

Determine the amount of $C_{14}H_9N_4NaO_5 \cdot 3½H_2O$ dissolved by measuring the absorbance of the *Test solution* at the wavelength of maximum absorbance at about 395 nm in comparison with the appropriate *Standard solution,* using an 0.1-cm cell and *Medium* as the blank. All absorbance values are obtained on solutions within 2 hours of their preparation. Calculate the percentage of $C_{14}H_9N_4NaO_5 \cdot 3½H_2O$ dissolved by the formula:

$$\frac{A_U \times C_S \times 900 \times 100}{A_S \times 0.79186 \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution*, respectively; C_S is the concentration, in mg per mL, of dantrolene in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; 0.79186 is the correction for water of hydration and sodium contained in the dantrolene sodium monohydrate form of the drug, assuming that the bulk drug contains 15% of water and 6.84% of sodium; and *LC* is the capsule label claim, in mg.

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Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{14}H_9N_4NaO_5 \cdot 3½H_2O$ is dissolved in 40 minutes.

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

Related compounds—

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

Standard solution—Transfer 5 mg, accurately weighed, of USP Dantrolene Related Compound B RS into a 50-mL volumetric flask, and dissolve in 2.5 mL of dimethylformamide. Add 2.5 mL of glacial acetic acid, and dilute with acetone to volume. The final concentration is about 0.1 mg per mL. Quantitatively dilute this solution with *Diluent* to obtain a solution having a known concentration of about 0.0005 mg per mL of dantrolene related compound B.

Test solution—Use the *Assay preparation.*

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of dantrolene related compound B in the portion of Capsules taken by the formula:

$$100(r_U / r_S)(C_S / C_T)$$

in which r_U is the individual peak response for dantrolene related compound B obtained from the *Test solution;* r_S is the response of the corresponding peak in the *Standard solution;* C_S is the concentration, in mg per mL, of dantrolene related compound B in the *Standard solution;* and C_T is the concentration, in mg per mL, of dantrolene sodium in the *Test solution:* not more than 2% of dantrolene related compound B is found.

Assay—

Diluent—Prepare a solution of acetonitrile and water (70 : 30).

Buffer solution—Dissolve 3.3 g of ammonium acetate in 1 L of water.

Solution A—Prepare a filtered and degassed mixture of *Buffer solution,* acetonitrile, and glacial acetic acid (120 : 76 : 7).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and water (70 : 30).

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

System suitability solution—Use the *Standard solution,* prepared as directed in the test for *Related compounds.*

Standard preparation—Transfer 40 mg, accurately weighed, of USP Dantrolene RS to a 50-mL volumetric flask, and dissolve in 2.5 mL of dimethylformamide. Add 2.5 mL of glacial acetic acid, and dilute with acetone to volume. The final concentration is about 0.8 mg per mL. Quantitatively dilute this solution with *Diluent* to obtain a solution having a known concentration of about 0.08 mg per mL of dantrolene.

Assay preparation—Mix the combined contents of not fewer than 20 Capsules, and transfer an accurately weighed portion, equivalent to the average weight of one Capsule, to a 50-mL volumetric flask. Add 10 mL of dimethylformamide, and sonicate for 15 minutes to dissolve. Add 5 mL of glacial acetic acid, and dilute with acetone to volume. Quantitatively dilute this solution with *Diluent* to obtain a solution having 0.1 mg per mL of dantrolene sodium, and pass through a 0.45-µm nylon filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 365-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–8	100	0	isocratic
8–8.1	100→0	0→100	linear gradient
8.1–13	0	100	isocratic

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
13–13.1	0→100	100→0	linear gradient
13.1–20	100	0	re-equilibration

Separately inject the *System suitability solution* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections for dantrolene is not more than 1.0%. [NOTE—For the purpose of peak identification, the approximate relative retention times are 0.68 for dantrolene related compound B and 1.0 for dantrolene.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the dantrolene peaks. Calculate the percentage of dantrolene sodium ($C_{14}H_9N_4NaO_5 \cdot 3½H_2O$) in the portion of Capsules taken by the formula:

$$100(399.29/314.25)(r_U / r_S)(C_S / C_U)$$

in which 399.29 is the molecular weight of dantrolene sodium; 314.25 is the molecular weight of dantrolene; r_U and r_S are the peak responses for dantrolene obtained from the *Assay preparation* and the *Standard preparation,* respectively; C_S is the concentration, in mg per mL, of dantrolene in the *Standard preparation;* and C_U is the concentration, in mg per mL, of dantrolene sodium ($C_{14}H_9N_4NaO_5 \cdot 3½H_2O$) in the *Assay preparation.* ■2S (*USP30*)

BRIEFING

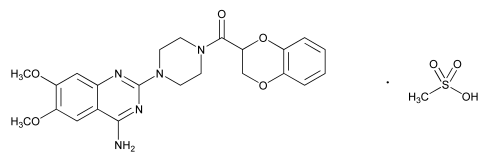
Doxazosin Mesylate, page 1470 of *PF* 29(5) [Sept.–Oct. 2003]. On the basis of comments received, it is proposed to revise the following test methods:

- *Loss on drying:* The limit in the test for *Loss on drying* is changed from 1% to 2%, which is in agreement with the FDA requirements.
- The test for *Chromatographic purity* is changed to a test for *Related compounds.*
- *Related compounds* and *Assay:* The revisions in the test for *Related compounds* and in the *Assay* are intended to provide a very sensitive detection of all impurities. The proposed changes are based on validated procedures and in agreement with the FDA requirements. The test for *Related compounds* and the *Assay* employ a reverse-phase HPLC method, using a LiChrospher 60 RP Select B 5-µm column. The typical retention time for doxazosin mesylate is about 24 minutes.

(MD-CV: S. Ramakrishna) RTS—C41770

Add the following:

■Doxazosin Mesylate



$C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ ~~547.59~~ 547.58

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine monomethanesulfonate [*77883-43-3*].

» Doxazosin Mesylate contains not less than 98.0 percent and not more than 102.0 percent of $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$, calculated on the ~~anhydrous~~ dried basis.

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Packaging and storage—Preserve in well-closed containers, and store below 30°.

USP Reference standards ⟨11⟩—*USP Doxazosin Mesylate RS. USP Doxazosin Related Compound A RS. USP Doxazosin Related Compound B RS. USP Doxazosin Related Compound C RS. USP Doxazosin Related Compound D RS. USP Doxazosin Related Compound E RS. USP Doxazosin Related Compound F RS. USP Terazosin Related Compound A RS. USP Terazosin Related Compound C RS.*

Identification—

A: *Infrared Absorption* ⟨~~197M~~⟩⟨197K⟩.

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

Loss on drying ⟨731⟩—Dry it in vacuum at 105° for 4 hours: it loses not more than ~~.0%~~ 2.0% of its weight.

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

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 20 µg per g.

~~**Chromatographic purity [To come.]**~~ **Related compounds—**

~~*Solution A*—Dissolve 17.3 g of sodium 1-octanesulfonate and 5.4 mL of phosphoric acid in 4 liters of water. Adjust with 1 M sodium hydroxide to a pH of 2.5, and mix.~~

~~*Solution B*—Use acetonitrile.~~

Solvent A, Solvent D, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Solvent B—Use acetonitrile.

Solvent C—Use water.

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

~~*Diluent*—Dissolve 2.7 mL of phosphoric acid in 2 liters of water. Adjust with 1 M sodium hydroxide to a pH of 2.5, and mix.~~

~~*Blank solution*—Prepare a solution of dimethyl sulfoxide and *Diluent* (1 in 100).~~

~~*System suitability solution*—Prepare a solution containing about 1.5 µg of USP Terazosin Related Compound A RS per mL, 0.5 µg of USP Terazosin Related Compound C RS per mL, and 0.5 µg of USP Doxazosin Mesylate RS per mL in *Blank solution.*~~

Standard ~~*stock*~~ *solution*—~~To an accurately weighed quantity of USP Doxazosin Mesylate RS, add a volume of dimethyl sulfoxide, equivalent to about 1% of the flask volume, sonicate for one minute, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL. Sonicate, if necessary, until dissolved.~~ Dissolve accurately weighed quantities of USP Doxazosin Mesylate RS, USP Doxazosin Related Compound A RS, USP Doxazosin Related Compound B RS, USP Doxazosin Related Compound C RS, USP Doxazosin Related Compound D RS, USP Doxazosin Related Compound E RS, USP Doxazosin Related Compound F RS, USP Terazosin Related Compound A RS, and USP Terazosin Related Compound C RS in approximately 2 mL of *Solvent D;* and dilute quantitatively, and stepwise if necessary, with *Solvent C* and *Solvent D* to obtain a solution having a known concentration of 0.0015 mg per mL of each of the Reference Standards. The final ratio of *Solvent C* and *Solvent D* is maintained at 9 : 1. Sonicate briefly to dissolve completely.

~~*Standard solution*—Quantitatively, and stepwise if necessary, dilute a volume of *Standard stock solution* with *Blank solution* to obtain a solution containing 0.5 µg of doxazosin mesylate per mL.~~

Test solution—~~Transfer about 50 mg of Doxazosin Mesylate, accurately weighed, to a 100-mL volumetric flask, add 1 mL of dimethyl sulfoxide, and sonicate for 1 minute. Dilute with *Diluent* to volume and sonicate, if~~

~~necessary, until dissolved.~~ Dissolve an accurately weighed quantity of Doxazosin Mesylate in approximately 2 mL of *Solvent D,* and dilute with *Solvent C* and *Solvent D* to obtain a solution having a known concentration of 0.6 mg per mL. The final ratio of *Solvent C* and *Solvent D* is maintained at 9 : 1. Sonicate briefly to dissolve completely.

~~*Chromatographic system* (see *Chromatography* ⟨621⟩) The liquid chromatographic system is equipped with a 245-nm detector and a 4.0- × 80-mm column that contains packing L7. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.~~

~~Time (min.)~~	~~*Solution A* (%)~~	~~*Solution B* (%)~~	~~Elution~~
~~0–20~~	~~75→45~~	~~25→55~~	~~linear gradient~~
~~20–35~~	~~45~~	~~55~~	~~isocratic~~
~~35–36~~	~~45→75~~	~~55→25~~	~~linear gradient~~
~~36–47~~	~~75~~	~~25~~	~~isocratic~~

~~Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution between terazosin related compound C and doxazosin is not less than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections for the main peak is not more than 5.0%. 2.0%.~~

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the percentage of each impurity in the portion of Doxazosin Mesylate taken by the formula:

~~$0.1F(C_S/C_T)(r_i/r_S)$,~~

~~$(100F(C_S/C_T)(r_i/r_S)$~~

$$100(C_S/C_T)(r_i/r_S)$$

in which ~~the response factor, *F,* is 0.6 for terazosin related compound A and 0.55 for terazosin related compound C;~~ C_S is the concentration, in mg per mL, of ~~USP Doxazosin Mesylate~~ each Reference Standard in the *Standard solution;* C_T is the concentration, in mg per mL, of doxazosin mesylate in the *Test solution;* r_i is the peak response for each individual impurity~~, excluding solvent peaks,~~ obtained from the *Test solution;* and r_S is the peak response for each individual impurity obtained from the *Standard solution:* not more than 0.3% of terazosin related compound A is found; not more than ~~0.1%~~ 0.25% of any other identified individual impurity is found; not more than 0.10% of any other unidentified impurity is found; and not more than 1.0% of total impurities is found. Calculate the percentages of doxazosin related compound G and doxazosin related compound H in the portion of Doxazosin Mesylate taken by the formula:

$$(100/F)(C_S/C_T)(r_i/r_S)$$

in which the response factor, *F,* is 0.735 for doxazosin related compound G and 0.769 for doxazosin related compound H; C_S is the concentration, in mg per mL, of USP Doxazosin RS in the *Standard solution;* C_T is the concentration, in mg per mL, of doxazosin mesylate in the *Test solution;* r_i is the peak response of doxazosin related compound G or doxazosin

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related compound H in the *Test solution;* and r_S is the peak response of USP Doxazosin Mesylate RS in the *Standard solution.*

Assay—

~~*Buffer solution*—Prepare a 0.05 M solution of monobasic potassium phosphate by disolving 0.68 g of monobasic potassium phosphate in 100 mL of water. Adjust with phosphoric acid to a pH of 3.0 ± 0.1.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of *Buffer solution*, methanol, and acetonitrile (6 : 4 : 1.5). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Doxazosin Mesylate RS in methanol to obtain a solution having a known concentration of about 0.30 mg per mL. Quantitatively dilute a volume of this solution with *Mobile phase* to obtain a solution having a known concentration of about 15.0 µg of USP Doxazosin Mesylate RS per mL.~~

~~*Assay preparation*—Transfer about 75 mg of Doxazosin Mesylate, accurately weighed, to a 250 mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Quantitatively dilute a known volume of this solution with *Mobile phase* to obtain a solution having a concentration of about 15.0 µg per mL.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 246-nm detector and a 3.9 mm × 15.0 cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k′, is not less than 4.5; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{32}H_{35}N_5O_8 \cdot CH_4SO_4$ in the portion of Doxazosin Mesylate taken by the formula:~~

~~$$5C(r_U/r_S),$$~~

~~in which C is the concentration, in µg per mL, of USP Doxazosin Mesylate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

~~*Buffer solution*—Transfer 3.4 g of monobasic potassium phosphate into a 1 liter flask, and add 800 mL of water and 4.0 mL of triethylamine to dissolve. Adjust with phosphoric acid to a pH of 4.5, and dilute with water to volume.~~

Solvent A—Dissolve 5 g of phosphoric acid (84%–86%) in 100 mL of water.

Solvent B—Use acetonitrile.

Solvent C—Use water.

Solvent D—Prepare a mixture of 100 mL of *Solvent B* and 2 g of phosphoric acid (84%–86%).

Mobile phase—~~Prepare a filtered and degassed mixture of methanol and *Buffer solution* (11 : 9).~~ Use variable mixtures of degassed *Solvent A, Solvent B,* and *Solvent C,* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Doxazosin Related Compound A RS and USP Doxazosin Related Compound B RS in approximately 2.5 mL of *Solvent D.* Further dilute this solution quantitatively, and stepwise if necessary, with *Solvent C* and *Solvent D* to obtain a final solution having a known concentration of 12 µg per mL of each of the related compounds. The final ratio of *Solvent C* and *Solvent D* is maintained at 9 : 1. Sonicate briefly to dissolve completely.

~~*Diluent:*—Dissolve 2.7 mL of phosphoric acid in 2 liters of water. Adjust with 1 M sodium hydroxide to a pH of 2.5, and mix. a mixture of methanol and 0.1 N hydrochloric acid (9 : 1).~~

Standard preparation—Dissolve an accurately weighed quantity of USP Doxazosin Mesylate RS ~~in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a final concentration of about 49 µg per mL.~~ in approximately 2 mL of *Solvent D,* and dilute with *Solvent C* and *Solvent D* to obtain a solution having a known concentration of 0.6 mg per mL. The final ratio of *Solvent C* and *Solvent D* is maintained at 9 : 1. Sonicate briefly to dissolve completely.

Assay preparation— ~~Transfer about 98 mg of Doxazosin Mesylate to a 200-mL volumetric flask, dissolve in and dilute with *Diluent* to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.~~ Dissolve an accurately weighed quantity of Doxazosin Mesylate in approximately 2 mL of *Solvent D,* and dilute with *Solvent C* and *Solvent D* to obtain a solution having a concentration of 0.6 mg per mL, based on the labeled quantity of doxazosin mesylate. The final ratio of *Solvent C* and *Solvent D* is maintained at 9 : 1. Sonicate briefly to dissolve completely.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~245~~ 210-nm detector and a 4-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about ~~1~~ 0.8 mL per minute, and the column temperature is maintained at ~~40°~~ 35°. The chromatograph is programmed as follows.

Time (min)	*Solvent A* (%)	*Solvent B* (%)	*Solvent C* (%)	Elution
0–10	20	10→22	70→58	linear gradient
10–35	20	22→50	58→30	linear gradient
35–40	20	50	30	equilibration

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the capacity factor, *k'*, for doxazosin is not less than 2.0; the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.~~ the resolution, *R,* between doxazosin related compound A and doxazosin related compound B is not less than 4.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the doxazosin mesylate peaks. Calculate the ~~quantity, in mg,~~ percentage of $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ in the portion of Doxazosin Mesylate taken by the formula:

$$~~2C(r_U/r_S)~~$$

~~in which *C* is the concentration, in µg per mL, of USP Doxazosin Mesylate RS in the *Standard preparation;* and R_U and r_S are the peak responses obtained from the *Assay preparation* and *Standard preparation,* respectively.~~

$$100C_S/C_T(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Doxazosin Mesylate RS in the *Standard preparation;* C_T is the concentration, in mg per mL, of USP Doxazosin Mesylate in the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S *(USP30)*

BRIEFING

Edetate Disodium, *USP 29* page 779; **Edetate Disodium Injection,** *USP 29* page 780. To address frequent inquiries, it is proposed to clarify the calculations in the *Assay.*

(MD-GRE: E. Gonikberg) RTS—C45005

Change to read:

Assay—

Assay preparation—Dissolve about 5 g of Edetate Disodium, accurately weighed, in about 100 mL of water contained in a 250-mL volumetric flask, add water to volume, and mix.

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Procedure—Place about 200 mg of chelometric standard calcium carbonate, previously dried at 110° for 2 hours, cooled in a desiccator, and accurately weighed, in a 400-mL beaker, add 10 mL of water, and swirl to form a slurry. Cover the beaker with a watch glass, and without removing the latter, add 2 mL of 3 N hydrochloric acid from a pipet. Swirl the contents of the beaker, and dissolve the calcium carbonate. Wash down the sides of the beaker, the outer surface of the pipet, and the watch glass with water, and dilute with water to about 100 mL. While stirring the solution, preferably with a magnetic stirrer, add about 30 mL of the *Assay preparation* from a 50-mL buret. Add 15 mL of 1 N sodium hydroxide and 0.30 g of hydroxy naphthol blue, and continue the titration with the *Assay preparation* to a blue endpoint. Calculate the weight, in mg, of $C_{10}H_{14}N_2Na_2O_8$ in the portion of Edetate Disodium taken by the formula:

~~$839.8(W/V)$,~~

■$(336.21/100.09)W(V_T/V)$■2S (*USP30*)

in which

■336.21 and 100.09 are the molecular weights of edetate disodium and calcium carbonate, respectively;■2S (*USP30*)
W is the weight, in mg, of calcium carbonate;

■V_T is the volume, in mL, of the *Assay preparation;*■2S (*USP30*)
and V is the volume, in mL, of the *Assay preparation* consumed in the titration.

BRIEFING

Edetate Disodium Injection, *USP 29* page 780—See briefing under *Edetate Disodium.*

(MD-GRE: E. Gonikberg) RTS—C45005

Change to read:

Assay—

Assay preparation—Dilute an accurately measured volume of Injection, equivalent to about 2 g of edetate disodium, with water to volume in a 100-mL volumetric flask, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Edetate Disodium*. ~~but use the formula:~~

~~$335.9(W/V)$,~~

~~in calculating the weight of $C_{10}H_{14}N_2Na_2O_8$.~~

■Calculate the weight, in mg, of $C_{10}H_{14}N_2Na_2O_8$ in the volume of Injection taken by the formula:

$(336.21/100.09)W(V_T/V)$

in which 336.21 and 100.09 are the molecular weights of edetate disodium and calcium carbonate, respectively; W is the weight, in mg, of calcium carbonate; V_T is the volume, in mL, of the *Assay preparation*; and V is the volume, in mL, of the *Assay preparation* consumed in the titration.■2S (*USP30*)

BRIEFING

Estradiol Vaginal Tablets, page 1617 of *PF* 31(6) [Nov.–Dec. 2005]. It is proposed to make the following revisions: (1) change the official title of this monograph to Estradiol Vaginal Inserts. The term "Inserts" was adopted by the Expert Committee on Nomenclature for vaginal preparations that are produced in the form of tablets or soft gel capsules. References to "Tablets" have been changed to "Inserts" throughout the monograph; (2) revise the *Thin-Layer Chromatographic Identification Test* to indicate that a high-performance thin-layer chromatographic plate is used; (3) revise the test for *Microbial limits* to provide limits that are consistent with the proposed harmonized General Chapter *Microbial Quality of Nonsterile Pharmaceutical Products* ⟨1111⟩; (4) and in the *Assay* change the concentration of the *Standard preparation* to match that of the *Assay preparation* and correct the formula.

(MD-PS: D. Bempong; MSA: R. Tirumalai) RTS—C44840; C44967

Add the following:

■Estradiol Vaginal ~~Tablets~~ Inserts

» Estradiol Vaginal ~~Tablets~~ Inserts contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of estradiol ($C_{18}H_{24}O_2$).

Packaging and storage—Each ~~Tablet~~ Insert is contained in a single-unit HG-polyethylene/polyethylene applicator. Each applicator with the inset ~~tablet~~ is packed separately in a laminated blister consisting of aluminum and polyvinylchloride foil. Preserve in a tight container, and store at controlled room temperature.

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USP Reference standards ⟨11⟩—*USP Estradiol RS. USP Estradiol Related Compound A RS. USP Estradiol Related Compound B RS. USP Estrone RS.*

Identification—

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

Adsorbent—Use a suitable high-performance thin-layer chromatographic plate.

Test solution—Place 30 ~~Tablets~~ Inserts into a vessel, add 500 mL of water, and allow to disintegrate by shaking overnight. Add 50.0 mL of ether, and shake for 2 minutes. Pass the ether layer through cotton wool and anhydrous sodium phosphate, shake with three 50-mL aliquots of ether, and evaporate to dryness. Dissolve the residue in 5 mL of ether, and quantitatively transfer to a fresh vessel. Evaporate to dryness, and reconstitute with 150 µL of absolute alcohol.

Standard solution—Dissolve suitable quantities of USP Estradiol RS, USP Estradiol Related Compound A RS, and USP Estrone RS, accurately weighed, in absolute alcohol to obtain a solution having known concentrations of 5 mg per mL, 0.25 mg per mL, and 0.25 mg per mL, respectively.

Application volume: 5 µL.

Developing solvent system: a mixture of chloroform and acetone (9 : 1).

Procedure—Proceed as directed in the chapter using the *Developing solvent system* described above. Develop the chromatogram three times over a path of about 8 cm, allowing the chromatogram to dry for 1 minute between each run. After the third run, allow the plate to air-dry. After removal of the plate, marking of the solvent front, and allowing solvent evaporation as described in the chapter, heat at 100° for about 15 minutes. Allow the plate to cool, and then immerse it in a mixture of absolute alcohol and concentrated sulfuric acid (95 : 5). Remove it immediately, place the plate on absorbing paper, and allow it to air-dry. Heat the plate at 100° until it is developed. Examine under UV light at λ = 365 nm. The principal spot obtained from the *Test solution* and the *Standard solution* has the same color and R_F value.

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

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed ~~1000 cfu per g~~ 100 cfu per g, and the total combined molds and yeasts count does not exceed ~~100 cfu per g. Tablets~~ 10 cfu per g. Inserts meet the requirements of the tests for absence of ~~*Salmonella* species and *Escherichia coli.*~~ *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Candida albicans*.

Dissolution ⟨711⟩—[To come.]

Loss on drying ⟨731⟩—Dry about 1200 mg of finely powdered ~~Tablets~~ Inserts in a tared evaporating dish at a pressure not exceeding 25 mm of mercury at 60° for 3 hours: it loses not more than 7.0% of its weight.

Chromatographic purity—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (5 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Estradiol RS and USP Estradiol Related Compound B RS to obtain a solution having a known concentration of about 100 µg per mL and about 0.525 µg per mL, respectively.

Test solution—Place 12 ~~Tablets~~ Inserts, equivalent to about 300 µg of estradiol, into a 50-mL volumetric flask. Add 50 mL of absolute alcohol, stir for 16 hours with a magnetic stirrer, and shake thoroughly. Centrifuge the suspension, and evaporate 10.0 mL of the supernatant to dryness. Dissolve the residue in 1.0 mL of water and 7.0 mL of a mixture of toluene and acetone (5 : 2), mix on a whirl mixer, allow to stand for 1 hour, and evaporate 5 mL of the organic phase to dryness.

The residue is reconstituted in 450 µL of absolute alcohol, to obtain a solution containing about 0.08 µg of estradiol per mL, and centrifuged. Use the supernatant as the *Test solution.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.96 for estradiol related compound B and 1.0 for estradiol; and the resolution, *R,* between estradiol related compound B and estradiol is not less than 2.0.

Procedure—Inject a volume (about 25 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all the peak responses. Calculate the percentage of each estradiol related impurity in the portion of ~~Tablets~~ Inserts taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 1.0% of any individual impurity is found; and not more than 3.0% of total impurities is found. The impurities meet the requirements specified in the table below.

Compound	Relative Retention Time	Relative Response Factor	Limit (%)
6α-Hydroxy estradiol	0.54	1.0	1.0
6β-Hydroxy estradiol	0.60	1.0	1.0
6-Keto estradiol	0.71	1.0	1.0
16-Keto estradiol	0.74	1.0	1.0
6-Keto estrone	0.85	1.0	1.0
β-Equilenol	0.91	1.0	1.0
Estradiol related compound B (6-Dehydroestradiol)	0.96	1.0	1.0
Estradiol	1.0	1.0	—
Estradiol related compound A (α-Estradiol)	1.05	1.0	1.0
Estrone	1.13	1.0	1.0
4-Methyl estradiol	1.17	1.0	1.0
Total impurities	—	—	1.0

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (5 : 1).

Solvent solution—Prepare a mixture of water and absolute alcohol (1 : 1).

Estrone standard stock solution—Prepare a solution of USP Estrone RS in absolute alcohol having a known concentration of 0.4 mg per mL.

Estradiol standard stock solution—Prepare a solution of USP Estradiol RS in absolute alcohol having a known concentration of 0.5 mg per mL.

System suitability preparation—Transfer 400 µL of *Estradiol standard stock solution* and 200 µL of *Estrone standard stock solution* to a 100-mL volumetric flask, and dilute with *Solvent solution* to volume.

Standard ~~solution~~ preparation—Pipet 500 µL of *Estradiol standard stock solution* into a 250-mL flask, and dilute with *Solvent solution* to volume to obtain a solution having a known concentration of about ~~1.0 µg per mL.~~ 2.5 µg per mL.

Assay preparation—Add 10 ~~Tablets~~ Inserts into a measured amount of *Solvent solution* to obtain a solution having an estradiol concentration of about 2.5 µg per mL. Stir the mixture overnight with a magnetic stirrer, shake thoroughly, and centrifuge if necessary.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 3.9-mm × 30-cm column that contains 4-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph

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the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between estradiol and estrone is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of estradiol ($C_{18}H_{24}O_2$) in the portion of ~~Tablets~~ Inserts taken by the formula:

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

$$DC(r_U/r_S)$$

in which D is the dilution factor used in the preparation of the *Assay preparation, C* is the concentration, in mg per mL, of USP Estradiol RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and *Standard preparation,* respectively.■2S (*USP30*)

BRIEFING

Conjugated Estrogens Tablets, *USP 29* page 851. It is proposed to add a *Dissolution Test 4* for a product labeled to contain 1.25 mg; a *Dissolution Test 5* for some products labeled to contain 0.3 mg, 0.45 mg, and 0.625 mg; and a *Dissolution Test 6* for a product labeled to contain 0.9 mg. The chromatographic procedures in all these tests were validated using a Bio-Sil ODS brand of column containing packing L1. In the absence of any adverse comments, it is proposed to implement this revision via the *Sixth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of December 1, 2006.

(BPC: M. Marques) RTS—C43053; C43963

Change to read:

Dissolution ⟨711⟩—Proceed as directed for *Extended-Release Articles.*

TEST 1 (for products labeled as 0.3-, 0.45-, and 0.625-mg tablets)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1.*

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

•*Times:* 2, 5, and 8 hours.•6

Mobile phase—Prepare a filtered and degassed mixture of 0.025 M monobasic potassium phosphate and acetonitrile (3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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

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

Chromatographic system—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 3.0-cm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph replicate injections of the *Standard solution,* and record the responses as directed for *Procedure:* the relative retention times are about 0.9 for equilin sulfate and 1.0 for estrone sulfate, the estrone sulfate peak being the last major peak in the chromatogram; the resolution, *R,* between equilin sulfate and estrone sulfate is not less than 1.5; and the relative standard deviation for the estrone sulfate peak is not more than 1.5%. [NOTE—If estrone is present it may be retained on the column for a period longer than 50 minutes and interfere in later chromatographic runs.]

Procedure—Separately inject equal volumes (between 20 and 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the estrone sulfate peaks. Calculate the percentage of estrone sodium sulfate released by the formula:

$$100(r_U/r_S)$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to *Acceptance Table 2.*

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

TEST 2 (for products labeled as 0.9-mg tablets)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium, Apparatus,

•*Times,*•6

Mobile phase, Standard solution, Test solution, Chromatographic system, and *Procedure*—Proceed as directed for *Test 1.*

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to *Acceptance Table 2.*

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

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TEST 3 (for products labeled as 1.25- and 2.50-mg tablets)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3.*

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

•*Times:* 2, 5, 8, and 12 hours.•[6]

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to *Acceptance Table 2.*

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

(Official April 1, 2006)

•TEST 4 (for products labeled as 1.25-mg tablets)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: acetate buffer, pH 4.5; 900 mL.

Apparatus 2: 50 rpm, with sinkers.

Times: 2, 4, 8, and 12 hours.

Mobile phase—Prepare a filtered and degassed mixture of 0.025 M monobasic potassium phosphate and acetonitrile (78 : 22). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Accurately weigh 20 Tablets and determine the average tablet weight. Grind the Tablets to a uniform fine powder. Accurately weigh a portion of the powdered Tablets equivalent to the average tablet weight, transfer to a 900-mL volumetric flask, and dilute with *Medium* to volume. Stir vigorously by mechanical means for at least 2 hours or until the dissolution of the powder is complete. Pass a portion of the extract through a suitable 10-µm filter.

Test solution—Pass a portion of the solution under test through a suitable 10-µm filter. [NOTE—It is recommended that the filters selected be tested for binding affinity.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 3.2-mm × 5.0-cm column that contains 5-µm packing L1. The flow rate is about 0.8 mL per minute. Chromatograph replicate injections of the *Standard solution,* and record the responses as directed for *Procedure:* the relative retention times are about 0.9 for equilin sulfate and 1.0 for estrone sulfate, the estrone sulfate peak being the last major peak in the chromatogram; the resolution, *R,* between equilin sulfate and estrone sulfate is not less than 1.2; and the relative standard deviation for the estrone sulfate peak is not more than 2.0%. [NOTE—If estrone is present, it may be retained on the column for a period longer than 50 minutes and interfere in later chromatographic runs.]

Procedure—Separately inject equal volumes (between 20 and 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the estrone sulfate peaks. Calculate the percentage of estrone sulfate released by the formula:

$$100\left(\frac{r_U}{r_S}\right)$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	between 11% and 31%
4	between 43% and 63%
8	between 75% and 95%
12	not less than 87%

TEST 5 (for products labeled as 0.3-, 0.45-, and 0.625-mg tablets)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium, Apparatus, Mobile phase, Standard solution, Test solution, Chromatographic system, and *Procedure*—Proceed as directed for *Test 4*.

Times: 1, 3, and 8 hours.

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 6% and 26%
3	between 48% and 68%
8	not less than 87%

TEST 6 (for products labeled as 0.9-mg tablets)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium, Apparatus, Mobile phase, Standard solution, Test solution, Chromatographic system, and *Procedure*—Proceed as directed for *Test 4*.

Times: 1, 3, and 8 hours.

Times and *Tolerances*—The percentages of estrone sodium sulfate dissolved at the times specified conform to *Acceptance Table 2*. •6

Time (hours)	Amount dissolved
1	between 3% and 23%
3	between 41% and 61%
8	not less than 80%

BRIEFING

Glipizide and Metformin Hydrochloride Tablets, page 1631 of *PF* 31(6) [Nov.–Dec. 2005]. It is proposed to add a *Dissolution* test to this monograph. The chromatographic procedure in this test was developed using the Symmetry C18 brand of column containing packing L1. Using this column the retention time for glipizide is about 6.3 minutes.

(BPC: M. Marques) RTS—C42796

Add the following:

■Glipizide and Metformin Hydrochloride Tablets

» Glipizide and Metformin Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of glipizide ($C_{21}H_{27}N_5O_4S$) and metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

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

USP Reference standards ⟨11⟩—*USP Glipizide RS. USP Glipizide Related Compound A RS. USP Metformin Hydrochloride RS. USP Metformin Related Compound A RS.*

Identification—

A: GLIPIZIDE—

Infrared Absorption ⟨197A⟩—Prepare the test specimen as follows. Transfer not fewer than 10 Tablets to a suitable container, add 10 mL of methanol, and shake to remove any tablet coating. Drain the methanol, add 20 mL of water, and stir until the Tablets dissolve (about 1 hour). Transfer the solution to a separatory funnel, and extract twice with 10-mL portions of chloroform, shaking for approximately 5 minutes. Transfer the lower organic layer into a beaker containing 3 to 4 g of anhydrous magnesium sulfate. Repeat the extraction of the solution in the separatory funnel two more times, each time using 20-mL portions of chloroform. Swirl the mixture

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in the beaker for about 1 minute. Filter, and collect the filtrate. Evaporate the solvent under vacuum, and dry the residue under vacuum for 4 hours at 105°. Mound the residue onto a diamond cell: the IR spectrum so obtained exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Glipizide RS.

B: GLIPIZIDE—

The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for glipizide.*

C: METFORMIN HYDROCHLORIDE—

The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for metformin hydrochloride.*

Dissolution ⟨711⟩ ~~[To come.]~~

Medium: 0.05 M phosphate buffer, pH 6.8 ± 0.05 (Prepared by dissolving 12.96 g of monobasic potassium phosphate and 1.66 g of sodium hydroxide in approximately 400 mL of water, and diluting with water to 2000 mL. Adjust the pH, if necessary, with diluted sodium hydroxide. [NOTE—Tight control of the pH is critical.]); 1000 mL.

Apparatus 2: 50 rpm.

Times: 45 minutes for glipizide, 30 minutes for metformin hydrochloride.

Determine the amount of glipizide ($C_{21}H_{27}N_5O_4S$) dissolved by employing the following method.

Buffer solution—Dissolve approximately 3.4 g of monobasic potassium phosphate in approximately 800 mL of water. Adjust with 10 N sodium hydroxide solution to a pH of 6.0 ± 0.1. Dilute with water to 1000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (13 : 12). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 50 mg of USP Glipizide RS, accurately weighed, to a 1000-mL low-actinic volumetric flask, and dissolve in 100 mL of methanol. Dilute with *Medium* to volume, and sonicate for about 5 minutes. [NOTE—This solution is stable for 7 days at 5° when protected from the light.]

Working standard solution—Dilute the *Standard solution* with *Medium* in order to obtain a solution containing *L*/1000 mg per mL, with *L* being the glipizide tablet label claim, in mg.

Test solution—After the specified time, withdraw about 10 mL of the solution under test. Pass the solution through a 0.45-µm PVDF filter or a 1.0-µm glass fiber filter, discarding the first mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms running for about 8 minutes, and measure the peak response for glipizide. Calculate the amount of glipizide ($C_{21}H_{27}N_5O_4S$) dissolved by the formula:

$$\frac{r_U \times C_S \times 1000 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of glipizide in the *Working standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim for glipizide, in mg.

Determine the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved by employing the following method.

Test solution—After the specified time, withdraw about 10 mL of the solution under test. Pass the solution through a 0.45-µm PVDF filter or a 1.0-µm glass fiber filter, discarding the first mL.

Procedure—Determine the amount of metformin hydrochloride dissolved by employing UV absorption at the wavelength of maximum absorbance at about 233 nm on portions of the *Test solution,* suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved by the formula:

$$\frac{A_U \times C_S \times 1000 \times 100}{A_S \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim for metformin hydrochloride, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{27}N_5O_4S$ is dissolved in 45 minutes. Not less than 80% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 minutes.

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

Related compounds—

GLIPIZIDE—

Ammonium phosphate buffer, Solution A, Solution B, and *Chromatographic system*—Prepare as directed in the *Assay for glipizide*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for glipizide*.

Procedure—Inject about 50 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of glipizide related compound A (approximate relative retention time 0.92) and other individual impurities in the portion of Tablets taken by the formula:

$$100(1/F)(r_i / r_s)$$

in which F is the relative response factor for each impurity and is equal to 1.4 for glipizide related compound A and 1.0 for all other peaks; r_i is the peak response of each impurity; and r_s is the sum of the responses of all the peaks: not more than 2.0% of glipizide related compound A is found; not more than 0.5% of any other individual glipizide related impurity (eluting after approximately 8 minutes) is found; and not more than 1.0% total impurities, excluding glipizide related compound A, is found. [NOTE—Disregard the broad peak due to metformin that elutes before 8 minutes. Disregard any peak observed in the blank, and disregard any peak less than 0.05%.]

Chromatographic purity—

METFORMIN HYDROCHLORIDE—

Solution A, Solution B, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay for metformin hydrochloride*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay for metformin hydrochloride.*

Procedure—Inject about 25 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

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in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Disregard any peak less than 0.05%, and disregard any peak observed in the blank.]

Assay for glipizide—

Ammonium phosphate buffer—Dissolve 2.6 g of dibasic ammonium phosphate in water, and dilute with water to 1000 mL. Adjust with ammonium hydroxide to a pH of 8.0.

Solution A—Prepare a degassed mixture of water, *Ammonium phosphate buffer,* and acetonitrile (14 : 5 : 1).

Solution B—Prepare a degassed mixture of acetonitrile, *Ammonium phosphate buffer,* and water (2 : 1 : 1).

Diluent—Use a mixture of acetonitrile and water (60 : 40).

Standard stock preparation—Transfer an accurately weighed quantity of USP Glipizide RS to a suitable low-actinic volumetric flask. Dissolve first in acetonitrile, using 60% of the final volume, by sonicating for about 20 minutes, then dilute with water to volume to obtain a solution having a known concentration of about 0.1 mg of glipizide per mL. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

Standard preparation—Transfer 25.0 mL of *Standard stock preparation* to a 200-mL low-actinic volumetric flask. Dilute first with 75 mL of *Diluent,* and bring to volume with water to obtain a solution having a known glipizide concentration of approximately 0.0125 mg per mL. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

System suitability preparation—Transfer approximately 5 mg of USP Glipizide Related Compound A RS to a 500-mL volumetric flask, and fill halfway with acetonitrile. Sonicate for about 30 minutes to dissolve, and dilute with acetonitrile to volume. Transfer 1 mL of this solution to a 50-mL low-actinic volumetric flask, and dilute with *Standard preparation* to volume.

Assay preparation—Transfer not fewer than 5 Tablets to a suitable volumetric flask, and fill halfway with *Diluent*. Sonicate for 30 minutes, and shake vigorously for another 30 minutes to dissolve. Dilute with water to volume, and mix to obtain a solution with a final glipizide concentration of about 0.0125 mg per mL. Pass a portion of this solution through a nylon or PVDF filter having a 0.2-µm porosity, and use the filtrate. [NOTE—The solution is stable for 2 weeks when stored at 5° protected from light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 223-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–3	100	0	isocratic
3–18	100→0	0→100	linear gradient
18–20	0	100	isocratic
20–22	0→100	100→0	linear gradient
22–30	100	0	re-equilibration

Chromatograph the *System suitability preparation* and the *Standard preparation,* and record the peak responses as directed for *Procedure*. For the *System suitability preparation,* the relative retention times are about 0.92 for glipizide related compound A and 1.0 for glipizide; the resolution, *R,* between glipizide related compound A and glipizide is greater than 1.2. For the *Standard preparation,* the relative standard deviation for replicate injections is less than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the glipizide peaks. Calculate the quantity, in mg per Tablet, of glipizide ($C_{21}H_{27}N_5O_4S$) by the formula:

$$CV(r_U / r_S) / N$$

in which C is the concentration, in mg per mL, of USP Glipizide RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation;* r_U and r_S are the glipizide peak

responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and *N* is the number of Tablets taken to prepare the *Assay preparation.*

Assay for metformin hydrochloride—

Solution A—Prepare a 50 mM hexanesulfonic acid solution by dissolving 9.41 g of sodium 1-hexanesulfonate in 1000 mL of water, and adjusting with trifluoroacetic acid to a pH of 2.0.

Solution B—Prepare a solution of water and acetonitrile (60 : 40).

Mobile phase—Prepare a degassed mixture of water, *Solution A,* and *Solution B* (50 : 30 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent pH 2.0—Prepare a mixture of water, *Solution A*, and acetonitrile (63 : 30 : 7).

Standard preparation—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Diluent pH 2.0* to obtain a solution having a known concentration of about 0.1 mg per mL.

System suitability preparation—Dissolve a suitable quantity of USP Metformin Related Compound A RS in water to obtain a solution containing about 5 µg per mL. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with the *Standard preparation* to volume.

Assay preparation—Quantitatively dilute a portion of the *Assay preparation,* obtained as directed for *Assay for glipizide,* with *Diluent pH 2.0,* to obtain a solution having an expected concentration of about 0.1 mg of metformin hydrochloride per mL, based on the label claim. Pass a portion of this solution through a nylon or PVDF filter having a 0.2-µm porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.26 for metformin related compound A and 1.0 for metformin; the resolution, *R,* between the two peaks is not less than 3.0; and the relative standard deviation for replicate injections, determined from the metformin peak, is less than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) by the formula:

$$CVD(r_U / r_S)/N$$

in which *C* is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation*, as prepared under the *Assay for glipizide; D* is the dilution factor of the *Assay preparation;* r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively; and *N* is the number of Tablets used to prepare the *Assay preparation.* ■2S (*USP30*)

BRIEFING

Glyburide Tablets, *USP 29* page 1011. It is proposed to add *Dissolution* tests for some of the products approved for the USA market. The liquid chromatographic procedures in *Dissolution Test 1* are based on analyses performed with a Rexchrom Workhorse II brand of L1 column. The liquid chromatographic procedures in *Dissolution Test 2* are based on analyses performed with a Lichrosorb RP-8 brand of L7 column. The liquid chromatographic procedures in *Dissolution Test 3* are based on analyses performed with a Zorbax C8 brand of L7 column.

(BPC: M. Marques) RTS—C41785; C41796; C44745

Add the following:

■**Labeling—**When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used. ■2S (*USP30*)

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Add the following:

■**Dissolution** ⟨711⟩—

TEST 1—

Medium: 0.05 M phosphate buffer, pH 9.5; 500 mL.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Determine the percentage of the labeled amount of $C_{23}H_{28}ClN_3O_5S$ dissolved using the following method. [NOTE—Use low-actinic volumetric flasks.]

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (1 : 1), and add 4.0 mL of phosphoric acid per L of solution. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 15 mg of USP Glyburide RS, accurately weighed, to a 100-mL volumetric flask, dissolve in *Medium* with sonication until dissolved, about 25 minutes, and dilute with *Medium* to volume.

Standard solutions—Dilute the *Standard stock solution* quantitatively, and stepwise if necessary, with *Medium* to obtain solutions having known concentrations of 0.003 mg per mL (for Tablets labeled to contain 1.5 mg), 0.006 mg per mL (for Tablets labeled to contain 3.0 mg), 0.009 mg per mL (for Tablets labeled to contain 4.5 mg), and 0.012 mg per mL (for Tablets labeled to contain 6.0 mg).

Test solution—Pass a portion of the solution under test through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 30-cm column that contains 10-µm packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 4000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of $C_{23}H_{28}ClN_3O_5S$ dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{23}H_{28}ClN_3O_5S$ is dissolved in 45 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.05 M phosphate buffer, pH 8.5; 900 mL.

Apparatus 2: 50 rpm.

Time: 60 minutes.

Determine the percentage of the labeled amount of $C_{23}H_{28}ClN_3O_5S$ dissolved using the following method.

Mobile phase—Prepare a filtered and degassed mixture of 520 mL of water containing 2.6 g of monobasic ammonium phosphate and 480 mL of acetonitrile. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 67 mg of USP Glyburide RS, accurately weighed, to a 500-mL volumetric flask, dissolve in 40 mL of methanol with sonication for 5 minutes, and dilute with *Medium* to volume.

Standard solutions—Dilute the *Standard stock solution* quantitatively, and stepwise if necessary, with *Medium* to obtain solutions having known concentrations of 0.0017 mg per mL (for Tablets labeled to contain 1.5 mg), 0.0034 mg per

mL (for Tablets labeled to contain 3 mg), 0.0047 mg per mL (for Tablets labeled to contain 4.5 mg), and 0.0067 mg per mL (for Tablets labeled to contain 6 mg).

Test solution—Pass a portion of the solution under test through a suitable 0.5-µm filter.

Chromatographic system—The liquid chromatograph is equipped with a 215-nm detector and a 4.0-mm × 25-cm column that contains 10-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of $C_{23}H_{28}ClN_3O_5S$ dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Tolerances—Not less than 60% *(Q)* of the labeled amount of $C_{23}H_{28}ClN_3O_5S$ is dissolved in 60 minutes.

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

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the percentage of the labeled amount of $C_{23}H_{28}ClN_3O_5S$ dissolved using the following method.

Mobile phase—Proceed as directed for the *Assay.*

Diluent—Prepare a mixture of acetonitrile and water (5 : 1).

Standard solution—Transfer about 66.6 mg of USP Glyburide RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Medium* to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, and dilute with *Medium* to volume.

Test solution—Pass a portion of the solution under test through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 2 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 75 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of $C_{23}H_{28}ClN_3O_5S$ dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{23}H_{28}ClN_3O_5S$ is dissolved in 45 minutes. ■2S *(USP30)*

In-Process Revision

BRIEFING

Hydrocortisone Tablets, *USP 29* page 1069. It is proposed to revise the test for *Uniformity of dosage units* and the *Assay* to provide information needed to perform these tests because the cross reference provided in the monograph is no longer valid. It is also proposed to revise the *USP Reference standards* section to add USP Prednisone RS, which is used as an internal standard in the *Assay* and in the test for *Uniformity of dosage units*.

(MD-PS: D. Bempong) RTS—C44869

Change to read:

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

■*USP Prednisone RS.*■2S (*USP30*)

Change to read:

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

PROCEDURE FOR CONTENT UNIFORMITY—

~~*Mobile solvent, Internal standard solution,* and *Standard preparation*—Prepare as directed in the *Assay* under *Hydrocortisone.*~~

■*Mobile phase, Internal standard solution,* and *Standard preparation*—Prepare as directed in the *Assay.*■2S (*USP30*)

Test preparation—Transfer 1 Tablet to a suitable container and add about 0.3 mL of water directly on the Tablet. Allow the Tablet to stand for about 5 minutes. Shake the container to break up the Tablet and sonicate briefly to ensure complete disintegration. Add a few small glass beads and 50.0 mL of *Internal standard solution* to the container. Shake the container for about 30 minutes. Dilute an accurately measured volume of the clear supernatant with a known, accurately measured volume of *Internal standard solution* to obtain a final concentration of 0.1 mg per mL. Shake the contents of the container to mix, and analyze the clear solution as directed for *Procedure*.

~~*Procedure*~~

■*Chromatographic system* and *Procedure*—■2S (*USP30*)
~~Proceed as directed for *Procedure* in the *Assay* under *Hydrocortisone*~~

■Proceed as directed in the *Assay.*■2S (*USP30*)
Calculate the quantity, in mg, of $C_{21}H_{30}O_5$ in the Tablet taken by the formula:

$$50(F_2/F_1)C(R_U/R_S)$$

in which F_1 is the volume, in mL, of the supernatant aliquot of the solution from the Tablet taken for dilution; F_2 is the final volume, in mL, of the *Test preparation;* and the other terms are as defined for ~~*Procedure* in the *Assay* under *Hydrocortisone*.~~

■*Procedure* in the *Assay.*■2S (*USP30*)

Change to read:

Assay—

~~*Mobile solvent, Internal standard solution,* and *Standard preparation*—Prepare as directed in the *Assay* under *Hydrocortisone.*~~

■*Mobile phase*—Prepare a solution containing a mixture of butyl chloride, water-saturated butyl chloride, tetrahydrofuran, methanol, and glacial acetic acid (95 : 95 : 14 : 7 : 6).

Internal standard solution—Prepare a solution of USP Prednisone RS in water-saturated chloroform containing 0.06 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Hydrocortisone RS in *Internal standard solution* to obtain a solution having a known concentration of about 0.1 mg per mL.■2S (*USP30*)

Assay preparation—Weigh and finely powder not fewer than 10 Tablets. Weigh a portion of the powder, equivalent to about 5 mg of hydrocortisone, and transfer to a suitable container. Add 50.0 mL of *Internal standard solution.* Shake vigorously for 30 minutes, and centrifuge a portion of this mixture. Use the clear supernatant.

■*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L3. The flow rate is 0.9 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between hydrocortisone and prednisone is not less than 3.0; and the relative standard deviation for four replicate injections is not more than 2.0%.■2S (*USP30*)

Procedure—~~Proceed as directed for *Procedure* in the *Assay* under *Hydrocortisone.*~~

■Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks.■2S (*USP30*)
Calculate the quantity, in mg, of hydrocortisone ($C_{21}H_{30}O_5$) in the portion of Tablets taken by the formula:

$$50C(R_U/R_S)$$

in which ~~the terms are as defined therein.~~

■C is the concentration, in mg per mL, of USP Hydrocortisone RS in the *Standard preparation;* and R_U and R_S are the peak response ratios of the hydrocortisone peak to the internal standard peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

In-Process Revision

BRIEFING

Hypromellose Ophthalmic Solution, *USP 29* page 1099 and page 3572 of the *First Supplement.* On the basis of comments received, it is proposed to revise the formula in the *Procedure* in the *Assay.*

(MD-OOD: F. Mao) RTS—C45710

Change to read:

Assay—

Standard preparation—Dissolve a suitable quantity of USP Hypromellose RS, accurately weighed, in water, and dilute quantitatively with water to obtain a solution having a known concentration of about 100 µg per mL.

Assay preparation—Dilute an accurately measured volume of Ophthalmic Solution quantitatively with water to obtain a solution having an equivalent concentration of about 100 µg of hypromellose per mL.

Procedure—Pipet 2 mL each of the *Standard preparation,* the *Assay preparation,* and water to provide a blank, into separate, glass-stoppered test tubes. To each tube add 5.0 mL of diphenylamine solution (prepared by dissolving 3.75 g of colorless diphenylamine crystals in 150 mL of glacial acetic acid and diluting the solution with 90 mL of hydrochloric acid), mix, and immediately insert the tubes into an oil bath at 105° to 110° for 30 minutes, the temperature being kept uniform within 0.1° during heating. Remove the tubes, and place them in an ice-water bath for 10 minutes or until thoroughly cool. At room temperature and using a suitable spectrophotometer, concomitantly determine the absorbances of the solutions from the *Standard preparation* and the *Assay preparation* at 635 nm, using the water solution as the blank. Calculate the quantity, in mg, of hypromellose in each mL of the Ophthalmic Solution taken by the formula:

~~$0.001C(d/V)(A_u/A_s)$~~

■$0.001Cd(A_U/A_S)$■2S (*USP30*)

in which C is the concentration, in µg per mL, of USP Hypromellose RS in the *Standard preparation;* ~~*V* is the volume, in mL, of Ophthalmic Solution taken;~~

■■2S (*USP30*)
d is the dilution factor ~~of *V*~~

■■2S (*USP30*)
used to obtain the *Assay preparation;* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Irbesartan, *USP 29* page 1177 and page 799 of *PF* 32(3) [May–June 2006]. It is proposed to revise the test for *Related compounds* to change the quantitation of other impurities from using the related compound A peak as the reference peak to using the drug substance peak as the reference peak. Also, the *Dilute standard solution* under the test for *Related compounds* and the *Assay* is being deleted as it is not a part of the original submission and is not used in any part of the monograph.

(MD-CV: S. Ramakrishna) RTS—C45897

Change to read:

Limit of azide—

Mobile phase—Prepare a filtered and degassed 0.1 N sodium hydroxide solution (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 25 mg of sodium azide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 250 µL of this solution into a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 0.312 µg of sodium azide per mL.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductimetric detector and a 4.0-mm × 25-cm column that contains packing ~~L46~~

■L31.■1S (*USP30*)
The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the azide peak is not less than 10.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas for azide. Calculate the amount of azide, in ppm, in the portion of Irbesartan taken by the formula:

$$1000(C_S/C_T)(42.02/65.01)(r_U/r_S)$$

in which C_S is the concentration, in µg per mL, of sodium azide in the *Standard solution;* C_T is the concentration, in mg per mL, of Irbesartan in the *Test solution;* 42.02 is the molecular weight of azide; 65.01 is the molecular weight of sodium azide; r_U is the peak area for azide obtained from the *Test solution;* and r_S is the peak area for azide obtained from the *Standard solution:* not more than 10 ppm of azide is found.

Change to read:

Related compounds—

pH 3.2 Phosphate buffer and *Mobile phase* ~~and *Dilute standard solution*~~

■■2S (*USP30*)
—Proceed as directed in the *Assay.*

Standard solution—Prepare as directed for the *Resolution solution* in the *Assay.*

■*Test solution*—Dissolve a quantity of Irbesartan, accurately weighed, in methanol to obtain a solution having a known concentration of about 1 mg per mL.■1S (*USP30*)

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Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area for the irbesartan related compound A peak. Calculate the percentage of irbesartan related compound A in the portion of Irbesartan taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Irbesartan Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Irbesartan in the *Test solution;* r_U is the peak response for irbesartan related compound A obtained from the *Test solution;* and r_S is the peak response for irbesartan related compound A obtained from the *Standard solution.*

■Calculate the percentage of other impurities in the portion of Irbesartan taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Irbesartan RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Irbesartan in the *Test solution;* and r_U and r_S are the peak responses for each of the other impurities and USP Irbesartan RS obtained from the *Test solution* and the *Standard solution,* respectively:■2S (*USP30*)
not more than 0.2% of irbesartan related compound A is found; not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.

Change to read:

Assay—

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

Mobile phase—Prepare a filtered and degassed mixture of *pH 3.2 Phosphate buffer* and acetonitrile (67 : 33). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve accurately weighed quantities of USP Irbesartan RS and USP Irbesartan Related Compound A RS in methanol to obtain a solution having known concentrations of about 0.05 mg of each per mL.

~~*Dilute standard solution*—Dissolve an accurately weighed quantity of USP Irbesartan RS in methanol to obtain a solution having a known concentration of about 1 µg per mL.~~

■■2S (*USP30*)

Standard preparation—Dissolve an accurately weighed quantity of USP Irbesartan RS in methanol to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Irbesartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

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

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg, of $C_{25}H_{28}N_6O$ in the portion of Irbesartan taken by the formula:

$$100C(r_U / r_S)$$

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

BRIEFING

Levodopa, *USP 29* page 1242. In ICH guidelines, there are no specific requirements given for the total unknown impurity category. The difference between the total impurities limit and the sum of all the individual impurities serves as the control for total unknown impurities. Based on this guideline, it is proposed to delete the redundant acceptance criterion for total unknown impurities.

(MD-PP: R. Ravichandran) RTS—C43540

Change to read:

Related compounds—[NOTE—Protect all solutions from light and maintain them at 10° until they are injected into the chromatograph.]

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

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

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

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Levodopa taken by the formula:

$$(10{,}000F)(C/W)(r_i / r_S)$$

in which F is the relative response factor of each impurity according to the table below; C is the concentration, in mg per mL, of USP Levodopa RS in the *Standard solution;* W is the weight, in mg, of Levodopa, on the dried basis, used to prepare the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for levodopa in the *Standard solution:* the impurities meet the requirements given in the table below.

Compound Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Levodopa related compound A	about 0.9	2.4	0.1
Levodopa	1.0	—	—
L-Tyrosine	about 1.3	2.7	0.1
3-Methoxytyrosine	about 1.6	1.2	0.5
1-Veratrylglycine	about 2.7	1.3	0.1
~~Unknown impurities~~	—	1.0	

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Compound Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
■Individual unknown impurity■2S *(USP30)*			0.1 ~~individual~~ ~~0.2 total unknown~~ ■■2S *(USP30)*
Total	—	—	1.1

BRIEFING

Lisinopril Tablets, *USP 29* page 1263 and page 1090 of *PF* 31(4) [July–Aug. 2005]. As suggested by the monograph originator, it is proposed to revise the *Assay* based on the modifications of the current validated test method. The proposed changes include modifications in the *Mobile phase* and parts of the *Chromatographic system* (flow rate, theoretical plates, capacity factor, %RSD of the replicate injections) which are inconsistent with the most recent validated procedure.

(MD-CV: S. Ramakrishna) RTS—C41606

Change to read:

Dissolution ~~*Procedure for a Pooled Sample*~~
■■2S *(USP29)*
⟨711⟩—
Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 2: 50 rpm.
Time: 30 minutes.
Determine the amount of lisinopril dissolved using the following method.
Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*
~~*Procedure*~~

■PROCEDURE FOR POOLED SAMPLE—Proceed as directed for *Procedure* in *Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms* under *Dissolution* ⟨711⟩. Combine equal volumes of the filtered solutions of the 6 or 12 individual specimens withdrawn, and use the pooled sample as the test solution.■2S *(USP29)*
Inject a volume of ~~a filtered portion of the solution under test~~

■the pooled sample■2S *(USP29)*
into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $C_{21}H_{31}N_3O_5$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in the same medium and similarly chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{31}N_3O_5$ in the Tablets is dissolved in 30 minutes:

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

Acceptance Table for a Pooled Sample

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

PROCEDURE FOR UNIT SAMPLE—Proceed as directed for *Procedure* in *Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms* under *Dissolution* ⟨711⟩. Inject a volume of a filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the amount of $C_{21}H_{31}N_3O_5$ dissolved in comparison with a Standard solution having a known concentration of USP Lisinopril RS in *Medium* and similarly chromatographed.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{21}H_{31}N_3O_5$ is dissolved in 30 minutes.■2S *(USP29)*

Change to read:

Assay—
Phosphate solution—Dissolve 4.1 g of monobasic potassium phosphate in about 900 mL of water in a 1000-mL volumetric flask, and adjust with phosphoric acid to a pH of 2.0. Dilute with water to volume, and mix.
Mobile phase—Dissolve 1.0 g of sodium 1-hexanesulfonate in ~~800 mL~~

■820 mL■2S *(USP30)*
of *Phosphate solution*. Add ~~200 mL~~

■180 mL■2S *(USP30)*

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of acetonitrile, mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of water and methanol (4 : 1).

Standard preparation—Dissolve an accurately weighed quantity of USP Lisinopril RS in *Diluent* to obtain a solution having a known concentration of about 0.2 mg per mL.

Assay preparation—Transfer to a suitable size volumetric flask 10 Tablets, which when diluted with *Diluent* will yield a solution having a concentration of about 0.2 mg per mL. Add *Diluent,* and sonicate for 5 minutes. Shake the flask by mechanical means for 20 minutes, dilute with *Diluent* to volume, mix, and filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 20-cm column that contains packing L7 and is maintained at a temperature of 40°. The flow rate is about ~~1.5 mL~~

■1 mL■2S (*USP30*)
per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency determined from the analyte peak is not less than ~~850~~

■700■2S (*USP30*)
theoretical plates, the tailing factor for the analyte peak is not more than 2.0, the capacity factor, k', for the analyte peak is ~~not less than 2.0~~

■greater than 1.5,■2S (*USP30*)
and the relative standard deviation for replicate injections is not more than ~~2.0%~~

■2%.■2S (*USP30*)

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of $C_{21}H_{31}N_3O_5$ in each Tablet taken by the formula:

$$(L/D)C(r_U/r_S)$$

in which L is the labeled quantity, in mg, of lisinopril in each Tablet, D is the concentration, in mg per mL, of lisinopril in the *Assay preparation* based on the labeled quantity per Tablet and the extent of dilution; C is the concentration, in mg per mL, calculated on the anhydrous basis, of USP Lisinopril RS in the *Standard preparation;* and r_U and r_S are the lisinopril peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Magnesium Hydroxide, *USP 29* page 1298; **Magnesium Hydroxide Paste,** *USP 29* page 1298. It is proposed to replace the current test for *Lead* ⟨251⟩, which uses a wet chemistry color comparison method, with a new test for *Limit of lead* that uses inductively coupled plasma (ICP) methodology. In the Magnesium Hydroxide monograph, it is also proposed to tighten the limit of lead to 0.00015% (1.5 ppm). The procedure was validated using an inductively coupled plasma–mass spectrometer (ICP–MS). Manufacturers who can provide validation data using an inductively coupled plasma–atomic emission spectrometer (ICP–AES) are encouraged to submit the information to the Expert Committee.

It is also proposed to add the test for *Limit of lead* to the Magnesium Hydroxide Paste monograph.

(MD-GRE: E. Gonikberg) RTS—C41832

Delete the following:

■~~**Lead** ⟨251⟩—Prepare a *Test Preparation* by dissolving 1 g of Magnesium Hydroxide in 20 mL of 3 N hydrochloric acid. Use 10 mL of *Diluted Standard Lead Solution* (10 µg of Pb) for the test: the limit is 0.001%.~~■2S (*USP30*)

Add the following:

■**Limit of lead—**[NOTE—When water is specified as a diluent, use deionized ultra-filtered water.]

Blank solution—Transfer 3.0 mL of nitric acid to a 50-mL volumetric flask, and dilute with water to volume.

Thallium internal standard 20 ppb—[NOTE—Use this solution only if an ICP–MS instrument is used. This internal standard is added in-line via a mixing block between the sample probe and the spray chamber.] Dilute 20.0 mL of a commercially prepared thallium ICP standard solution (1000 ppb) with water to 1 L.

Dilute nitric acid—Dilute 2.0 mL of nitric acid with water to 100 mL.

Standard stock solution 100 ppb—Prepare this solution fresh every two months. Quantitatively dilute an accurately measured volume of a commercially prepared lead ICP standard (1000 ppm) with *Dilute nitric acid*, to obtain a solution containing 10 ppm of lead. Further dilute this solution with *Dilute nitric acid* to obtain a solution containing 1000 ppb of lead. Transfer 10.0 mL of this solution to a separate 100-mL volumetric flask, add 2.0 mL of nitric acid, and dilute with water to volume.

Standard solutions—Prepare these solutions fresh weekly. [NOTE—The concentrations specified below are recommended if an ICP–MS instrument is used. If an ICP–AES instrument is used, the concentrations of the *Standard solutions* may be modified to adapt to the working range of the instrument.] Transfer 5.0 mL of the *Standard stock solution 100 ppb* to a 50-mL volumetric flask, add 3.0 mL of nitric acid, and dilute with water to volume (*Standard lead solution 10 ppb*). Transfer 5.0 mL of *Standard lead solution 10 ppb* to a 50-mL volumetric flask, add 3.0 mL of nitric acid, and dilute with water to volume (*Standard lead solution 1 ppb*).

Test solution—[NOTE—The concentration specified below is recommended if an ICP–MS instrument is used. If an ICP–AES instrument is used, the concentration of the *Test solution* may be modified to adapt to the working range of the instrument.] Accurately weigh about 0.25 g of Magnesium Hydroxide. Cautiously add 3.0 mL of nitric acid, and mix until the sample is dissolved. Accurately transfer this solution to a 50-mL volumetric flask, and dilute with water to volume.

Procedure (see *Plasma Spectrochemistry* ⟨730⟩)—The inductively coupled plasma–mass spectrometer (ICP–MS) is equipped with a quadrupole mass spectrometer and an ion detector maintained under vacuum. The instrument should read all isotopes for lead (206, 207, and 208 amu) and the thallium internal standard (205 amu), and should report the total lead content using the most naturally abundant isotope at 208 amu. Alternatively, lead could be determined using an inductively coupled plasma–atomic emission spectrometer (ICP–AES) by measuring the emission at 220.353 nm, with the settings optimized as directed by the manufacturer. [NOTE—To minimize matrix interference when using an ICP–AES instrument, it is recommended that the method of standard additions be used.]

Instrument performance must be verified to conform to the manufacturer's specifications for resolution and sensitivity. Before analyzing samples, the instrument must pass a suitable performance check. Generate the calibration curve using the *Blank solution, Standard lead solution 1 ppb,* and *Standard lead solution 10 ppb:* a linear regression coefficient is not less than 0.999.

Aspirate the *Test solution,* at least in duplicate, and calculate the amount of lead using the calibration curve. Report the average reading as the lead content of the sample. Calculate the content of lead in the portion of Magnesium Hydroxide taken: not more than 0.00015% (1.5 ppm) is found.■2S (*USP30*)

BRIEFING

Magnesium Hydroxide Paste *USP 29* page 1298—See briefing under *Magnesium Hydroxide.* In addition to adding a test for *Limit of lead,* it is proposed to widen the acceptance criteria in the Definition to "not less than 28.0 percent and not more than 70.0 percent", to include currently manufactured grades of Magnesium Hydroxide Paste. This range only slightly broadens the current lower limit of 29.0% and avoids an overlap with the highest concentration permitted in the *Milk of Magnesia* monograph. The proposed upper limit in the Definition for Magnesium Hydroxide Paste is based on data that demonstrates that the product at this concentration still has the consistency of a heavy paste. The test for *Soluble alkalies* is also revised to clarify the amount of Paste taken for the test.

(MD-GRE: E. Gonikberg) RTS—C41291

Change to read:

» Magnesium Hydroxide Paste is an aqueous paste of magnesium hydroxide. ~~each 100 g of which contains not less than 29.0 g and not more than 33.0 g of magnesium hydroxide [$Mg(OH)_2$].~~

■It contains not less than 93.0 percent and not more than 107.0 percent of the labeled amount of magnesium hydroxide [$Mg(OH)_2$], the labeled amount being not less than 28.0 percent and not more than 70.0 percent of magnesium hydroxide.■2S (*USP30*)

Change to read:

Soluble alkalies—~~Mix 25.0 g of Paste with 75.0 mL of water,~~

■Accurately weigh a portion of Paste, equivalent to about 7.75 g of magnesium hydroxide, and mix with 75.0 mL of water.■2S (*USP30*)
Transfer about 25 mL of this diluted Paste to a filter, and reject the first 5 mL of the filtrate. [NOTE—Retain the remaining diluted Paste for the tests for *Carbonate and acid-insoluble matter,* ~~*Arsenic,*~~ ■■2S (*USP30*) and *Heavy metals*.] Dilute 5 mL of the clear filtrate with 40 mL of water. Add 1 drop of methyl red TS, and titrate the solution with 0.10 N sulfuric acid to the production of a persistent pink color: not more than 1.0 mL of the acid is required.

Add the following:

■Limit of lead—

Blank solution, Thallium internal standard 20 ppb, Dilute nitric acid, Standard stock solution 100 ppb, and *Standard solutions*—Proceed as directed for the test for *Limit of lead* under *Magnesium Hydroxide.*

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Test solution—Accurately weigh an amount of Paste equivalent to 0.25 g of magnesium hydroxide. Cautiously add 3.0 mL of nitric acid, and mix until the sample is dissolved. Accurately transfer this solution to a 50-mL volumetric flask, and dilute with water to volume. [NOTE—This concentration is recommended if an ICP–MS instrument is used. If an ICP–AES instrument is used, the concentration of the *Test solution* may be modified to adapt to the working range of the instrument.]

Procedure—Proceed as directed for the test for *Limit of lead* under *Magnesium Hydroxide.* Calculate the content of lead in the portion of Paste taken based on the content of magnesium hydroxide in the Paste, as determined in the *Assay:* not more than 0.00015% (1.5 ppm) is found.■2S (*USP30*)

Chromatographic chamber—Line a suitable chamber (see *Chromatography* ⟨621⟩) with absorbent paper, and pour into the chamber 250 mL of a mixture of chloroform, methanol, and ammonium hydroxide (80 : 15 : 2). Saturate the chamber for 1.5 hours before using.

Detecting reagent—Prepare separate solutions of potassium iodide (1 in 100) and soluble starch (prepared by triturating 3 g in 10 mL of cold water and adding the mixture to 90 mL of boiling water with constant stirring). Just prior to use, mix 10 mL of each solution with 3 mL of alcohol.

Procedure—Apply separately 5-µL portions of the *Test solution* and each of the *Standard dilutions* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. Place the plate in the *Chromatographic chamber,* seal the chamber, and allow the chromatogram to develop until the solvent front has moved about three-fourths of the length of the plate. Remove the plate, and dry in a current of warm air until the odor of ammonia is no longer perceptible (about 45 minutes). Place a beaker containing 0.5 g of potassium permanganate in a chamber. Add 5 mL of 6 N hydrochloric acid to the beaker, and allow to equilibrate for 5 minutes. Place the plate in the chamber for 5 minutes. Remove the plate from the chamber, allow to stand in a current of cool air for 1 hour, and spray with *Detecting reagent.* If spots other than the principal spot are observed in the lane of the *Test solution,* estimate the concentration of each by comparison with the *Standard dilutions:* the spots from the 1.0, 0.5, 0.2, and 0.1 mg per mL *Standard dilutions* correspond to 1.0%, 0.5%, 0.2%, and 0.1% of impurities, respectively; and the sum of any observed impurities in the *Test solution* is not greater than 1.0%.

BRIEFING

Metoprolol Tartrate, *USP 29* page 1420. On the basis of comments received, it is proposed to revise the test for *Chromatographic purity* to change the diluent used in the preparation of the *Standard solution,* the *Standard dilutions,* and the *Test solution* from chloroform to methanol. The proposed change is intended to avoid the streaking of the metoprolol spot which could be related to the lack of absorption of the material onto the stationary phase prior to development followed by a gradual dissolution during the chromatographic development process.

(MD-CV: S. Ramakrishna) RTS—C41259

Change to read:

Chromatographic purity—

Standard solution and *Standard dilutions*—Dissolve a suitable quantity of USP Metoprolol Tartrate RS, accurately weighed, in ~~chloroform~~

■methanol,■2S (*USP30*)
and dilute quantitatively and stepwise with ~~chloroform~~

■methanol■2S (*USP30*)
to obtain solutions having known concentrations of 1.0, 0.5, 0.2, and 0.1 mg per mL, respectively.

Test solution—Dissolve a quantity of Metoprolol Tartrate in ~~chloroform~~

■methanol■2S (*USP30*)
to obtain a solution containing 100 mg per mL.

BRIEFING

Netilmicin Sulfate, *USP 29* page 517. In the Definition and in the *Assay,* it is proposed to delete the drying procedures, which were inadvertently added in *PF* 30(1).

(MD-ANT: B. Gilbert) RTS—C44360

Change to read:

» Netilmicin Sulfate~~, previously dried in a vacuum at a pressure not exceeding 5 mm mercury for 1 hour,~~

■■2S (*USP30*)
has a potency equivalent to not less than 595 µg of netilmicin ($C_{21}H_{41}N_5O_7$) per mg,

■calculated on the dried basis. [NOTE—Netilmicin Sulfate is extremely hygroscopic. Protect from exposure to moisture.]■2S (*USP30*)

Change to read:

Assay—

Dilute phosphoric acid—Dilute 5.0 mL of phosphoric acid with water to 1000 mL, and mix.

Mobile phase—Dissolve 20.22 g of sodium 1-heptanesulfonate in *Dilute phosphoric acid,* dilute with *Dilute phosphoric acid* to 1000 mL, and mix. To 620 mL of this solution add 380 mL of acetonitrile, mix, and pass through a filter having a 0.45-µm porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution in *Mobile phase* containing about 1 mg of USP Netilmicin Sulfate RS and 1 mg of USP Sisomicin Sulfate RS per mL.

Standard preparation—~~Transfer about 50 mg of USP Netilmicin Sulfate RS to a low-actinic, previously accurately tared, 50-mL volumetric flask. Place the flask in a vacuum desiccator under a vacuum of less than 5 mm of mercury for 1 hour. Accurately weigh the flask, and determine the dry weight of the USP Netilmicin Sulfate RS taken. Dissolve in and dilute with *Mobile phase* to volume, and mix.~~

■[NOTE—Use low-actinic glassware.] Dissolve an accurately weighed quantity of USP Netilmicin Sulfate RS in *Mobile phase* to obtain a solution having a known concentration of about 1 mg per mL.■2S *(USP30)*

Assay preparation—~~Transfer about 50 mg of Netilmicin Sulfate to a low-actinic, previously accurately tared, 50-mL volumetric flask. Place the flask in a vacuum desiccator under a vacuum of less than 5 mm of mercury for 1 hour. Accurately weigh the flask, and determine the dry weight of the Netilmicin Sulfate taken. Dissolve in and dilute with *Mobile phase* to volume, and mix.~~

■[NOTE—Use low-actinic glassware.] Transfer about 50 mg of Netilmicin Sulfate, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.■2S *(USP30)*

Chromatographic system (see *Chromatography* ⟨621⟩)—The chromatograph is equipped with a 205-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between sisomicin and netilmicin is not less than 1. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3000 theoretical plates; the tailing factor is not more than 2; and the relative standard deviation for replicate injections is not more than 1%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and measure the area responses for the major peaks. Calculate the quantity, in µg, of netilmicin ($C_{21}H_{41}N_5O_7$) per mg of Netilmicin Sulfate taken by the formula:

$$(W_S P/W_U)(r_U/r_S)$$

in which W_S is the dry weight, in mg, of USP Netilmicin Sulfate RS taken to prepare the *Standard preparation; P* is the designated potency, in µg of netilmicin ($C_{21}H_{41}N_5O_7$) per mg, of the USP Netilmicin Sulfate RS; W_U is the dry weight, in mg, of the Netilmicin Sulfate taken to prepare the *Assay preparation;* and r_U and r_S are the netilmicin peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Nevirapine Oral Suspension. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with a 3.5-µm Zorbax SB-CN brand of L10 column. Typical retention times are about 22 minutes for nevirapine, about 20 minutes for nevirapine related compound A, and about 23 minutes for nevirapine related compound B. The chromatographic procedure in the *Dissolution* test was developed using a Symmetry C18 brand of L1 column.

(MD-AA: B. Davani; BPC: M. Marques) RTS—C43396

Add the following:

■Nevirapine Oral Suspension

» Nevirapine Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of nevirapine ($C_{15}H_{14}N_4O$).

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

USP Reference standards ⟨11⟩—*USP Nevirapine Anhydrous RS. USP Nevirapine Related Compund A RS. USP Nevirapine Related Compound B.*

Identification—

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

Ferric chloride–potassium ferricyanide reagent—Dissolve 1.35 g of ferric chloride in 25 mL of water. Dissolve 1.64 g of potassium ferricyanide in 25 mL of water. Mix the two solutions immediately before use.

Test solution—Transfer a volume of Oral Suspension, equivalent to about 10 mg of nevirapine, to an 8-mL glass stoppered tube. Pipet 2.0 mL of chloroform into the tube, and shake. Allow the two phases to separate, and then using a disposable glass Pasteur pipet, remove some of the organic layer from the bottom, and transfer to another container.

In-Process Revision

Standard solution—Dissolve a suitable quantity of USP Nevirapine Anhydrous RS in chloroform to obtain a solution having a known concentration of about 5 mg per mL.

Procedure—Separately apply 5-µL portions of the *Test solution* and the *Standard solution* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel 60 F254. Allow the spots to dry, and develop the chromatogram in a chamber saturated with a solvent system consisting of a mixture of ethyl acetate, isopropanol, and concentrated ammonium hydroxide (18 : 2 : 0.1) until the solvent front has moved about 6 to 7 cm from the point of application. Remove the plate from the chamber, mark the solvent front, and dry. Examine the chromatograms under UV light at 254 nm, and outline the spots with a soft pencil. Spray the plate with *Ferric chloride–potassium ferricyanide reagent:* the R_F value (approximately 0.4 to 0.5) of the principal blue spot under UV and after spraying, obtained from the *Test solution,* corresponds to that obtained from the *Standard solution.*

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

Viscosity ⟨911⟩**:** not less than 400 centipoises, determined using a suitable rotational viscometer with Spindle No. 3, a spindle speed of 100 rpm, and at a temperature of 25 ± 0.1° for the Standard and the sample.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Escherichia coli.* The total aerobic microbial count does not exceed 100 cfu per mL, and the total combined molds and yeasts count does not exceed 10 cfu per mL.

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 25 rpm.

Time: 45 minutes.

Determine the amount of $C_{15}H_{14}N_4O$ dissolved by employing the following method.

Diluent: a mixture of dehydrated alcohol and water (1 : 1).

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (77 : 23). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 10 mg of USP Nevirapine Anhydrous RS and 15 mg of methylparaben into a 250-mL volumetric flask. Dissolve in approximately 2 mL of *Diluent,* and dilute with *Medium* to volume.

Standard solution—Transfer about 28 mg of USP Nevirapine Anhydrous RS, accurately weighed, into a 500-mL volumetric flask. Add 2 mL of *Diluent,* and sonicate for about 1 minute. Note that the Standard will not be completely dissolved at this point. Dilute with *Medium* to volume, and visually examine the solution to ensure that the Standard is completely dissolved. The final concentration is about 0.056 mg of nevirapine per mL.

Test solution—For sample mixing, gently shake the bottle for approximately 10 seconds by inverting it slowly and rotating it from side to side. The sample should be free of air bubbles. Do not sonicate the sample. Using a 1- to 10-mL suitable positive displacement pipet set at 5 mL, withdraw the equivalent of 50 mg of nevirapine. Remove excess Oral Suspension by wiping the outside of the tip carefully so as not to touch the opening of the tip. Introduce the sample into the dissolution vessel over a 1- to 2-second time period by immersing the tip of the pipet midway between the paddle and the side of the vessel, approximately 1 cm below the meniscus. Similarly dispense the Oral Suspension into the other vessels. At 45 minutes, withdraw 5 mL of the solution under test, and pass through a 0.45-µm nylon filter, discarding the first 2 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The chromatograph is equipped with a 214-nm detector, a 3.9-mm × 20-mm guard column that contains packing L1, and a 3.9-mm × 15-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the

peak responses as directed for *Procedure:* the resolution, *R,* between nevirapine and methylparaben is not less than 5.0; and the tailing factor for the nevirapine peak is not more than 1.8. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least 14 minutes, and measure the responses for the nevirapine peaks. Calculate the percentage of $C_{15}H_{14}N_4O$ dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times V \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the *Standard solution;* 900 is the volume, in mL, of the *Medium;* 100 is the conversion factor to percentage; V is the volume, in mL, of Oral Suspension taken; and LC is the Oral Suspension label claim, in mg per mL.

Tolerances—Not less than 80% (Q) of the labeled amount of $C_{15}H_{14}N_4O$ is dissolved in 45 minutes.

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

PROCEDURE FOR CONTENT UNIFORMITY—

Test solution—Proceed as directed for the *Assay preparation* in the *Assay,* except to withdraw the equivalent of 1 dosage unit of Oral Suspension.

pH ⟨791⟩**:** between 5.4 and 6.0.

Related compounds—

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

System suitability solution—Proceed as directed in the *Assay.*

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

Standard solution—Dilute the *Standard stock solution* quantitatively with *Diluent* to obtain a solution having a known concentration of about 0.3 µg of nevirapine per mL.

Weight determination—Use the weight obtained as directed for *Weight determination* in the *Assay.*

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

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay:* the relative standard deviation for replicate injections of the *Standard solution* is not more than 10.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each unknown impurity in the portion of Oral Suspension taken by the formula:

$$200(C/W_U)(W_A/5)(r_U/r_S)(100/L)$$

in which C is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the *Standard solution;* W_U is the sample weight, in g, taken to prepare the *Test solution;* W_A is the weight, in g, of 5 mL of Oral Suspension, obtained as directed for *Weight determination;* L is the labeled amount, in mg per mL, of nevirapine in the Oral Suspension; r_U is the peak response obtained for each impurity in the *Test solution;* and r_S is the peak response for nevirapine in the *Standard solution*. Not more than 0.1% of any individual unknown impurity is found; and not more than 0.2% of total impurities is found. [NOTE—The excipients and their degradation products should not be included in the determination of impurities.]

In-Process Revision

Assay—

Diluent—Prepare a mixture of water and methanol (80 : 20).

Potassium phosphate buffer—Dissolve 13.6 g of monobasic potassium phosphate in approximately 1900 mL of water, and adjust with phosphoric acid to a pH of 3.0. Transfer to a 2000-mL volumetric flask, and dilute with water to volume. Mix, filter, and degas.

Solution A: a mixture of *Potassium phosphate buffer* and acetonitrile (97 : 3).

Solution B: a mixture of *Potassium phosphate buffer* and acetonitrile (76 : 24).

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

Standard stock preparation—Transfer about 50 mg of USP Nevirapine Anhydrous RS, accurately weighed, into a 50-mL volumetric flask. Add 20 mL of methanol, and sonicate with intermittent swirling until the sample dissolves. Add water to about 1 cm below the meniscus, cool to room temperature, and dilute with water to volume. The concentration is about 1 mg of nevirapine per mL.

Standard preparation—Dilute the *Standard stock preparation* quantitatively with *Diluent* to obtain a solution having a known concentration of about 0.3 mg of nevirapine per mL.

Stock impurity preparation—Transfer about 3 mg of USP Nevirapine Related Compound A RS and 3 mg of USP Nevirapine Related Compound B RS, accurately weighed, into a 100-mL volumetric flask, add 20 mL of methanol, and sonicate to dissolve. Add water to about 1 cm below the meniscus, cool to room temperature, dilute with water to volume, and mix.

System suitability solution—Transfer 15.0 mL of *Standard stock preparation* and 2.0 mL of *Stock impurity preparation* into a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Weight determination—Using a 1- to 10-mL suitable pipet and a positive displacement tip, withdraw 5.0 mL of the Oral Suspension. The sample should be free of air bubbles. Dispense into a tared vial, and record the weight of the Oral Suspension to ± 0.1 mg.

Assay preparation—Using a 1- to 10-mL suitable pipet and a positive displacement tip, withdraw the equivalent of 60 mg of nevirapine. The sample should be free of air bubbles. Remove the excess Oral Suspension by wiping the outside of the tip carefully so as not to touch the opening of the tip, and deliver the sample into a 200-mL tared volumetric flask. Record the sample weight to the nearest ± 0.1 mg. Add 40 mL of methanol, and sonicate for about 5 minutes with intermittent swirling. Add water to about 1 cm below the meniscus. Do not shake the flask. Allow the solution to attain room temperature, and dilute with water to volume. Shake the flask gently, and allow to stand for about 5 minutes.

Chromatographic system ⟨621⟩—The liquid chromatograph is equipped with a 254-nm detector, a 4.6-mm × 12.5-mm guard column that contains 5-µm packing L10, and a 4.6-mm × 15-cm analytical column that contains 3.5-µm packing L10. The column temperature is maintained at 35°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–1	100	0	isocratic
1–31	100→0	0→100	linear gradient
31–32	0→100	100→0	linear gradient
32–42	100	0	equilibration

Chromatograph the *System suitability solution* (about 20 µL), and record the peak responses as directed for *Procedure:* the resolution, *R,* between nevirapine and nevirapine related compound A is not less than 3.0, and the resolution, *R,* between nevirapine and nevirapine related compound B is not less than 1.7; and the tailing factor for the nevirapine peak is not more than 1.5. Chromatograph the *Standard preparation,*

and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the nevirapine peak. Calculate the quantity, in mg, of nevirapine ($C_{15}H_{14}N_4O$) in each mL of the Oral Suspension taken by the formula:

$$200(C/W_U)(W_A/5)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the *Standard preparation;* W_U is the sample weight, in g, of Oral Suspension taken to prepare the *Assay preparation;* W_A is the weight, in g, of 5 mL of Oral Suspension obtained as directed for *Weight determination;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(USP30)*

BRIEFING

Norgestimate, *USP 29* page 1560 and page 1390 of *PF* 31(5) [Sept.–Oct. 2005]. It is proposed to change the name of the impurity USP Norgestimate Oxime Mixture RS to USP Deacetylnorgestimate RS to distinguish the impurity from the drug substance which is also an oxime mixture.

(MD-PS: D. Bempong) RTS—C45811

Change to read:

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

■*USP Norgestimate Related Compound A RS.* ~~*USP Norgestimate Oxime Mixture RS.*~~■*USP Deacetylnorgestimate RS.*■2S *(USP30)*■2S *(USP29)*

Change to read:

Limit of residual solvents ⟨467⟩—

Internal standard solution—Prepare a solution of isobutyl alcohol in dimethylformamide containing 2 µL of isobutyl alcohol per 100 mL of solution.

Standard solution—Prepare a solution in *Internal standard solution* containing 5 µL each of acetone, alcohol, chloroform, diisopropyl ether, and methanol per 100 mL of solution.

System suitability solution—Dilute a portion of the *Standard solution* with *Internal standard solution* to obtain a solution containing 0.05 µL each of acetone, alcohol, chloroform, diisopropyl ether, and methanol per 100 mL of solution.

Test solution—Transfer about 40 mg of Norgestimate and 2 mL of *Internal standard solution* to a 5-mL volumetric flask or a suitable vial, and shake well to dissolve.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused-silica capillary column bonded with a 1-µm layer of phase G16, and a split injection system. The detector temperature is about 250°, and the injection port temperature is about 180°. The column temperature is programmed as follows. It is maintained at about 65° for 2.5 minutes, increased at a rate of 35° per minute to 100°, maintained for 2 minutes, then at a rate of 30° per minute increased to 160°, and maintained for 2.5 minutes. The carrier gas is helium, flowing at a rate of about 6 mL per minute, and the split flow rate is about 16 mL per minute. Chromatograph the *Internal standard solution,* the *Standard solution,* and the *System suitability solution,* and record the peak responses as directed for *Procedure:* there are no interfering peaks due to dimethylformamide; the retention time of isobutyl alcohol in the chromatogram of the *Internal standard solution* is between 4 and 5 minutes; the signal-to-noise ratio for alcohol obtained from the *System suitability solution* is not less than 2.0; and the relative standard deviation for replicate injections of the *Standard solution,* determined from the peak response ratios of each solvent to the internal standard, is not more than 3.0%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each solvent in the portion of Norgestimate taken by the formula:

$$200(CD/W)(R_U/R_S)$$

in which C is the concentration, in mL per mL, of each solvent in the *Standard solution; D* is the density, in mg per mL, of each solvent; W is the weight, in mg, of Norgestimate taken to prepare the *Test solution;* and R_U and R_S are the peak response ratios of the appropriate analyte to the internal standard obtained from the *Test solution* and the *Standard solution,* respectively.

■*Option 1:* not■2S *(USP29)*
more than 0.5% each of acetone and alcohol is found; not more than 0.05% of diisopropyl ether is found; not more than 0.006% of chloroform is found; and not more than 0.3% of methanol is found.

■or *Option 2:* meets the requirements.■2S *(USP29)*

Change to read:

Chromatographic purity—

TEST 1—

Diluent, Mobile phase, ~~*System suitability solution,*~~

■*Sensitivity solution,*■2S *(USP29)*
and *Chromatographic system*—Proceed as directed in the *Assay.*

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

Test solution—Use the *Assay preparation.*

In-Process Revision

■*System suitability solution*—Dissolve accurately weighed quantities of USP Norgestimate RS, USP Norgestimate Related Compound A RS and ~~USP Norgestimate–Oxime Mixture RS~~ ■USP Deacetylnorgestimate RS■2S (*USP30*) in *Diluent* to obtain a solution containing about 0.5 mg per mL of each.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 244-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.2 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.50 for ~~syn-17-deacetyl norgestimate,~~ ■*(Z)*-17-deacetylnorgestimate,■2S (*USP30*) about 0.56 for ~~anti-17-deacetyl norgestimate,~~ ■*(E)*-17-deacetylnorgestimate,■2S (*USP30*) about 0.72 for norgestimate related compound A, and 1.0 for ~~norgestimate~~ ■*(E)*-norgestimate;■2S (*USP30*) the resolution, *R,* between ~~syn-17-deacetyl norgestimate and anti-17-deacetyl norgestimate~~ ■*(Z)*-17-deacetylnorgestimate and *(E)*-17-deacetylnorgestimate■2S (*USP30*) is not less than 1.5; and that between ~~anti-17-deacetyl norgestimate~~ ■*(E)*-17-deacetylnorgestimate■2S (*USP30*) and norgestimate related compound A is not less than 1.5.■2S (*USP29*)

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Norgestimate taken by the formula:

$$5000(CP/W)(r_i/Fr_S)$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard solution; P* is the fraction of (*E*)-norgestimate in USP Norgestimate RS; *W* is the weight, in mg, of Norgestimate taken to prepare the *Test solution;* r_i is the peak area for each impurity obtained from the *Test solution; F* is the relative response factor ~~and it is equal to 0.83 for any peak having a relative retention time of 0.50, 1.13 for any peak having a relative retention time of 0.56, 0.85 for any peak having a relative retention time of 0.72, and 1.0 for any other peak;~~

■for each impurity;■2S (*USP29*)
and r_S is the peak area of *(E)*-norgestimate,

■eluting at about 13.5 minutes,■2S (*USP29*)
obtained from the *Standard solution.* ~~Not more than 0.3% of total impurities having relative retention times of 0.50 and 0.56 is found; not more than 0.3% of the impurity having a relative retention time of 0.72 is found; and not more than 0.1% of any other impurity is found.~~

■The impurities meet the requirements specified in the table below.

Impurities	Relative Response Time	Relative Response Factor	Limit (not more than)
~~syn-17-Deacetyl norgestimate~~■*(Z)*-17-Deacetyl-norgestimate■2S (*USP30*)*	0.50	0.83	0.3
~~anti-17-Deacetyl norgestimate~~■*(E)*-Deacetylnorgestimate■2S (*USP30*)*	0.56	1.13	0.3
Norgestimate related compound A (levonorgestrel acetate)	0.72	0.85	0.3%
Any other impurity	—	1.0	0.1%

* Provided as a mixture called ~~USP Norgestimate–Oxime Mixture RS~~ ■USP Deacetylnorgestimate RS;■2S (*USP30*) their combined limits are not more than 0.3%.

■2S (*USP29*)

TEST 2—

Mobile phase—Prepare a filtered and degassed mixture of cyclohexane and absolute alcohol (50 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Norgestimate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL.

System suitability solution—Dilute a portion of the *Standard solution,* quantitatively and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.5 µg per mL.

Test solution—Transfer about 10 mg of Norgestimate, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L20. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for *(E)*-norgestimate is not less than 3.0. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the retention time is about 18.6 minutes for *(E)*-norgestimate; the relative retention times are about 1.0 for *(E)*-norgestimate and 1.1 for *(Z)*-norgestimate; the tailing factor is not more than 1.5; the resolution, *R,* between *(Z)*-norgestimate and *(E)*-norgestimate is not less than 1.5; and the relative standard deviation for replicate injections, determined from the peak area of *(Z)*-norgestimate to *(E)*-norgestimate, is not more than 2.0%.

In-Process Revision

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Norgestimate taken by the formula:

$$1000(CP/W)(r_i / Fr_S)$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard solution;* P is the fraction of *(E)*-norgestimate in USP Norgestimate RS; W is the weight, in mg, of Norgestimate taken to prepare the *Test solution;* r_i is the peak area for each impurity obtained from the *Test solution;* F is the relative response factor and is equal to 1.4 for any peak having a relative retention time of 0.74, 1.5 for any peak having a relative retention time of 0.78, and 1.2 for any peak having a relative retention time of 0.91; and r_S is the peak area of *(E)*-norgestimate obtained from the *Standard solution.* Not more than 0.2% of the impurity having a relative retention time of 0.74 is found; and not more than 0.1% each of the impurities having relative retention times of 0.78 and 0.91 is found. Not more than 1.0% of total impurities is found, the results for *Test 1* and *Test 2* being added.

Change to read:

Assay—

Diluent—Prepare a mixture of methanol and water (4 : 1).

Mobile phase—Prepare a filtered and degassed mixture of water, tetrahydrofuran, and acetonitrile (30 : 11 : 9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Norgestimate RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.5 mg per mL.

~~*System suitability solution*~~

■*Sensitivity solution*—■2S (*USP29*)
Dilute a portion of *Standard preparation,* quantitatively and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.05 µg per mL.

Assay preparation—Transfer about 25 mg of Norgestimate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 244-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at about 40°. Chromatograph the ~~*System suitability solution,*~~

■*Sensitivity solution,*■2S (*USP29*)
and record the peak areas as directed for *Procedure:* the signal-to-noise ratio for *(Z)*-norgestimate is not less than 3.0. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.86 for *(Z)*-norgestimate and 1.0 for *(E)*-norgestimate; the resolution, *R,* between *(Z)*-norgestimate and *(E)*-norgestimate is not less than 1.5; the tailing factor for *(E)*-norgestimate and for *(Z)*-norgestimate is not more than 1.5; and the relative standard deviation for replicate injections, determined from the peak area ratio of *(E)*-norgestimate to *(Z)*-norgestimate, is not more than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{23}H_{31}NO_3$ in the portion of Norgestimate taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard preparation;* and r_U and r_S are the sums of the peak areas of *(Z)*-norgestimate and *(E)*-norgestimate obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the percentages of the *(Z)*- and *(E)*-isomers, U_Z and U_E, respectively, in the portion of Norgestimate taken by the formula:

$$5000(CP/W)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard preparation;* P is the fraction of *(E)*- or *(Z)*-norgestimate in USP Norgestimate RS; W is the weight, in mg, of Norgestimate taken to prepare the *Assay preparation;* and r_U and r_S are the peak responses of the appropriate norgestimate isomer obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the ratio of *(E)*-norgestimate to *(Z)*-norgestimate, that is, the ratio of U_E to U_Z.

BRIEFING

Ondansetron Injection, *USP 29* page 1584 and page 1651 of *PF* 31(6) [Nov.–Dec. 2005]. It is proposed to include in the test for *Chromatographic purity* the injection of the *System suitability solution* from the test for *Limit of ondansetron related compound D* to aid in identifying the peaks due to ondansetron related compound C and ondansetron related compound D. It is also proposed to add a *Note* in the *Procedure* instructing the analyst to disregard the contribution of ondansetron related compound D because it is determined in the test for *Limit of ondansetron related compound D.*

(MD-PP: R. Ravichandran) RTS—C44289

Change to read:

Chromatographic purity—

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

~~*Standard solution*—Proceed as directed for *Standard preparation* in the *Assay.*~~

▲*USP30*

■*System suitability solution*—Use the *System suitability solution* prepared as directed in the test for *Limit of ondansetron related compound D* under *Ondansetron Hydrochloride.*■2S (*USP30*)

Test solution—Use the *Assay preparation*.

Procedure—

■Inject about 20 µL of the *System suitability solution,* record the chromatogram, and identify the peaks due to ondansetron related compound C and ondansetron related compound D based on their approximate relative retention times of 0.35 and 0.37, respectively.■2S (*USP30*)
Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses.

■[NOTE—Ignore the peak due to ondansetron related compound D.]■2S (*USP30*)

In-Process Revision

Calculate the percentage of each impurity in the volume of Injection taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all of the peaks: not more than 0.2% of any individual impurity is found, and the total of all impurities,

▲including the percentage of ondansetron related compound D determined in the test for *Limit of ondansetron related compound D,*▲*USP30* is not more than 0.5%.

BRIEFING

Pancuronium Bromide Injection. Because there is no existing *USP* monograph for this drug product, a new monograph, based on submitted data, is being proposed. The typical migration time for pancuronium bromide in the capillary electrophoresis procedure in the test for *Related compounds* and in the *Assay* is about 10.4 minutes.

(MD-PS: D. Bempong) RTS—C43837

Add the following:

■Pancuronium Bromide Injection

» Pancuronium Bromide Injection is a sterile isoosmotic solution of Pancuronium Bromide in Water for Injection. It contains not less than 92.0 percent and not more than 105.0 percent of the labeled amount of pancuronium bromide ($C_{35}H_{60}Br_2N_2O_4$). It contains a suitable tonicity-adjusting agent.

Packaging and storage—Preserve in tight, light-resistant, single-dose *Containers for Injections,* as described under *Injections* ⟨1⟩, preferably of Type 1 glass. Store in a refrigerator between 2° and 8°, protected from light.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Pancuronium Bromide RS. USP Pancuronium Bromide Related Compound A RS. USP Pancuronium Bromide Related Compound B RS. USP Pancuronium Bromide Related Compound C RS. USP Pancuronium Internal Standard RS. USP Vecuronium Bromide Related Compound C RS.*

Identification—

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

Adsorbent: a 0.2-mm layer of chromatographic silica gel 60 mixture.

Test solution—Pipet a measured volume of Injection, equivalent to 1 mg of pancuronium bromide, into a suitable container, and evaporate at room temperature with the aid of a stream of nitrogen. Dilute with acetonitrile to obtain a solution having a concentration of about 0.5 mg of pancuronium bromide per mL, sonicate for about 1 minute, and centrifuge.

Standard solution—Dissolve an accurately weighed quantity of USP Pancuronium Bromide RS in acetonitrile to obtain a solution having a concentration of about 0.5 mg of pancuronium bromide per mL of acetonitrile.

Application volume: 2 µL.

Developing solvent system: a mixture of 2-propanol, acetonitrile, and a 400 g per L solution of sodium iodide (85 : 10 : 5).

Procedure—Proceed as directed in the chapter. After chromatography is completed, dry the plate at room temperature for at least 30 minutes. Spray the plate with a 20 g per L solution of sodium nitrite, and allow to dry for 5 minutes. Spray the plate with Dragendorff's TS, and cover the plate with a transparent glass cover. Visualize the spots in daylight: the intensity and R_F value of the principal spot obtained from the *Test solution* correspond to those obtained from the *Standard solution.*

B: The migration time of the major peak in the electropherogram of the *Assay preparation* corresponds to that in the electropherogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩**:** not more than 50 USP Endotoxin Units per mg of pancuronium bromide.

pH ⟨791⟩**:** between 3.8 and 4.2.

Particulate matter ⟨788⟩**:** meets the requirements for small-volume injections.

Related compounds (see *Capillary Electrophoresis* ⟨727⟩)—

Operating buffer and *Diluent*—Prepare as directed in the *Assay.*

Internal standard I solution—Dissolve an accurately weighed quantity of USP Vecuronium Bromide Related Compound C RS in *Diluent* to obtain a solution having a known concentration of about 2 µg per mL.

Standard stock solution—Dissolve an accurately weighed quantity of USP Pancuronium Bromide Related Compound A RS, USP Pancuronium Bromide Related Compound B RS, and USP Pancuronium Bromide Related Compound C RS in *Internal standard I solution* to obtain a solution having a known concentration of about 40 µg, 100 µg, and 100 µg per mL, respectively.

Standard solution—Transfer 2.0 mL of the *Standard stock solution* to a 50-mL volumetric flask. Dilute with *Internal standard I solution* to volume, and mix.

Test solution—Pipet a measured volume of Injection, equivalent to 4 mg of pancuronium bromide, into a 20-mL volumetric flask, dilute with *Internal standard I solution* to volume, and mix.

Electrophoretic system (see *Capillary Electrophoresis* ⟨727⟩)—Proceed as directed in the *Assay.* Inject the *Standard solution,* record the electropherogram, and measure the peak responses as directed for *Procedure:* the relative migration times, based on the migration time of the pancuronum bromide, are 0.931, 0.968, 0.974, and 0.939 for pancuronium bromide related compound A, pancuronium bromide related compound B, pancuronium bromide related compound C, and vecuronium bromide related compound C, respectively; the resolution, *R,* between pancuronium bromide related compound B and pancuronium bromide related compound C in the electropherogram of the *Standard solution* is not less than 1.5; and the relative standard deviation for replicate injections of the *Standard solution,* determined from the relative area responses of the impurity peaks, is not more than 10%.

Procedure—For the *Test solution* and the *Standard solution,* proceed as directed in the *Assay* for the *Assay preparation* and the *Standard preparation.* Calculate the percentage of each pancuronium bromide related compound in the portion of Injection taken by the formula:

$$100C_S / C_T[(20 - V)/V](R_U / R_S)$$

in which C_S is the concentration, in mg per mL, of each impurity in the *Standard solution;* C_T is the concentration, in mg per mL, of pancuronium bromide in the Injection; V is the volume, in mL, of Injection taken to prepare the *Test solution;* and R_U and R_S are the ratios of the individual peak area responses of the impurities to the peak area response of vecuronium bromide related compound C in the electropherograms obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.4% of pancuronium bromide related compound A is found; not more than 3.0% of pancuronium bromide related compound B is found; not more than 2.0% of pancuronium bromide related compound C is found; and not more than 5.0% of total impurities is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay (see *Capillary Electrophoresis* ⟨727⟩)—

Diluent: 1 mM phosphoric acid.

Internal standard II solution—Dissolve an accurately weighed quantity of USP Pancuronium Internal Standard RS in *Diluent* to obtain a solution having a known concentration of about 0.15 mg per mL.

Operating buffer—Prepare a solution of tubocurarine chloride in water having a concentration of 2.52 mg per mL. Adjust the solution with a 2.5% phosphoric acid solution to a pH of 3.0, pass through a 0.22-µm filter, and degas.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Pancuronium Bromide RS in *Internal standard II solution* to obtain a solution having a known concentration of about 1 mg per mL.

Standard preparation—Transfer 10 mL of the *Standard stock preparation* to a 50-mL volumetric flask, dilute with *Internal standard II solution* to volume, and mix.

Assay preparation—Pipet a measured volume of Injection, equivalent to 4 mg of pancuronium bromide, into a 20-mL volumetric flask, dilute with *Internal standard II solution* to volume, and mix.

Control solution—Using *Internal standard II solution,* prepare a solution containing 200 µg of pancuronium bromide and each of the following related compounds having the following concentrations: 0.8 µg per mL of USP Pancuronium Bromide Related Compound A RS, 2 µg per mL of USP Pancuronium Bromide Related Compound B RS, and 2 µg per mL of USP Pancuronium Bromide Related Compound C RS.

Electrophoretic system (see *Capillary Electrophoresis* ⟨727⟩)—The capillary electrophoretic system is equipped with a 235-nm and 350-nm detector and a 50-µm × 56-cm capillary that contains a polyvinyl alcohol coating. The capillary is maintained at 20°, and the polarity is positive. Inject the *Standard preparation,* the *Internal standard II solution,* and the *Control solution,* and record the ratio of the peak area responses as directed for *Procedure:* in the electropherogram of the *Internal standard II solution,* the relative area of the impurity peak, which may be present at the position of the pancuronium bromide peak, should contribute not more than 3% with respect to the relative area of the pancuronium bromide peak in the *Standard preparation;* in the electropherogram of the *Control solution,* the resolution, *R,* between pancuronium bromide related compound B and pancuronium bromide related compound C is not less than 1.5, and that between the pancuronium bromide peak and any related compound eluting close to the pancuronium bromide peak is not less than 1.5; and the relative standard deviation for replicate injections of the *Standard preparation,* determined from the relative area responses of the pancuronium bromide peaks, is not more than 1.5%.

Procedure—Before performing each injection, flush the capillary with *Operating buffer* for 3 minutes. Separately inject equal volumes (about 50 mbar for 20 seconds) of the *Standard preparation* and the *Assay preparation,* each injection followed by a coinjection of *Operating buffer* (about 50 mbar for 2 seconds). Between 0 and 1 minute, increase the voltage at an equal rate from 0 to 25 kV; and between minutes 1 and 13 after the hydrodynamic injection, apply a constant voltage of 25 kV. Perform an indirect detection at 350 nm, using a reference wavelength of 235 nm, both with a bandwidth of 8 nm. Calculate the quantity, in mg, of pancuronium bromide ($C_{35}H_{60}Br_2N_2O_4$) in each mL of Injection taken by the formula:

$$C[(20 - V)/V](R_U/R_S)$$

in which C is the concentration, in mg per mL, of USP Pancuronium Bromide RS in the *Standard preparation; V* is the volume, in mL, of Injection taken to prepare the *Assay preparation;* and R_U and R_S are the ratios of the peak area responses of pancuronium bromide to those of the pancuronium internal standard obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP30*)

In-Process Revision

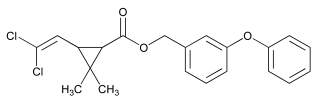
BRIEFING

Permethrin. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedure in the *Assay* is based on analysis performed with the Inertsil-OD-2 brand of L1 column. The typical retention time is about 10.7 minutes for the first eluted isomer of permethrin and about 12.6 minutes for the second eluted isomer.

(MD-OOD: C. Anthony) RTS—C30631

Add the following:

■Permethrin



$C_{21}H_{20}Cl_2O_3$ 391.29

Cyclopropanecarboxylic acid, 3-(2,2-dichloroethenyl)-2,2-dimethyl-, (3-phenoxyphenyl)methyl ester.

m-Phenoxybenzyl (±)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate.

(±)-3-Phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate [*52645-53-1*].

» Permethrin is a mixture of *cis* and *trans* isomers. It contains not less than 23.0 percent and not more than 27.0 percent of the *cis* isomer, not less than 73.0 percent and not more than 77.0 percent of the *trans* isomer, and the sum of both isomers is not less than 98.0 percent and not more than 102.0 percent of $C_{21}H_{20}Cl_2O_3$, calculated on the as-is basis.

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

USP Reference standards ⟨11⟩—*USP Permethrin RS. USP Permethrin Related Compound A RS. USP Permethrin Related Compound B RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

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

Related compounds—[NOTE—Prior to and during sampling, Permethrin and USP Permethrin RS should be gradually warmed to between 65° and 70°, and uniformly mixed by means of a hot plate with mechanical stirring, to preserve the *cis/trans* isomer ratio.]

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

Standard solution—Dissolve accurately weighed quantities of USP Permethrin RS, USP Permethrin Related Compound A RS (3-phenoxybenzyl alcohol), and USP Permethrin Related Compound B RS (3-phenoxybenzaldehyde) in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of 250 µg per mL, 1.25 µg per mL, and 1.25 µg per mL, respectively.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 272-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention time is 1.2 for the *cis* isomer with respect to the *trans* isomer; the resolution, *R,* between the *cis* and *trans* isomers of permethrin is not less than 2.8; the relative standard deviation for replicate injections is not more than 2.0% for the sum of the *cis* and

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trans isomers of permethrin, and not more than 10.0% for permethrin related compound A and permethrin related compound B.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentages of permethrin related compound A and permethrin related compound B in the portion of Permethrin taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Permethrin Related Compound A RS or USP Permethrin Related Compound B RS in the *Standard solution; W* is the weight, in mg, of Permethrin taken; and r_U and r_S are the peak responses for each related compound obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.5% of either permethrin related compound A or permethrin related compound B is found. Calculate the percentage of any other unknown impurity in the portion of Permethrin taken by the formula:

$$100(r_U/r_s)$$

in which r_U is the peak response for each individual impurity other than permethrin related compound A and permethrin related compound B; and r_s is the sum of the peak responses for all of the peaks: not more than 0.5% of any individual impurity is found, and not more than 2.0% of total impurities, including permethrin related compound A and permethrin related compound B is found.

Assay—[NOTE—Prior to and during sampling, Permethrin and USP Permethrin RS should be gradually warmed to between 65° and 70°, and uniformly mixed by means of a hot plate with mechanical stirring, to preserve the *cis/trans* isomer ratio.]

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Permethrin RS in acetonitrile, and dilute quantitatively with *Mobile phase* to obtain a solution having a known concentration of 0.25 mg per mL.

Assay preparation—Transfer about 125 mg of Permethrin, accurately weighed, to a 50-mL volumetric flask, dissolve in acetonitrile, dilute with *Mobile phase* to volume, and mix. Transfer 10 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 272-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the *cis* and *trans* isomers of permethrin is not less than 2.8; and the relative standard deviation for replicate injections is not less than 2.0% for the *cis* and *trans* isomers of permethrin.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{21}H_{20}Cl_20_3$ in the portion of Permethrin taken by the formula:

$$500C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Permethrin RS in the *Standard preparation;* and r_U and r_S are the sums of the peak responses for the *cis* and *trans* isomers obtained from the *Assay preparation* and the *Standard*

preparation, respectively. Calculate the percentage of *cis* or *trans* isomer in the portion of Permethrin taken by the formula:

$$50{,}000(C/W)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of *cis*- or *trans*-permethrin isomer in the *Standard preparation; W* is the weight, in mg, of Permethrin taken; r_U is the peak response for the *cis*- or *trans*-permethrin isomer obtained from the *Assay preparation;* and r_S is the peak response for the *cis*- or *trans*-permethrin isomer obtained from the *Standard preparation.* ■2S (*USP30*)

USP Reference standards ⟨11⟩—*USP Permethrin RS. USP Permethrin Related Compound A RS. USP Permethrin Related Compound B RS.*

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

Microbial limits ⟨61⟩**—**It meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The total aerobic microbial count does not exceed 100 cfu per g or 100 cfu per mL, and the total combined molds and yeasts count does not exceed 10 cfu per g or 10 cfu per mL.

Minimum fill ⟨755⟩**:** meets the requirements.

pH ⟨791⟩**:** between 4.5 and 6.5.

Test solution—Prepare a 10% w/w mixture of the substance under test in a solution containing 2 mg of potassium chloride per 1 mL of water.

Related compounds—[NOTE—Prior to and during sampling, Permethrin Cream and USP Permethrin RS should be gradually warmed to between 65° and 70°, and uniformly mixed by means of a hot plate with mechanical stirring, to preserve the *cis/trans* isomer ratio.]

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

Standard solution—Dissolve accurately weighed quantities of USP Permethrin RS, USP Permethrin Related Compound A RS (3-phenoxybenzyl alcohol), and USP Permethrin Related Compound B RS (3-phenoxybenzaldehyde) in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of 250 µg per mL, 1.25 µg per mL, and 1.25 µg per mL, respectively.

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

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 272-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing

BRIEFING

Permethrin Cream. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedures in the *Assay* are based on analyses performed with the Symmetry brand of L1 column. The typical retention time is about 10.7 minutes for the first eluted isomer of permethrin and about 12.6 minutes for the second eluted isomer.

(MD-OOD: C. Anthony; MSA: R. Tirumalai) RTS—C30631

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Add the following:

■Permethrin Cream

» Permethrin Cream contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of permethrin ($C_{21}H_{20}Cl_2O_3$) in a suitable cream base.

Packaging and storage—Preserve in well-closed containers. Protect from freezing.

L1. The flow rate is 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention time is 1.2 for the *cis* isomer with respect to the *trans* isomer; the resolution, *R,* between the *cis* and *trans* isomers of permethrin is not less than 2.8; and the relative standard deviation for replicate injections is not more than 2.0% for the sum of the *cis* and *trans* isomers of permethrin, and not more than 10.0% for permethrin related compound A and permethrin related compound B.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentages of permethrin related compound A and permethrin related compound B in the portion of Cream taken by the formula:

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

in which C is the concentration, in µg per mL, of USP Permethrin Related Compound A RS or USP Permethrin Related Compound B RS in the *Standard solution; W* is the weight, in mg, of Cream taken; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively, for each related compound: not more than 0.5% of either permethrin related compound A or permethrin related compound B is found. Calculate the percentage of any other unknown impurity in the portion of Cream taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak response for each individual impurity other than permethrin related compound A and permethrin related compound B; and r_s is the sum of the peak responses for all of the peaks: not more than 0.5% of any individual impurity is found, and not more than 2.0% of total impurities, including permethrin related compound A and permethrin related compound B, is found.

Assay—[NOTE—Prior to and during sampling, Permethrin Cream and USP Permethrin RS should be gradually warmed to between 65° and 70°, and uniformly mixed by means of a hot plate with mechanical stirring, to preserve the *cis/trans* isomer ratio.]

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

Assay preparation—Transfer an accurately weighed quantity of Cream, equivalent to about 50 mg of permethrin, to a 200-mL volumetric flask, dissolve in *Mobile phase,* using sonication if necessary, and dilute with *Mobile phase* to volume. Mix well, and pass a portion through a filter having a porosity of 0.45-µm.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 272-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the *cis* and *trans* isomers of permethrin is not less than 2.8; and the relative standard deviation for replicate injections is not more than 2.0% for the *cis* and *trans* isomers of permethrin.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{21}H_{20}Cl_20_3$ in the portion of Cream taken by the formula:

$$200C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Permethrin RS in the *Standard preparation;* and r_U and r_S are the sums of the peak responses for the *cis* and *trans* isomers obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(USP30)*

BRIEFING

PEG 3350 and Electrolytes for Oral Solution, *USP 29* page 1749. The previous revision proposal that was published on page 1393 of *PF* 31(5) [Sept.–Oct. 2005] has been canceled. It is proposed to change the official title of this monograph to Polyethylene Glycol 3350 and Electrolytes for Oral Solution. In accordance with the procedures of the USP Nomenclature Expert Committee, the term PEG is not appropriate for official titles; the proposed revision eliminates its use. In addition, minor editorial style changes have been made. In the absence of any significant adverse comments, the revision to the official title will appear in the *Second Supplement* to *USP 30–NF 25,* but with a delayed implementation date of **August 1, 2012.**

(MD-PS: D. Bempong; NOM: L. Paul) RTS—C44746

Change to read:

~~PEG 3350 and Electrolytes for Oral Solution~~

■Polyethylene Glycol 3350 and Electrolytes for Oral Solution■2S (*USP30*)

(Title for this monograph—to become official August 1, 2012). (Prior to August 1, 2012, the current practice of labeling the article of commerce with the name PEG 3350 and Electrolytes for Oral Solution may be continued. Use of the name Polyethylene Glycol 3350 and Electrolytes for Oral Solution will be permitted as of August 1, 2007, but the use of this name will not be mandatory until August 12, 2012. The 60-month extension will provide the time needed by the manufacturers and users to make necessary changes.)

Change to read:

» ~~PEG 3350 and Electrolytes for Oral Solution~~

■Polyethylene Glycol 3350 and Electrolytes for Oral Solution■2S (*USP30*)
is a mixture of Polyethylene Glycol 3350, Sodium Bicarbonate, Sodium Chloride, Sodium Sulfate (anhydrous), and Potassium Chloride. When constituted as directed in the labeling it contains not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of polyethylene glycol 3350, potassium (K^+), sodium (Na^+), bicarbonate (HCO_3^-), chloride (Cl^-), and sulfate ($SO_4^=$), the labeled amounts per L being 10 mmol (10 mEq) of potassium, 125 mmol (125 mEq) of sodium, 20 mmol (20 mEq) of bicarbonate, 35 mmol (35 mEq) of chloride, and 40 mmol (80 mEq) of sulfate.

Change to read:

Assay for potassium and sodium—

Mobile phase—Dilute 0.5 mL of nitric acid with water to obtain 4000 mL of solution. Degas, and place the solution in a suitable plastic container. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Dissolve a suitable quantity of ammonium bromide in water to obtain a solution having a concentration of about 2 mg per mL.

Standard preparation—To a 100-mL volumetric flask transfer about 90 mg of potassium chloride, previously dried at 105° for 2 hours and accurately weighed, and about 880 mg of sodium chloride, previously dried at 105° for 2 hours and accurately weighed, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 500-mL volumetric flask, add 10.0 mL of *Internal standard solution,* dilute with water to volume, and mix. Pass this solution through a filter having a 0.5-µm or finer porosity, and store the filtrate in a suitable plastic container. This *Standard preparation* contains about 9 µg (0.00012 mEq) of potassium chloride and about 88 µg (0.0015 mEq) of sodium chloride per mL.

Assay preparation—Constitute the contents of a container of ~~PEG 3350 and Electrolytes for Oral Solution~~

■Polyethylene Glycol 3350 and Electrolytes for Oral Solution■2S (*USP30*)
with an accurately measured volume of water, as specified in the labeling. Transfer 6.0 mL of this stock solution, equivalent to about 0.06 mEq of potassium, to a 500-mL volumetric flask, add 10 mL of *Internal standard solution,* dilute with water to volume, and mix. This solution contains about 0.00012 mEq of potassium and 0.0015 mEq of sodium per mL. [NOTE—Reserve the remaining portion of the stock solution for the *Assay for bicarbonate,* and reserve the remaining portion of the *Assay preparation* for the *Assay for chloride and sulfate* and the *Assay for polyethylene glycol 3350*.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector, a 4-mm × 5-cm guard column containing packing L22, and a 4-mm × 30-cm analytical column maintained at 35 ± 1° containing packing L22. The flow rate is about 0.9 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the relative retention times are about 0.6 for sodium, 0.8 for ammonium, and 1.0 for potassium; the resolution, *R,* between the sodium and ammonium peaks is not less than 1.1, and between the ammonium and potassium peaks is not less than 0.9. [NOTE—Maintain column backpressure at less than 1000 pounds per square inch. Backpressure may be reduced by changing the in-line filters and frits in the columns. Column efficiency may be improved by backflushing the analytical column with 30 mL of 0.1 *N* nitric acid or by injecting four successive 100-µL portions of 0.1 *N* nitric acid into the chromatograph.]

Procedure—[NOTE—Use peak heights where peak responses are indicated.] Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the mEq of potassium per L of constituted Oral Solution taken by the formula:

$$(500 / 74.55)(C / 6)(R_U / R_S)$$

in which 74.55 is the molecular weight of potassium chloride; C is the concentration, in µg per mL, of potassium chloride in the *Standard preparation;* and R_U and R_S are the peak response ratios of potassium to ammonium obtained from the *Assay preparation* and the *Standard preparation*, respectively. Calculate the mEq of sodium per L of constituted Oral Solution taken by the formula:

$$(500 / 58.44)(C / 6)(R_U / R_S)$$

in which 58.44 is the molecular weight of sodium chloride; C is the concentration, in µg per mL, of sodium chloride in the *Standard preparation;* and R_U and R_S are the peak response ratios of sodium to ammonium obtained from the *Assay preparation* and the *Standard preparation,* respectively.

In-Process Revision

BRIEFING

Promethazine Hydrochloride, *USP 29* page 1824 and page 365 of *PF* 32(2) [Mar.–Apr. 2006]; **Promethazine Hydrochloride Tablets,** *USP 29* page 1826 and page 367 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to change the name of the impurity Reference Standard USP Promethazine Related Compound A RS to USP Phenothiazine RS, because the currently available USP Phenothiazine RS and USP Promethazine Related Compound A RS are the same compound. The proposed changes are found in the *USP Reference standards* section and in the test for *Related compounds.*

(MD-PS: D. Bempong) RTS—C45837

Change to read:

USP Reference standards ⟨11⟩—*USP Promethazine Hydrochloride RS.* ■~~USP Promethazine Related Compound A RS.~~■ 1S *(USP30)*

■*USP Phenothiazine RS.*■ 2S *(USP30)*

Change to read:

Related ~~substances~~

■compounds—■ 2S *(USP30)*

~~*Standard preparation* and *Standard dilutions*—Dissolve an accurately weighed quantity of USP Promethazine Hydrochloride RS in methylene chloride to obtain a solution containing 10.0 mg per mL (*Standard preparation*). Prepare a series of quantitative dilutions of the *Standard preparation* in methylene chloride to contain 0.2, 0.1, 0.05, and 0.025 mg per mL (*Standard dilutions*) corresponding to 2.0%, 1.0%, 0.5%, and 0.25% of impurities, respectively.~~

~~*Test solution*—Dissolve 100 mg, accurately weighed, of Promethazine Hydrochloride in 10.0 mL of methylene chloride.~~

~~*Procedure*—Using a 20- × 20-cm thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of silica gel mixture, apply 10-µL portions of the *Test preparation,* the *Standard preparation,* and each of the *Standard dilutions* 2.5 cm from the lower edge of the plate. Develop the plate in an unsaturated tank containing a mixture of ethyl acetate, acetone, alcohol, and ammonium hydroxide (90 : 45 : 2 : 1). After the solvent has moved not less than 10 cm, air-dry the plate, and view under short-wavelength UV light: the R_F value of the principal spot obtained from the *Test preparation* corresponds to that from the *Standard preparation.* Estimate the concentration of any other spots observed in the lane for the *Test preparation* by comparison with the *Standard dilutions:* the sum of the impurities is not greater than 2.0%, and no single impurity is greater than 1.0%.~~

■*Buffer solution*—Dissolve 1.35 g of monobasic potassium phosphate in 500 mL of water, and adjust with triethylamine to a pH of 7.0 ± 0.5.

Mobile phase—Prepare a mixture containing 450 mL of *Buffer solution,* 350 mL of acetonitrile, and 200 mL of methanol. Pass the mixture through a membrane filter having a porosity of 0.45 µm, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve suitable quantities of USP Promethazine Hydrochloride RS and ~~USP Promethazine Related Compound A RS~~ USP Phenothiazine RS in *Mobile phase,* and dilute quantitatively with *Mobile phase* to obtain a solution having known concentrations of about 1.0 µg per mL and 0.4 µg per mL, respectively.

Test solution—Transfer 20 mg of Promethazine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, add about 50 mL of *Mobile phase,* and shake to dissolve. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 25°, and the samples are maintained at about 4° in a refrigerated autosampler. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ~~promethazine related compound A~~ phenothiazine and promethazine is not less than 2.0; and the relative standard deviation for replicate injections, calculated for promethazine, is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than two times the retention time of promethazine. Record the chromatograms, and measure the peak responses. Calculate the percentage of ~~promethazine related compound~~

~~A~~ phenothiazine in the portion of Promethazine Hydrochloride taken by the formula:

$$100(C_S / C_U)(r_A / r_S)$$

in which C_S is the concentration, in mg per mL, of ~~USP Promethazine Related Compound A RS~~ USP Phenothiazine RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Promethazine Hydrochloride in the *Test solution;* r_A is the peak response for ~~promethazine related compound A~~ phenothiazine obtained from the *Test solution;* and r_S is the peak response for ~~promethazine related compound A~~ phenothiazine obtained from the *Standard solution*. Calculate the percentage of any other impurity in the portion of Promethazine Hydrochloride taken by the formula:

$$100(1/F)(C_S / C_U)(r_i / r_S)$$

in which F is the relative response factor (see accompanying table for values) for each impurity; C_S is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard solution;* C_U is the concentration, in mg per mL, of Promethazine Hydrochloride in the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for phenothiazine obtained from the *Standard solution.* The limits are as specified in the accompanying table.

Compound Name	Relative Retention Time	Relative Response Factor (F)	Limit (w/w, %)
Promethazine sulfoxide[1]	about 0.13	0.23	0.2
~~Promethazine related compound A (phenothiazine)~~ Phenothiazine	about 0.8	—	0.2
Promethazine hydrochloride	1.0	—	—
Isopromethazine hydrochloride[2]	about 1.6	1.0	0.5
Individual unknown impurity	—	1.0	0.10
Total impurities	—	—	1.0

[1] (2*RS*)-*N,N*-dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine *S*-oxide.
[2] (2*RS*)-*N,N*-dimethyl-2-(10*H*-phenothiazin-10-yl)propan-1-amine.

■2S (*USP30*)

In-Process Revision

BRIEFING

Promethazine Hydrochloride Tablets, *USP 29* page 1826 and page 367 of *PF* 32(2) [Mar.–Apr. 2006]—See briefing under *Promethazine Hydrochloride.*

(MD-PS: D. Bempong) RTS—C45837

Change to read:

USP Reference standards ⟨11⟩—*USP Promethazine Hydrochloride RS.*

■~~*USP Promethazine Related Compound A RS.*~~■1S ~~(*USP30*)~~

■*USP Phenothiazine RS.*■2S (*USP30*)

NOTE—Throughout the following procedures, protect

■from light■2S (*USP30*)
the test or assay specimens, the Reference ~~Standard~~

■Standards,■2S (*USP30*)
and solutions containing them by conducting the procedures without delay, and under subdued light or using low-actinic glassware.

Add the following:

■**Related compounds—**

Buffer solution and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution—Dissolve suitable quantities of USP Promethazine Hydrochloride RS and ~~USP Promethazine Related Compound A RS~~ USP Phenothiazine RS in *Mobile phase,* and dilute with *Mobile phase* to obtain a solution having known concentrations of about 1.0 µg per mL and 0.4 µg per mL, respectively.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 20 mg of promethazine hydrochloride, to a 100-mL volumetric flask, and add about 50 mL of *Mobile phase*. Sonicate for about 1 minute, and shake by mechanical means for 5 minutes. Cool to room temperature, dilute with *Mobile phase* to volume, mix, and pass through a nylon filter having a porosity of 0.45 µm. Discard the first 10 mL of filtrate.

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between ~~promethazine related compound A~~ phenothiazine and promethazine is not less than 2.0; and the relative standard deviation for replicate injections, calculated for promethazine, is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than two times the retention time of promethazine. Record the chromatograms, and measure the peak responses. Calculate the percentage of ~~promethazine related compound A~~ phenothiazine in the portion of Tablets taken by the formula:

$$100(C_S / C_U)(r_A / r_S)$$

in which C_S is the concentration, in mg per mL, of ~~USP Promethazine Related Compound A RS~~ USP Phenothiazine RS in the *Standard solution;* C_U is the concentration, in mg per mL, of promethazine hydrochloride in the *Test solution,* based on the label claim; r_A is the peak response of ~~promethazine related compound A~~ phenothiazine obtained from the *Test solution;* and r_S is the peak response of ~~promethazine related compound A~~ phenothiazine obtained

from the *Standard solution.* Calculate the percentage of any other impurity in the portion of Tablets taken by the formula:

$$100(1/F)(C_S/C_U)(r_i/r_S)$$

in which F is the relative response factor (see accompanying table for values) for each impurity; C_S is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard solution;* C_U is the concentration of promethazine hydrochloride (based on the label claim), in mg per mL, in the *Test solution;* r_i is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of promethazine obtained from the *Standard solution.* The limits are as specified in the accompanying table.

Change to read:

Assay—

~~*Buffered palladium chloride solution*—Transfer 500 mg of palladium chloride to a 250-mL beaker, add 5 mL of hydrochloric acid, and warm on a steam bath. Add 200 mL of hot water in small quantities while stirring until solution is complete. Cool, dilute with water to 500 mL, and mix. Transfer 25 mL of this solution to a 500-mL volumetric flask. Add 50 mL of 1 N sodium acetate and 48 mL of 1 N hydrochloric acid, dilute with water to volume, and mix.~~

~~*Standard preparation*—Transfer about 31 mg of USP Promethazine Hydrochloride RS, accurately weighed, to a low-actinic 250-mL volumetric flask. Dissolve in 0.1 N hydrochloric acid, dilute with 0.1 N hydrochloric acid to volume, and mix.~~

~~*Assay preparation*—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6.25 mg of promethazine hydrochloride, to a low-actinic 125-mL separator. Add 20 mL of saturated potassium chloride solution, 10 mL of 1 N sodium hydroxide, and 10 mL of methanol, and extract the promethazine with three 20-mL portions of *n*-heptane. Filter the heptane extracts through anhydrous sodium sulfate and collect them in a low-actinic 125-mL separator. Extract the promethazine from the *n*-heptane solution with three 15-mL portions of 0.1 N hydrochloric acid, collect the acid extracts in a low-actinic 50-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.~~

~~*Procedure*—Into separate test tubes, pipet 2 mL portions of the *Standard preparation,* the *Assay preparation,* and 0.1 N hydrochloric acid to provide a blank. Add 3.0 mL of *Buffered palladium chloride solution* to each tube, and mix. Concomitantly determine the absorbances of the solutions at the wavelength of maximum absorbance at about 470 nm, using a suitable spectrophotometer, and using the blank in the reference cell. Calculate the quantity, in mg, of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) in the portion of Tablets taken by the formula:~~

~~$$50C(A_U/A_S)$$~~

~~in which C is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard preparation;* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively.~~

■*Buffer solution*—Dissolve 1.35 g of potassium phosphate monobasic in 500 mL of water, and adjust with triethylamine to a pH of 7.0 ± 0.5.

Mobile phase—Mix 450 mL of *Buffer solution,* 350 mL of acetonitrile, and 200 mL of methanol. Pass through a membrane filter having a porosity of 0.45 µm, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Promethazine Hydrochloride RS in *Mobile phase,* and dilute with *Mobile phase* to obtain a solution having a known concentration of about 4 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 50 mg of promethazine

Compound Name	Relative Retention Time	Relative Response Factor (F)	Limit (w/w, %)
Promethazine sulfoxide[1]	about 0.13	0.23	0.2
~~Promethazine-related compound A~~ ~~(phenothiazine)~~ Phenothiazine	about 0.8	—	0.2
Promethazine hydrochloride	1.0	—	—
Isopromethazine hydrochloride[2]	about 1.6	1.0	0.5
Individual unknown impurity	—	1.0	0.2
Total impurities	—	—	1.0

[1] (2*RS*)-*N,N*-Dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine *S*-oxide.
[2] (2*RS*)-*N,N*-Dimethyl-2-(10*H*-phenothiazin-10-yl)propan-1-amine.

■2S (*USP30*)

In-Process Revision

hydrochloride, to a 250-mL volumetric flask, and add about 100 mL of *Mobile phase*. Sonicate for 30 minutes with intermittent shaking, and shake by mechanical means for an additional 30 minutes. Dilute with *Mobile phase* to volume, mix, and pass through a nylon filter having a porosity of 0.45 µm. Discard the first 10 mL of filtrate. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 25°, and the samples are maintained at 4° in a refrigerated autosampler. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the promethazine peaks. Calculate the quantity, in mg, of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) in the portion of Tablets taken by the formula:

$$(250)50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Promethazine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP30*)

BRIEFING

Risperidone Tablets. Because there is no existing USP monograph for this dosage form, a new monograph is being proposed. The liquid chromatographic procedures in the tests for *Dissolution* and *Uniformity of dosage units* were validated with a Zorbax SB brand of L1 column, in which risperidone elutes at about 2 minutes. An alternative column for these two tests is the Inertsil ODS. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* were also validated with a Zorbax SB brand of L1 column. The typical retention time obtained for risperidone in these tests is about 11 minutes.

(MD-PP: R. Ravichandran; BPC: M. Marques) RTS— C44132

Add the following:

■Risperidone Tablets

» Risperidone Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of risperidone ($C_{23}H_{27}FN_4O_2$).

Packaging and storage—Preserve in tight, light-resistant containers. Store at controlled room temperature.

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

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test solution—Grind an appropriate number of Tablets to prepare a 550 ± 50 µg per mL solution of risperidone in ethyl acetate. Shake the solution for 30 minutes, and centrifuge for 20 minutes. Evaporate 5 mL of the supernatant with the aid of a stream of nitrogen to 2 mL on a warm water bath. Add 150 ± 50 mg of KBr powder, mix well, and evaporate to dryness. Grind the dried mixture, and press a small amount into a transparent pellet.

Standard solution—Grind about 2 mg of USP Risperidone RS with about 200 mg of KBr powder, and press into a transparent pellet.

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

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 500 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amount of $C_{23}H_{27}FN_4O_2$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (65 : 35), and add 1 mL of trifluoroacetic acid to each 1 L of the mixture. Adjust with ammonium hydroxide to a pH of 3.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Risperidone RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of about 0.006 mg per mL.

Test solution—Use portions of the solution under test, and pass through a suitable filter having a porosity of 35 µm.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 237-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution* and the *Test solution* as directed for *Procedure:* the retention time of risperidone is about 2.1 minutes, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of $C_{23}H_{27}FN_4O_2$ dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution*, respectively; C_S is the concentration, in mg per mL, of USP Risperidone RS in the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{23}H_{27}FN_4O_2$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩—

Mobile phase and *Chromatographic system*—Proceed as directed for *Dissolution*.

Standard solution—Dissolve an accurately weighed quantity of USP Risperidone RS in a suitable volumetric flask, and dilute quantitatively with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 0.03 mg of risperidone per mL.

Test solution—Transfer one Tablet into a 100-mL volumetric flask, add 50 mL of 0.1 N hydrochloric acid, and shake mechanically for about 30 minutes. Dilute with 0.1 N hydrochloric acid to volume, and mix. Pass a portion of this solution through a suitable filter having a 0.2-µm or finer porosity, and use the filtrate.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the risperidone peak. Calculate the quantitiy, in mg, of risperidone ($C_{23}H_{27}FN_4O_2$) in the portion of Tablets taken by the formula:

$$C(r_U/r_S)100$$

in which C is the concentration, in mg per mL, of USP Risperidone RS in the *Standard solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Related compounds—

Mobile phase and *Diluent*—Proceed as directed in the *Assay.*

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

Diluted sodium hydroxide—To 1 L of water in a beaker, add 0.1 N sodium hydroxide dropwise to obtain a pH of about 8.5.

Diluted hydrogen peroxide—Dilute 1 mL of hydrogen peroxide with water to 500 mL.

Peak identification solution—Suspend 10 mg of USP Risperidone RS in 10 mL of *Diluted sodium hydroxide* in a 100-mL volumetric flask. Store the flask at 90° for 24 hours. Cool the solution to room temperature. Add 10 mL of aqueous *Diluted hydrogen peroxide* to the flask, and store at 90° for an additional two hours. Cool the mixture to room temperature, and dilute with methanol to volume.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph about 20 µL of the *Peak identification solution,* record the peak responses as directed for *Procedure,* and identify the peaks using the relative retention times given in *Table 1:* the resolution, R, between the *trans-N*-oxide and *cis-N*-oxide is not less than 1.2. [NOTE—The approximate relative retention times given in *Table 1* are for identification purposes only.]

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the responses for all of the peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(1/R)(r_i/r_S)$$

in which R is the appropriate relative response factor as listed in *Table 1;* r_i is the peak response for each impurity in the *Test solution;* and r_S is the peak response of risperidone in the *Test solution:* not more than 0.3% of any individual unidentified impurity is found, not more than 0.5% of any individual specified impurity is found, and not more than 1.0% of total impurities is found.

Assay—

Diluent—Prepare a degassed mixture of methanol and water (80 : 20).

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluroacetic acid (80 : 19.5 : 0.1). Adjust with ammonium hydroxide to a pH of 3.0.

Solution B—Prepare a filtered and degassed mixture of water, methanol, and trifluoroacetic acid (61 : 39 : 0.1). Adjust with ammonium hydroxide to a pH of 3.0.

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

Standard preparation—Transfer an accurately weighed quantity of USP Risperidone RS to a suitable volumetric flask, and dissolve in and dilute quantitatively with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Transfer an accurately weighed portion of not fewer than 10 Tablets to a volumetric flask that can accommodate a final concentration of 0.1 mg of risperidone per mL. Add an appropriate amount of water equivalent to 20% of the total volume of the volumetric flask, and mechanically shake for about 30 minutes. Add a volume of methanol equivalent to 60% of the total volume of the volumetric flask, and mechanically shake for about 30 minutes. Dilute with methanol to volume, and mix to obtain the final 0.1 mg per mL concentration. Pass a portion of this solution through a suitable filter having a 0.45-µm or finer porosity, and use the filtrate.

Table 1

Peak Identfication	Approximate Relative Retention Time *(RRT)*	Relative Response Factor *(R)*	Limit of Impurity
Bicyclorisperidone[1]	0.68	0.81	Not more than 0.5%
Risperidone	1.0	1.0	—
Risperidone *trans-N*-oxide[2]	1.65	—	Not quantified. Used for identification and system suitability check only.
Risperidone *cis-N*-oxide[3]	1.81	0.95	Not more than 0.5%
Any other unidentified impurity	—	1.0	Not more than 0.3%
Total impurities	—	—	Not more than 1.0%

[1] 3-(4-fluoro-2-hydroxyphenyl)-1-[2-(6,7,8,9-tetrahydro-2-methyl-4-oxo-*4H*-pyrido-[1,2-a]pyrimidin-3-yl)ethyl]-2-aza-1-azoniabicyclo[2.2.2]oct-2-ene iodide.
[2] *trans*-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-*4H*-pyrido[1,2-a]pyrimidin-4-one, *N*-oxide monohydrate.
[3] *cis*-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-*4H*-pyrido[1,2-a]pyrimidin-4-one, *N*-oxide monohydrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 2.5 mL per minute. The column is maintained at room temperature. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–8	100	0	isocratic
8–16	100→0	0→100	linear gradient
16–20	0	100	isocratic
20–21	0→100	100→0	linear gradient
21–30	100	0	re-equilbration

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor of risperidone is not more than 2.5, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the risperidone peak. Calculate the quantity, in mg, of risperidone ($C_{23}H_{27}FN_4O_2$) in the portion of Tablets taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Risperidone RS in the *Standard preparation;* C_U is the concentration of risperidone in the *Assay preparation;* and r_U and r_S are the peak responses of risperidone obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

In-Process Revision

BRIEFING

Ritonavir, page 3577 of the *First Supplement* and page 370 of *PF* 32(2) [Mar.–Apr. 2006]. The test for *X-ray diffraction* ⟨941⟩ is currently used as one of the *Identification* tests in this monograph because Ritonavir has several polymorphic forms with different solubility properties and thus different bioavailability characteristics. Therefore, it is important to control the polymorphic form of the drug substance for the appropriate use. However, it is also suggested that the control of the polymorph in the drug substance depends on the dosage form and the manufacturing process. For instance, the polymorphic form may not be critical for liquid dosage forms. In addition, *X-ray diffraction* used as an *Identification* test may unnecessarily exclude the use of different polymorphs of the drug substance and can be considered a lock-out specification. Based on these comments, the following revisions have been proposed:

1. The test for *X-ray diffraction* is moved from the *Identification* section to a test section.
2. A statement is added to *X-ray diffraction* that states the test is needed only if the drug substance is used for the solid dosage forms.

These revisions are also consistent with the USP flexible monograph policy which allows the use of different polymorphic forms when approved by FDA. The details of this policy are highlighted in *Policies Relating to Polymorphism, Degree of Hydration, Particle Size, Specific Surface Area, and Impurities* under *Policies and Announcements* on page 690 of *PF* 31(3) [May–June 2005].

(MD-AA: B. Davani) RTS—C43967

Change to read:

Identification—

A: *Infrared Absorption* ⟨~~197S~~⟩

■⟨197⟩—■1S (*USP30*)

Test specimen—Dissolve 50 mg of Ritonavir in 1.0 mL of chloroform. Add 1 drop of this solution to the surface of a potassium bromide or a sodium chloride disk, and evaporate to dryness.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* is within 2% of the retention time of the major peak in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

~~**C:** *X-Ray diffraction* ⟨941⟩—The X-ray diffraction pattern conforms to that of USP Ritonavir RS.~~

■■2S (*USP30*)

Add the following:

■**X-ray diffraction** ⟨941⟩—The X-ray diffraction pattern conforms to that of USP Ritonavir RS if the drug substance is used for the solid dosage forms.■2S (*USP30*)

Change to read:

Related compounds—[NOTE—Ritonavir is ~~alkaline~~

■alkali■1S (*USP30*)
sensitive. All glassware should be prerinsed with distilled water prior to use to remove residual detergent contamination.]

Monobasic potassium phosphate solution (0.03M), Diluent, Solution A, Solution B, and *Mobile phase*—Prepare as directed in the *Assay.*

Standard stock solution and *Intermediate stock solution*—Prepare as directed for *Standard stock preparation* and *Intermediate standard preparation* in the *Assay.*

Ritonavir identity standard solution—Transfer about 50 mg of USP Ritonavir Related Compounds Mixture RS, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Standard solution—Transfer 5.0 mL of the *Intermediate standard solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. [NOTE—This solution may be used for 48 hours if stored at room temperature.]

Test solution—Transfer about 50 mg of Ritonavir, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L26 and is maintained at a constant temperature of about 60°. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibrium
0–60	100	0	isocratic
60–120	100→0	0→100	gradient
120.1	0→100	100→0	step gradient
120.1–155	100	0	isocratic

The run time for the *Standard solution* is 40 minutes and the run time for the *Test solution* is 155 minutes. Chromatograph the *Ritonavir identity standard solution* and the *Standard solution,* and record the responses as directed for *Procedure:* the retention time of ritonavir is between 30 and 35 minutes; the resolution, *R,* between impurity E and impurity F in the *Ritonavir identity standard solution* is not less than 1.0; the ratio of peak (H_p) to valley (H_v) of

■Ritonavir and■1S (*USP30*)
impurity N (regioisomer) is not less than 1; the capacity factor, *k′,* using the main component peak of the first *Standard solution* injection, is not less than 13; the column efficiency, using the main component peak of the first *Standard solution* injection, is not less than 5000 theoretical plates; the tailing factor, using the main component peak of the first *Standard solution* injection, is between 0.8 and 1.2; and the relative standard deviation of the peak area response of the main component peak, for replicate injections of the *Standard solution,* is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Diluent, Ritonavir identity standard solution, Standard solution,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak area responses. Calculate the percentage of each impurity in the portion of Ritonavir taken by the formula:

$$0.0025(W_S/W_T)(R_T/R_S)(1/F)P$$

in which W_S is the the weight, in mg, of USP Ritonavir RS taken to prepare the *Standard solution;* W_T is the weight, in mg, of Ritonavir taken to prepare the *Test solution;* R_T is the area of the impurity peak obtained from the *Test solution;* R_S is the average peak area of ritonavir obtained from the replicate injections of the *Standard solution; F* is the response factor for the impurity (see values in *Table 1*); and *P* is the purity, in percentage, of USP Ritonavir RS taken to prepare the *Standard solution.* Not more than 0.3% of impurity E and O is found; not more than 0.2% of impurity T is found; not more than 0.1% of any other impurity is found; and not more than 1.0% of total impurities is found.

Table 1. Approximate Relative Retention Time (RRT) for Known Related Impurities

Impurity Identity	Common Name	Response Factor	RRT
A + B	Mixture of 2,4-Wing acid and monoacyl valine	—	0.07
C	Monoacylacetamide	—	0.15
D	5-Wing diacyl	1.37	0.24
E	Oxidation impurity	—	0.36
F	Acid hydrolysis product	0.73	0.39
G	Ritonavir hydroperoxide	—	0.45
H	Acid/base by-product	0.76	0.47
I	Ethyl analog	—	0.64
J + K	Mixture of Boc-monoacyl and monoacyl isobutyl carbamate	0.74	0.81
L	Base cyclization product	0.53	0.87
M	2,4-Wing isobutyl ester	—	0.94
N	Regioisomer	—	1.05
O	Isomer #2	—	1.11
P	Di-monoacyl urea	—	1.14
Q	Isomer #4	—	1.23
R	Isomer #1	—	1.32
S	Di-monoacyl valine urea	—	1.62
T	2,4-Wing diacyl	0.73	2.87
U	Triacyl impurity	—	3.20

BRIEFING

Saccharin Calcium, *USP 29* page 1937 and page 3579 of the *First Supplement;* **Saccharin Sodium,** *USP 29* page 1938, page 3580 of the *First Supplement,* and page 1226 of *PF* 31(4) [July–Aug. 2005]. On the basis of data received, the current drying condition "at 105° for 2 hours" in *Identification* test *A* is not sufficient. Therefore, it is proposed to change the specimen drying condition for this test to dry at "105° to constant weight".

(EM1: K. Moore) RTS—C46104

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩—
Test specimen—Dry the specimen at 105° ~~for 2 hours before use.~~

■to constant weight.■2S (*USP30*)

B: To a solution (1 in 10) add 2 drops of methyl red TS, and neutralize with 6 N ammonium hydroxide. Add 3 N hydrochloric acid, dropwise, until the solution is acid to the indicator. Upon the addition of ammonium oxalate TS, a white precipitate is formed. This precipitate is insoluble in 6 N acetic acid but dissolves in hydrochloric acid.

C: Calcium salts moistened with hydrochloric acid impart a transient yellowish-red color to a nonluminous flame.

BRIEFING

Saccharin Sodium, *USP 29* page 1938, page 3580 of the *First Supplement,* and page 1226 of *PF* 31(4) [July–Aug. 2005]—See briefing under *Saccharin Calcium*.

(EM1: K. Moore) RTS—C46102

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩—
Test specimen—Dry the specimen at 105° ~~for 2 hours before use~~

■to constant weight.■2S (*USP30*)

B: To a solution (1 in 10) add 2 mL of 15% potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of ~~potassium pyroantimonate TS~~

■*Potassium pyroantimonate solution,*■2S (*USP29*)
and heat to boiling. Allow to cool in ice water and, if necessary, rub the inside of the test tube with a glass rod. A dense precipitate is formed.

■*Potassium pyroantimonate solution*—Dissolve 2 g of potassium pyroantimonate in 95 mL of hot water. Cool quickly, and add a solution containing 2.5 g of potassium hydroxide in 50 mL of water and 1 mL of sodium hydroxide solution (8.5 in 100). Allow to stand for 24 hours, filter, and dilute with water to 150 mL.■2S (*USP29*)

C: Sodium salts impart an intense yellow color to a nonluminous flame.

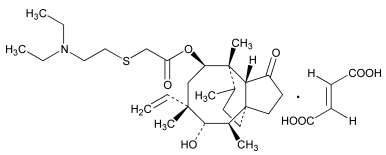
In-Process Revision

BRIEFING

Tiamulin Fumarate, *USP 29* page 2144. On the basis of data and information received, it is proposed to make several changes to this monograph. In the chemical information section, the synonym for this drug substance "Tiamulin Hydrogen Fumarate" is added. This change is for information only and does not reflect a proposed change in official title. The following changes are proposed to reflect the approved quality of this drug substance in distribution. In the Definition, the *Assay* limits are changed to not less than 97.0 percent and not more than 102.0 percent on the dried basis. The upper limit for the *Melting temperature* is raised from 149° to 152°. In the test for *Chromatographic purity* the impurity limit is raised from not more than 2.0% to not more than 3.0%.

(VET: I. DeVeau) RTS—C44528

Change to read:



$C_{28}H_{47}NO_4S \cdot C_4H_4O_4$ 609.82

■Tiamulin Hydrogen Fumarate.■2S (*USP30*)

Acetic acid, [[2-(diethylaminoethyl]thio]-, 6-ethenyl-decahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3a*H*-cyclopentacycloocten-8-yl ester [3a*S*-(3aα,4*β*,5α,6α,8-*β*,9α,9a*β*,10*S**)]-, (*E*)-2-butenedioate (1 : 1) (salt).
[[2-(Diethylamino)ethyl]thio]acetic acid 8-ester with (3a*S*,4*R*,5*S*,6*S*,8*R*,9*R*,9a*R*,10*R*)-octahydro-5,8-dihydroxy-4,6,9,10-tetramethyl-6-vinyl-3a,9-propano-3a*H*-cyclopentacycloocten-1(4*H*)-one fumarate (1 : 1) (salt) [*55297-96-6*].

Change to read:

» Tiamulin Fumarate contains not less than ~~98.0~~ ■97.0■2S (*USP30*) percent and not more than 102.0 percent of $C_{28}H_{47}NO_4S \cdot C_4H_4O_4$, calculated on the dried basis.

Change to read:

Melting temperature ⟨741⟩: between 143° and ~~149°~~ ■152°.■2S (*USP30*)

Change to read:

Chromatographic purity—

Dilute perchloric acid solution, Buffer solution, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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

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

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatogram, identify the tiamulin fumarate peak, and measure all the peak responses. [NOTE—Possible tiamulin fumarate impurities include, but are not limited to, pleuromutilin, mutilin, 14-acetyl mutilin, 11-monoacetyl mutilin, tiamulin related compound A, 11,14-diacetyl mutilin, 8-dimethylderivative, bisdimethyl-thioderivative, and 11-ketoderivative, their retention times, relative to tiamulin fumarate, being about 0.25, 0.3, 0.5, 0.6, 0.8, 1.1, 1.3, 1.4, and 2.3, respectively.] Calculate the area percentage of each impurity, relative to tiamulin fumarate, in the portion of Tiamulin Fumarate taken by the formula:

$$100(r_i / r_U)$$

in which r_i and r_U are the peak responses of each impurity and tiamulin fumarate, respectively: not more than 1.0% of any identified impurity is found; not more than 0.5% of any unidentified impurity is found; and not more than ~~2.0%~~ ■3.0%■2S (*USP30*) of total impurities is found.

BRIEFING

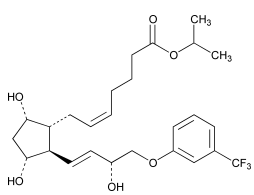
Travoprost, page 1119 of *PF* 31(4) [July–Aug. 2005]. On the basis of comments received, it is proposed to make the following changes:

1. Indicate that the *Assay* calculation is based on the anhydrous and solvent-free basis.
2. Revise the cautionary statement.
3. In *Identification* test *A,* replace *Infrared Absorption* with *Thin-Layer Chromatographic Identification Test*.
4. In the test for *Limit of ethyl acetate,* change the column inner diameter.
5. In the test for *Limit of ethyl acetate,* change the retention time of ethyl acetate and add a *Note*.
6. In *Table 1* in the test for *Related compounds,* change the impurity names and the relative response factor for the 15-*epi* diastereomer.

(MD-OOD: F. Mao) RTS—C43225

Add the following:

■Travoprost



$C_{26}H_{35}F_3O_6$ 500.55

[1*R*-[1α(*Z*),2β(1*E*,3*R**),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethyl ester.

(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1*E*,3*R*)-3-hydroxy-4-[(α,α,α-trifluoro-*m*-isopropyl-tolyl)oxy]-1-butenyl]cyclopentyl]-5-heptenoate [*157283-68-6*].

» Travoprost contains not less than 96.0 percent and not more than 102.0 percent of $C_{26}H_{35}F_3O_6$, calculated on the anhydrous and solvent-free basis.

Caution—Great care should be taken to avoid ~~inhalation and~~ contact with the body.

Packaging and storage—Preserve at –25° to –15° in tight, light-resistant containers under a nitrogen atmosphere.

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

Identification—

A: ~~*Infrared Absorption* ⟨197F⟩~~ *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Use the *Assay preparation.*

Standard solution—Use USP Travoprost RS.

Developing solvent system: a mixture of ethyl acetate and ethanol (4 : 1).

Spray reagent: 20% solution of phosphomolybdic acid in ethanol.

Procedure—Separately apply 20 µL each of the *Test solution* and the *Standard solution* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with silica gel that contains 20% silver nitrate. [NOTE—To keep the spot size small, it is usually necessary to apply approximately 1 to 2 µL at a time, allowing the spot to dry between each application.] Proceed as directed in the chapter. Spray the plate with *Spray reagent,* and heat it in an oven at 80° to 100°. The travoprost will appear as black spots.

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

Specific rotation ⟨781S⟩**:** from +52.0° to +58.0°, at 365 nm.

Test solution: 20 mg per mL, in dehydrated alcohol.

Water, *Method Ia* ⟨921⟩**:** not more than 1.0%, determined on a 0.2-g specimen. Use a solvent mixture of acetonitrile and methanol (1 : 1) and a titrant for which 1 mL is equivalent to 2 mg of water.

Limit of ethyl acetate—

Standard solution—Dilute an accurately measured quantity of ethyl acetate in *N,N*-dimethylacetamide to obtain a solution having a known concentration of about 50 µg per mL.

Test solution—Dissolve an accurately weighed quantity of Travoprost in *N,N*-dimethylacetamide to obtain a solution having a concentration of about 20 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and contains a ~~0.53-m~~ 0.53-mm × 30-m column coated with a 1-µm film of liquid phase G16. The carrier gas is helium, flowing at a rate of 4 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 55° for 6 minutes, then the temperature is increased at a rate of 25° per minute to 240° and maintained at 240° for 20 minutes. The injection port temperature is maintained at 140°, and the detector temperature is maintained at 240°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the retention time is about ~~3.5 minutes~~ 2 to 5 minutes for ethyl acetate [NOTE—For the purpose of the peak identification, the approximate retention time range of ethyl acetate is given.]; the resolution, *R,* between ethyl acetate and any adjacent peak is not less than 1.5; and the relative standard deviation for replicate injections is not more than 15.0%.

In-Process Revision

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the concentration, in ppm, of ethyl acetate in the portion of Travoprost taken by the formula:

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

in which C_S is the concentration, in µg per mL, of ethyl acetate in the *Standard solution;* C_U is the concentration, in g per mL, of Travoprost in the *Test solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; not more than 5000 ppm of ethyl acetate is found.

Related compounds—

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

Test solution—Use the *Assay preparation*.

Procedure—Inject a volume (about 100 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Travoprost taken by the formula:

$$100(1/F)(r_i / r_s)$$

in which F is the relative response factor for each impurity; r_i is the individual peak response of each individual impurity; and r_s is the sum of the responses of all the peaks. In addition to not exceeding the limits for each impurity in *Table 1,* not more than 0.1% of any other individual impurity is found, and not more than 4.0 % of total impurities is found.

Assay—

Buffer—Add 2.0 mL of phosphoric acid to 1 L of water. Adjust with sodium hydroxide to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (7 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Use USP Travopost RS without dilution (0.5 mg per mL).

Assay preparation—Transfer about 25 mg of Travoprost, accurately weighed, to a 50-mL volumetric flask, and dissolve in 15 mL of acetonitrile. Add 25 mL of water, mix, and wait until the solution reaches room temperature. Dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 3.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between travoprost and any adjacent peak is not less than 1.5; the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{26}H_{35}F_3O_6$ in the portion of Travoprost taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Travoprost RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

In-Process Revision

Table 1

Name	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
~~acid derivative~~ USP Travoprost Related Compound A RS~~+~~	about 0.11	1.0	0.2
epoxide derivative~~2~~ [1]	about 0.55	1.0	0.4
15-*epi* diastereomer~~3~~ [2]	about 0.90	~~1.0~~ 1.1	0.1
5,6-*trans* isomer~~4~~ [3]	about 1.16	1.0	3.5
15-keto derivative~~5~~ [4]	about 1.45	1.6	0.3

~~+~~ ~~acid derivative—(5*Z*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid~~

~~2~~ [1] ~~epoxide derivative—~~(5*Z*,~~13*E*~~)-(9*S*,11*R*,15~~*RS*~~)-9,11,15-Trihydroxy-~~12,13~~13,14-~~dihydro~~ epoxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,~~13~~-prostadienoic acid, isopropyl ester;

~~3~~ [2] ~~15-epi diastereomer—~~(5*Z*,13*E*)-(9*S*,11*R*,15*S*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester

~~4~~ [3] ~~5,6-trans isomer—~~(5*E*,13*E*)-(9*S*,11*R*,15*R*)-9,11,15-Trihydroxy-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester

~~5~~ [4] ~~15-keto derivative—~~(5*Z*,13*E*)-(9*S*,11*R*~~,15*R*~~)-9,11,-Dihydroxy-15-oxo-16-(*m*-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester

BRIEFING

Travoprost Ophthalmic Solution, page 1121 of *PF* 31(4) [July–Aug. 2005]. On the basis of comments received, it is proposed to revise the cautionary statement. It is also proposed to revise the limit of travoprost related compound A in the test for *Limit of travoprost related compound A*.

(MD-OOD: F. Mao) RTS—C43225

Add the following:

■Travoprost Ophthalmic Solution

» Travoprost Ophthalmic Solution is a sterile buffered aqueous solution of Travoprost. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of travoprost ($C_{26}H_{35}F_3O_6$). It may contain suitable stabilizers, buffers, and antimicrobial agents.

Caution—Great care should be taken to avoid ~~inhalation of Travoprost and~~ exposure to the body.

Packaging and storage—Preserve in tight, light-resistant containers. Store between 2° to 25°.

USP Reference standards ⟨11⟩—*USP Travoprost RS. USP Travoprost Related Compound A RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Sterility—It meets the requirements under *Sterility Tests* ⟨71⟩ when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined.*

pH ⟨791⟩**:** between 5.5 and 6.5.

Limit of travoprost related compound A—

Buffer—Add 2.0 mL of phosphoric acid to 2.0 L of water, and adjust with sodium hydroxide to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (19 : 6). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

In-Process Revision

Standard solution—Dilute USP Travoprost Related Compound A RS with a mixture of water and acetonitrile (80 : 20), and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.3 µg of travoprost related compound A per mL.

Test solution—Use the Ophthalmic Solution without dilution.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 3.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of USP Travoprost Related Compound A RS in each mL of the Ophthalmic Solution taken by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Travoprost Related Compound A RS in the *Standard solution;* and r_U and r_S are the peak responses of travoprost related compound A obtained from the *Test solution* and the *Standard solution,* respectively: not more than ~~0.3%~~ 0.2% is found.

Limit of degradation products—

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

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

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

Procedure—Measure the responses for the 5,6-*trans* isomer and the 15-keto derivative. Calculate the quantity, in mg, of each degradation product in each mL of the Ophthalmic Solution taken by the formula:

$$(C/F)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of travoprost in the *Standard solution; F* is the relative response factor for each known degradation product; r_U is the peak response for each degradation product obtained from the *Test solution;* and r_S is the travoprost peak response obtained from the *Standard solution:* not more than 5.0% of the 5,6-*trans* isomer (relative retention time of about 1.1 and relative response factor, F, = 1.0) is found; not more than 0.3% of the 15-keto derivative (relative retention time of about 1.4 and relative response factor, F, = 1.7) is found; and the sum of all degradation products, including the amount of travoprost related compound A obtained in the test for the *Limit of travoprost related compound A* is not more than 5.5%.

Assay—

Buffer—Dissolve 4.35 g of sodium 1-octanesulfonate, in 2.0 L of water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (33 : 17). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dilute USP Travoprost RS with a mixture of water and acetonitrile (7 : 3), and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.04 mg of travoprost per mL.

Assay preparation—Use the Ophthalmic Solution without dilution.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as

directed for *Procedure:* the resolution, *R,* between travoprost and any adjacent peak is not less than 1.5; the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections for the travoprost peak is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of travoprost ($C_{26}H_{35}F_3O_6$) in each mL of the Ophthalmic Solution taken by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Travoprost RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(USP30)*

BRIEFING

Triamcinolone Diacetate, *USP 29* page 2186. Because this monograph provides a test for *Water* and not a test for *Loss on drying,* it is proposed to revise the Definition and *Identification* test *B* to delete references to "dried basis" determinations and to indicate that determinations are made on the "anhydrous basis".

(MD-PS: D. Bempong) RTS—C44818

Change to read:

» Triamcinolone Diacetate contains not less than 97.0 percent and not more than 103.0 percent of $C_{25}H_{31}FO_8$, calculated on the ~~dried basis~~

■anhydrous basis.■2S *(USP30)*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 20 µg per mL.
Medium: dehydrated alcohol.
Absorptivities at 238 nm, calculated on the ~~dried basis~~

■anhydrous basis,■2S *(USP30)* do not differ by more than 3.0%.

DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Cat's Claw, page 1071 of *PF* 30(3) [May–June 2004]; **Powdered Cat's Claw,** page 1075 of *PF* 30(3) [May–June 2004]; **Powdered Cat's Claw Extract,** page 1075 of *PF* 30(3) [May–June 2004]; **Cat's Claw Capsules,** page 1077 of *PF* 30(3) [May–June 2004]; **Cat's Claw Tablets,** page 1078 of *PF* 30(3) [May–June 2004]. These new monographs, which previously appeared in *Pharmacopeial Previews,* are now forwarded with some changes to *In-Process Revision.* Changes are proposed in *Identification* test *A* and the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles* in order to improve the chromatographic procedures. Changes are also proposed in the test for *Microbial enumeration* to comply with the general chapter *Microbiological Attributes of Nonsterile Nutritional and Dietary Supplements* ⟨2023⟩.

(DSB: M. Sharaf) RTS—C45484

Add the following:

■Cat's Claw

» Cat's Claw consists of the inner bark of the stems of *Uncaria tomentosa* (Willd.) DC. (Fam. Rubiaceae). It contains not less than 0.3 percent of pentacyclic oxindole alkaloids, calculated on the dried basis, as the sum of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine.

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

Labeling—The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.*

Botanic characteristics—[NOTE—The pharmacopeial article is constituted only by the stem inner bark of *U. tomentosa* (Willd.) DC. Descriptions of other parts of the plant are given to aid in the collection of the right species. Compliance should be determined using the entire monograph and not only the botanical description.]

Macroscopic—Cat's Claw is a woody vine with a main stem up to 20 cm in diameter and 30 m long. The branches are obtusely quadrangular and generally puberulous. Stipules in the buds are densely tomentose in the upper side (different from *U. guianensis* in which the stipules are glabrous) with the hairs, often with curved tips, meshed together and with the longer hairs of the leaf helping to connect the pair of stipules along the margins, but split when older (different from *U. guianensis* in which the stipules separate early in the bud development). Thorns are straight to sickle-shaped, not spirally twisted (different from *U. guianensis*), very pungent and woody, from 8 to 20 mm long and 3 to 6 mm wide. When recently cut, the color of the inner bark can be whitish gray, yellowish brown, or dark red, with longitudinal fissures and persistent rhytidome. The internal part has a slightly dusty fibrous and laminar texture with a characteristic ferruginous dust and an extremely astringent taste. The terminal branches have a quadrangular section and yellowish green internal medulla.

Microscopic—The periderm with cork (phellem) is constituted by 6 to 8 rows of cells having walls evenly thickened, a compressed phellogen [NOTE—The periderm and phellogen should be absent in the pharmacopeial article], and a phelloderm with 1 to 7 rows of sclereids. The secondary cortex with concentric rings of fibers are separated by rings of parenchyma; rings of fibers are frequently interrupted by radial rows of parenchyma cells (predominately 1 cell broad) or narrow medullary rays (few cells broad), forming rectangular bundles of fibers in a regular network; in longitudinal view the fibers appear with numerous conspicuous pits; calcium oxalate microcrystals (sand-like) are abundant in the parenchyma, but usually absent as large polyhedral crystals or in the form of styloids with bifurcated endings, the latter forms typically present in the parenchyma of *U. guianensis;* a brown substance is dispersed in parenchyma cells; starch is abundant, granules are solitary (circular in outline, up to 10 µm in diameter) or compound (2 to 3 components up to 15 µm in diameter).

Identification—

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

Test solution—Transfer about ~~1 g~~ 5 g of the powdered Cat's Claw to a screw-capped centrifuge tube. Add 10 mL of methanol, and sonicate for 5 minutes, shaking occasionally. Heat the mixture in a water bath at 60° for 15 minutes, cool, and filter. Apply 20 µL to the plate in bands that are 1 cm in length.

Standard solution—~~Transfer about 100 mg of USP Powdered Cat's Claw Extract RS to a screw-capped centrifuge tube. Add 10 mL of methanol, and sonicate for 5 minutes, shaking occasionally. Heat in a water bath at 60° for 15 minutes, cool, and filter. Apply 20 µL to the plate in bands that are 1 cm in length.~~ Transfer about 100 mg of USP Powdered Cat's Claw Extract RS to a screw-capped centrifuge tube. Add 2 mL of methanol, and sonicate for 5 minutes, shaking occasionally, cap, heat in a water bath at 60° for 15 minutes, cool, and centrifuge. Apply 20 µL to the plate in bands that are 1 cm in length.

Developing solvent system—Prepare a solution of ethyl acetate and hexane (95 : 5).

Spray reagent A—Dissolve 0.85 g of basic bismuth nitrate in 10 mL of glacial acetic acid and 40 mL of water by heating. Filter if necessary (Solution A). Dissolve 8 g of potassium

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iodide in 30 mL of water (Solution B). Mix Solution A and Solution B (1 : 1) to obtain a stock solution. Dilute 1 mL of the stock solution with 2 mL of glacial acetic acid and 10 mL of water.

Spray reagent B—Use a 10% solution of sodium nitrite in water.

Procedure—Develop the chromatogram to a length of not less than 12 cm, and dry the plate in a current of air. Examine the plates under short UV light: ~~the chromatogram obtained from the *Test solution* shows quenching zones that correspond in R_F value to those for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine in the chromatogram obtained from the *Standard solution.* Other quenching zones of varying intensities may be observed in the chromatogram obtained from the *Test solution.*~~ the chromatogram obtained from the *Test solution* shows multiple zones that correspond in R_F values to those observed in the chromatogram obtained from the *Standard solution.* Other zones of varying intensities may be observed in the chromatogram obtained from the *Test solution.*

Spray the plate with *Spray reagent A* followed by *Spray reagent B,* and examine the plate under daylight: ~~the chromatogram obtained from the *Test solution* shows orange-brown zones that correspond in color and R_F value to those for speciophylline, pteropodine, and isopteropodine in the chromatogram obtained from the *Standard solution.* Other colored zones of varying intensities may be observed in the chromatogram obtained from the *Test solution.*~~ the chromatogram obtained from the *Test solution* shows multiple orange-brown zones that correspond in color and R_F values to those observed in the chromatogram obtained from the *Standard solution.* Other colored zones of varying intensities may be observed in the chromatogram obtained from the *Test solution.*

B: The chromatogram of the *Test solution* exhibits peaks for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention times that correspond to those in the chromatogram of *Standard solution 1,* as obtained in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles.*

Microbial enumeration ⟨2021⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic microbial count does not exceed 10^5 per g, the total combined molds and yeasts count does not exceed 10^3 per g, ~~and the enterobacterial count is not more than 10^2 per g.~~ and the bile-tolerant Gram-negative bacteria does not exceed 10^3 per g.

Loss on drying ⟨731⟩—Dry at 105° for 2 hours: it loses not more than 7.0% of its weight.

Foreign organic matter ⟨561⟩**:** not more than 2.0%.

Total ash ⟨561⟩**:** not more than 8.0%.

Acid-insoluble ash ⟨561⟩**:** not more than 2.0%.

Pesticide residues ⟨561⟩**:** meets the requirements.

Heavy metals, *Method III* ⟨231⟩**:** not more than 20 µg per g.

Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles—

Solution A—Prepare a filtered and degassed 10 mM pH 7.0 phosphate buffer by mixing 6 mL of 1 N sodium hydroxide, 10 mL of 1 M monobasic potassium phosphate, and sufficient water to make 1000 mL, and adjusting to a pH of 7.0 ± 0.1 by adding more of either solution.

Solution B—Use filtered and degassed acetonitrile.

Solution C—Prepare a filtered and degassed solution of methanol and glacial acetic acid (99 : 1).

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

Standard solution 1—Dissolve an accurately weighed quantity of USP Powdered Cat's Claw Extract RS in methanol, shaking for 1 minute. Dilute with methanol to

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obtain a solution having a known concentration of about 0.5 mg of the labeled amount of total oxindole alkaloids per mL. Pass through a filter having a 0.45-µm or finer porosity.

Standard solution 2—Dissolve an accurately weighed quantity of USP Isopteropodine RS in methanol. Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL. Pass through a nylon filter having a 0.45-µm or finer porosity.

Test solution—Accurately weigh approximately 750 mg of ground Cat's Claw, and place in a 10-mL centrifuge tube. Sonicate with 2.5 mL of methanol for 10 minutes. Centrifuge, and transfer this solution to a 10-mL volumetric flask. Repeat the above extraction three additional times combining the extracts in the 10-mL volumetric flask, and dilute with methanol to volume. Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a 0.45-µm or finer porosity, discarding the first part of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 245-nm detector and a 4.6-mm × 10-cm column that contains ~~end packed~~ endcapped 3-µm packing L1. The flow rate is about 0.75 mL per minute. The chromatograph is programmed as follows. Inject into the chromatograph *Standard solution 1,* and record the peak responses as directed for *Procedure:* the chromatograms obtained are similar to the Reference Chromatogram provided with the USP Powdered Cat's Claw Extract RS; the tailing factor for isopteropodine is not more than 2.0; and the relative standard deviation for replicate injections of *Standard solution 1* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of *Standard solution 1, Standard solution 2,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention times of the peaks corresponding to speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine by comparison of the chromatogram of *Standard solution 1* ~~with that obtained from the Reference Chromatogram.~~ with the Reference Chromatogram provided with the lot of the USP Powdered Cat's Claw Extract RS used. Separately calculate the percentages of speciophylline, uncarine F, mitraphylline, isomitraphylline, rhynchophylline, isorhynchophylline, pteropodine, and isopteropodine in the portion of Cat's Claw taken by the formula:

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

in which C is the concentration, in mg per mL, of USP Isopteropodine RS in *Standard solution 2; W* is the weight, in g, of Cat's Claw taken to prepare the *Test solution;* r_U is the peak response for each relevant alkaloid obtained from the *Test solution;* and r_S is the peak response for isopteropodine obtained from *Standard solution 2*. Calculate the content of pentacyclic oxindole alkaloids by adding the percentages of speciophylline, uncarine F, mitraphylline, isomitraphylline,

Time (minutes)	*Solution A* (%)	*Solution B* (%)	*Solution C* (%)	Elution
0–17	65	35	0	isocratic
~~17–22~~ 17–25	65→50	35→50	0	linear gradient
~~22–28~~ 25–30	50	50	0	isocratic
~~28–29~~ 30–31	50→0	50→0	0→100	linear gradient
~~29–34~~ 31–36	0	0	100	isocratic
~~34–39~~ 36–39	0→65	0→35	100→0	linear gradient
39–49	65	35	0	equilibration

pteropodine, and isopteropodine. Calculate the content of tetracyclic oxindole alkaloids by adding the individual percentages of rhynchophylline and isorhynchophylline: not more than 0.05 percent of tetracyclic oxindole alkaloids is found.■2S (*USP30*)

BRIEFING

Powdered Cat's Claw, page 1075 of *PF* 30(3) [May–June 2004]—See briefing under *Cat's Claw.*

(DSB: M. Sharaf) RTS—C45499

Add the following:

■Powdered Cat's Claw

» Powdered Cat's Claw is Cat's Claw reduced to a powder or very fine powder. It contains not less than 0.3 percent of pentacyclic oxindole alkaloids, calculated on the dried basis, as the sum of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine.

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

Labeling—The label states the Latin binomial and, following the official name, the part of the plant from which the article was derived.

USP Reference standards ⟨11⟩—*USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.*

Botanic characteristics—Presence of fragments of cork and suberized cells, with cell walls evenly thickened. Presence of phelloderm sclereids. Fragments of fibers crossed by vascular rays are darkened due to the presence of sand-like calcium oxalate microcrystals. Solitary or two- to three-compound starch grains up to 15 μm in diameter. Absence of styloids, typically present in *U. guianensis.*

Other requirements—It meets the requirements of the tests for *Identification, Microbial enumeration, Loss on drying, Total ash, Acid-insoluble ash, Pesticide residues, Heavy metals,* and *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids* under *Cat's Claw.*■2S (*USP30*)

BRIEFING

Powdered Cat's Claw Extract, page 1075 of *PF* 30(3) [May–June 2004]—See briefing under *Cat's Claw.*

(DSB: M. Sharaf) RTS—C45502

Add the following:

■Powdered Cat's Claw Extract

» Powdered Cat's Claw Extract is prepared from Cat's Claw by extraction with hydroalcoholic mixtures or other suitable solvents. The ratio of plant material to extract is between 4 : 1 and 6 : 1. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of pentacyclic oxindole alkaloids, calculated on the dried basis, as the sum of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine. It may contain suitable added substances.

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

Labeling—The label states the Latin binomial and, following the official name, the part of the plant from which the article was prepared. The label also indicates the content of pentacyclic oxindole alkaloids, the extracting solvent or solvent mixture used for preparation, and the ratio of the starting crude plant material to Powdered Extract. It meets the requirements for *Labeling* under *Botanical Extracts* ⟨565⟩.

USP Reference standards ⟨11⟩—*USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.*

Identification—

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

Standard solution, Developing solvent system, Spray reagent A, Spray reagent B, and *Procedure*—Proceed as directed for *Thin-Layer Chromatographic Identification Test* ⟨201⟩ under *Cat's Claw.*

Test solution—Shake a quantity of Powdered Extract, equivalent to 25 mg of the labeled amount of pentacyclic oxindole alkaloids, in 20 mL of methanol. Allow to stand for 15 minutes before use.

B: The chromatogram of the *Test solution* exhibits peaks for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention times that correspond to those in the chromatogram of *Standard solution 1,* as obtained in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids.* The sum of the peak areas for the tetracyclic oxindole alkaloids rhynchophylline and isorhynchophylline is less than 25% of the total peak areas detected for pentacyclic oxindole alkaloids.

Microbial enumeration ⟨2021⟩**:** meet the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic microbial count does not exceed 10^4 per g, and the total combined molds and yeasts count does not exceed 10^3 per g. ~~, and the enterobacterial count is not more than 10^2 per g.~~

Loss on drying ⟨731⟩**—**Dry 1g at 105° for 2 hours: it loses not more than 10.0% of its weight.

Heavy metals, *Method II* ⟨231⟩**:** not more than 10 µg per g.

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

Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles—

Solution A, Solution B, Solution C, Mobile phase, Standard solution 1, Standard solution 2, and *Chromatographic system*—Proceed as directed in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindoles* under *Cat's Claw.*

Test solution—Transfer an accurately weighed quantity of Powdered Extract, equivalent to about 5 mg of the labeled content of pentacyclic oxindole alkaloids, to a 10-mL centrifuge tube. Add 2.5 mL of methanol, and sonicate for 10 minutes. Centrifuge, and transfer the supernatant to a 10-mL volumetric flask. Repeat the above extraction three additional times combining the extracts in the 10-mL volumetric flask, and dilute with methanol to volume. Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a 0.45-µm or finer porosity, discarding the first part of the filtrate. ~~Centrifuge, or pass through a filter having a 0.45-µm or finer porosity.~~

Procedure—Proceed as directed in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids* under *Cat's Claw.* Separately calculate the percentage of each relevant alkaloid in the portion of Powdered Extract taken by the formula:

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

in which W is the weight, in g, of Powdered Extract taken to prepare the *Test solution;* and the other terms are as defined therein. Calculate the percentage of pentacyclic oxindole alkaloids in the Powdered Extract taken by adding the individual percentages of speciophylline, uncarine F, mitra-

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phylline, isomitraphylline, pteropodine, and isopteropodine. Calculate the percentage of tetracyclic oxindole alkaloids in the Powdered Extract taken by adding the individual percentages of rhynchophylline and isorhynchophylline: not more than 25% of the labeled amount of pentacyclic oxindole alkaloids is found.

Other requirements—It meets the requirements for *Residual Solvents* and *Pesticide Residues* under *Botanical Extracts* ⟨565⟩.■2S (*USP30*)

BRIEFING

Cat's Claw Capsules, page 1077 of *PF* 30(3) [May–June 2004]—See briefing under *Cat's Claw.*

(DSB: M. Sharaf) RTS—C45503

Add the following:

■Cat's Claw Capsules

» Cat's Claw Capsules contain Powdered Cat's Claw Extract. Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Powdered Extract, calculated as pentacyclic oxindole alkaloids.

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

Labeling—The label states the Latin binomial and, following the official name, the article from which the Capsules were prepared. If prepared with Extract, the label also indicates the quantity, in mg, of Extract per Capsule and the content, in mg, of pentacyclic oxindole alkaloids per 100 mg of Powdered Extract.

USP Reference standards ⟨11⟩—*USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.*

Identification—The chromatogram of the *Test solution* exhibits peaks for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention times that correspond to those in the chromatogram of *Standard solution 1,* as obtained in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids*. The content of tetracyclic oxindole alkaloids, calculated as the sum of rhynchophylline and isorhynchophylline, is not more than 25% of the labeled amount of pentacyclic oxindole alkaloids.

Microbial enumeration ⟨2021⟩: meet the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic microbial count does not exceed 10^4 per g, and the total combined molds and yeasts count does not exceed 10^3 per g. ~~, and the enterobacterial count is not more than 10^2 per g.~~

Disintegration ⟨2040⟩: meet the requirements for disintegration of botanical dosage forms.

Weight variation ⟨2091⟩: meet the requirements.

Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids—

Solution A, Solution B, Solution C, Mobile phase, Standard solution 1, Standard solution 2, and *Chromatographic system*—Proceed as directed in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids* under *Cat's Claw.*

Test solution—Weigh accurately the contents of not fewer than 20 Capsules, and pulverize, using a mortar and pestle. Transfer an accurately weighed quantity of the powder, equivalent to 20 mg of the labeled amount of pentacyclic oxindole alkaloids, to a 50-mL centrifuge tube. Sonicate with 10 mL of methanol for 10 minutes. Centrifuge, and transfer this solution to a 50-mL volumetric flask. Repeat the above extraction three additional times combining the extracts in the 50-mL volumetric flask, and dilute with methanol to volume.

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Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a 0.45-µm or finer porosity, discarding the first part of the filtrate.

Procedure—Proceed as directed in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids* under *Cat's Claw*. Calculate the content of each relevant alkaloid, in mg, in the portion of Capsules taken by the formula:

$$50C(r_U / r_S)$$

in which the terms are as defined therein. Calculate the content of total pentacyclic oxindole alkaloids by adding the individual contents of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine. Calculate the content of tetracyclic oxindole alkaloids by adding the individual contents of rhynchophylline and isorhynchophylline: not more than 25% of the labeled amount of pentacyclic oxindole alkaloids is found. ■2S (*USP30*)

BRIEFING

Cat's Claw Tablets, page 1078 of *PF* 30(3) [May–June 2004]—See briefing under *Cat's Claw.*

(DSB: M. Sharaf) RTS—C45504

Add the following:

■Cat's Claw Tablets

» Cat's Claw Tablets contain Powdered Cat's Claw Extract. Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Powdered Extract, calculated as pentacyclic oxindole alkaloids.

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

Labeling—The label states the Latin binomial and, following the official name, the article from which Tablets were prepared. The label also indicates the quantity, in mg, of Powdered Extract per Tablet. Label Tablets to indicate the content, in mg, of pentacyclic oxindole alkaloids per 100 mg of Powdered Extract.

USP Reference standards ⟨11⟩—*USP Isopteropodine RS. USP Powdered Cat's Claw Extract RS.*

Identification—The chromatogram of the *Test solution* exhibits peaks for speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine at retention times that correspond to those in the chromatogram of *Standard solution 1,* as obtained in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids*. The content of tetracyclic oxindole alkaloids, calculated as the sum of rhynchophylline and isorhynchophylline, is not more than 25% of the labeled amount of pentacyclic oxindole alkaloids.

Microbial enumeration ⟨2021⟩**:** meet the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic microbial count does not exceed 10^4 per g, and the total combined molds and yeasts count does not exceed 10^3 per g. ~~, and the enterobacterial count is not more than 10^2 per g.~~

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Disintegration ⟨2040⟩**:** meet the requirements for disintegration of botanical dosage forms.

Weight variation ⟨2091⟩**:** meet the requirements.

Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids—

Solution A, Solution B, Solution C, Mobile phase, Standard solution 1, Standard solution 2, and *Chromatographic system*—Proceed as directed in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids* under *Cat's Claw.*

Test solution—Weigh accurately not fewer than 20 Tablets, and pulverize, using a mortar and pestle. Transfer an accurately weighed quantity of the powder, equivalent to 20 mg of the labeled amount of pentacyclic oxindole alkaloids, to a 50-mL centrifuge tube. Sonicate with 10 mL of methanol for 10 minutes. Centrifuge, and transfer this solution to a 50-mL volumetric flask. Repeat the above extraction three additional times combining the extracts in the 50-mL volumetric flask, and dilute with methanol to volume. Transfer about 3 mL of the solution to a test tube containing 300 mg of polyamide powder, and shake for 1 minute. Pass through a nylon filter having a 0.45-µm or finer porosity, discarding the first part of the filtrate.

Procedure—Proceed as directed in the test for *Content of pentacyclic oxindole alkaloids and limit of tetracyclic oxindole alkaloids* under *Cat's Claw.* Calculate the content of each relevant alkaloid, in mg, in the portion of Tablets taken by the formula:

$$50C(r_U / r_S)$$

in which the terms are as defined therein. Calculate the content of total pentacyclic oxindole alkaloids by adding the individual contents of speciophylline, uncarine F, mitraphylline, isomitraphylline, pteropodine, and isopteropodine. Calculate the content of tetracyclic oxindole alkaloids by adding the individual contents of rhynchophylline and isorhynchophylline: not more than 25% of the labeled amount of pentacyclic oxindole alkaloids is found. ■2S (*USP30*)

BRIEFING

Black Cohosh, Powdered Black Cohosh, Powdered Black Cohosh Extract, Black Cohosh Tablets. These monographs, previously proposed in *PF* 28(5) [Sept.–Oct. 2002], have been canceled, and new monographs are proposed, with the following changes: in the *Identification* tests, changes were made, and a third test has been added. In *Identification* test *C,* it is proposed that the ratio of the peak areas of cimigenol–arabinoside to cimigenol–xyloside be not less than 0.4, as determined in the chromatogram of the test for *Content of triterpene glycosides.* This ratio, based on data available to USP, is proposed as a way to differentiate *Actaea racemosa* from *Cimicifuga foetida.* The *Microbial enumeration* test has been changed to comply with the general chapter *Microbial Attributes of Nonsterile Nutritional and Dietary Supplements* ⟨2023⟩. A test for *Loss on drying* has been added. Corrections have been made in the table showing relative retention times of characteristic markers in the test for *Content of triterpene glycosides.*

(DSB: M. Sharaf) RTS—C39733

Add the following:

■Black Cohosh

» Black Cohosh consists of the dried rhizome and roots of *Actaea racemosa* L. [*Cimicifuga racemosa* (L.) Nutt.] (Fam. Ranunculaceae). It is harvested in the summer. It contains not less than 0.4 percent of triterpene glycosides, calculated as 23-*epi*-26-deoxyactein* ($C_{37}H_{56}O_{10}$) on the dried basis.

Packaging and storage—Preserve in a well-closed, light-resistant container. Protect from moisture, and store at room temperature.

* 23-*epi*-26-deoxyactein is sometimes referred to as 27-deoxyactein.

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Labeling—The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Actein RS. USP 23-epi-26-Deoxyactein RS. USP Powdered Black Cohosh Extract RS.*

Botanic characteristics—

Macroscopic—The Black Cohosh rhizome is dark brown, longitudinally grooved, rough, strongly knotty, and somewhat curled and irregular. It is 15 cm long and up to 2.5 cm thick. The upper surface is covered with numerous round scars of the earlier stalks; laterally, it is clearly curled, and the lower surface is covered with thin, longitudinally grooved, dark brown, easily breakable roots. The fracture is horny and fibrous. The transverse surface shows a thin outer bark surrounding a ring of numerous pale, narrow wedges of vascular tissue alternating with dark medullary rays and a large central pith. Black Cohosh roots are dark brown, between 1 and 3 mm in diameter, brittle, nearly cylindrical or obtusely quadrangular, and longitudinally wrinkled. The fracture is short. The transverse surface shows a distinct cambium line separating a wide outer bark from a central region composed of three to six wedges of lignified xylem tissue united by their apices and separated by broad nonlignified medullary rays.

Microscopic—In a surface view, suberous epidermal cells are tabular with moderately thickened walls. The parenchymatous cortex is filled with starch. Xylem wedges are lignified and composed of numerous small vessels with bordered pits or reticulately thickened walls, thin-walled fibers, and xylem parenchyma. The parenchyma of the pith is unlignified. Medullary rays are filled with starch granules, which are spherical or polygonal and are mostly simple or two to three compounded but can be up to six compounded. Individual starch granules are between 3 and 15 µm in diameter, each with a somewhat central slit-shaped hilum.

Identification—

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

Adsorbent: chromatographic silica gel mixture with an average particle size of 10 to 15 µm (TLC plates).

Test solution—Transfer about 5 g of powdered Black Cohosh to a screw-capped centrifuge tube, add 10 mL of a mixture of alcohol and water (7 : 3), and heat on a steam bath for 10 minutes. Centrifuge, and use the clear supernatant.

Standard solution 1—Dissolve about 100 mg of USP Powdered Black Cohosh Extract RS in 1 mL of methanol.

Standard solution 2—Dissolve amounts of USP Actein RS, USP 23-*epi*-26-Deoxyactein RS, and isoferulic acid in methanol to obtain a solution having concentrations of about 1 mg per mL each.

Application volume: 10 µL.

Developing solvent system—Use the upper phase of a mixture of butyl alcohol, water, and glacial acetic acid (50 : 40 : 10).

Spray reagent—Prepare a mixture of methanol, glacial acetic acid, sulfuric acid, and *p*-anisaldehyde (85 : 10 : 5 : 0.5). [NOTE—Store in a refrigerator. The reagent is colorless; discard if color appears.]

Procedure—Develop the chromatograms until the solvent front has moved about 15 cm, and dry the plate with the aid of a current of air. Examine the plate under UV light at a wavelength of 365 nm: the chromatogram of the *Test solution* exhibits main zones similar in position and color to the main zones in the chromatogram of *Standard solution 1*. In the upper third of the plate, the chromatogram of the *Test solution* exhibits a blue fluorescent zone at the level of the zone due to isoferulic acid in the chromatogram of *Standard solution 2*. Spray the plate with *Spray reagent,* heat at 100° for 5 minutes, and examine in daylight. The chromatogram of the *Test solution* exhibits main zones similar in position and color to the main zones in the chromatogram of *Standard solution 1*. The chromatogram of *Standard solution 2* exhibits red-violet zones due to actein and 23-*epi*-26-deoxyactein. The

chromatogram of the *Test solution* exhibits several greenish-brown spots in the lower third of the plate and several violet zones above; two of these violet zones occur at R_F values similar to those due to actein and 23-*epi*-26-deoxyactein in the chromatogram of *Standard solution 2*.

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

Adsorbent: chromatographic silica gel mixture with an average particle size of 5 µm (HPTLC plates).

Test solution—Transfer about 0.5 g of powdered Black Cohosh to a screw-capped tube, add 5 mL of methanol, sonicate for 10 minutes, and filter into a 10-mL volumetric flask. Wash the residue on the filter paper four times, using 1 mL of methanol for each washing; add the washings to the volumetric flask; and dilute with methanol to volume.

Standard solution 1—Use about 0.5 mL of the *Standard solution 1* that was prepared in *Identification* test *A,* and dilute with methanol to 2 mL.

Standard solution 2—Use about 1.0 mL of the *Standard solution 2* that was prepared in *Identification* test *A,* and dilute with methanol to 5 mL.

Application volume: 2 µL as an 8-mm band.

Developing solvent system—Prepare a mixture of toluene, ethyl formate, and formic acid (50 : 30 : 20).

Spray reagent—Proceed as directed for *Identification* test *A.*

Procedure—Develop the chromatograms until the solvent front has moved about two-thirds of the length of the plate, and dry the plate with the aid of a current of air. Spray the plate with *Spray reagent,* heat at 100° for 5 minutes, and examine in daylight. The chromatogram of the *Test solution* exhibits main zones similar in position and color to the main zones in the chromatogram of *Standard solution 1.* The chromatogram of *Standard solution 2* exhibits red-violet zones due to actein and 23-*epi*-26-deoxyactein at R_F values of about 0.5 and 0.4, respectively. The chromatogram of the *Test solution* exhibits zones similar in color and R_F values to those due to actein and 23-*epi*-26-deoxyactein in the chromatogram of *Standard solution 2*.

C: The chromatogram of the *Test solution* exhibits peaks for cimiracemoside A, 26-deoxycimicifugoside, (26*S*)-actein, 23-*epi*-26-deoxyactein, cimigenol–arabinoside, and cimigenol–xyloside at retention times corresponding to those compounds in the chromatogram of the *Standard solution*, as obtained in the test for *Content of triterpene glycosides*. The ratio of the peak areas of cimigenol–arabinoside to cimigenol–xyloside is not less than 0.4 (distinction from *Cimicifuga foetida*).

Microbial enumeration ⟨2021⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*. The total aerobic microbial count does not exceed 10^5 cfu per g, the total combined molds and yeast count does not exceed 10^3 cfu per g, and the bile-tolerant Gram-negative bacteria count does not exceed 10^3 cfu per g.

Loss on drying ⟨731⟩—Dry it at 105° for two hours: it loses not more than 12.0% of its weight.

Foreign organic matter ⟨561⟩**:** not more than 2.0% of foreign organic matter, and not more than 5.0% of stem bases.

Total ash ⟨561⟩**:** not more than 10.0%.

Acid-insoluble ash ⟨561⟩**:** not more than 4.0%.

Alcohol-soluble extractives, *Method 2* ⟨561⟩**:** not less than 8.0%, using a mixture of alcohol and water (1 : 1) instead of alcohol.

Pesticide residues ⟨561⟩**:** meets the requirements.

Heavy metals ⟨231⟩**:** not more than 10 µg per g.

Content of triterpene glycosides—

Solution A—Use filtered and degassed 0.05% trifluoroacetic acid in water.

Solution B—Use filtered and degassed acetonitrile.

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

System suitability solution—Dissolve amounts of USP Actein RS and USP 23-*epi*-26-Deoxyactein RS in methanol to obtain a solution having concentrations of about 0.1 mg per mL of each.

Standard solution—Dissolve an accurately weighed quantity of USP Powdered Black Cohosh Extract RS in methanol with shaking for 1 minute, and dilute with methanol to obtain a solution having a known concentration of about 30 mg per mL. Pass through a membrane filter having a 0.45-µm or finer porosity.

23-epi-26-Deoxyactein standard solutions—Dissolve an accurately weighed quantity of USP 23-*epi*-26-Deoxyactein RS in methanol with shaking for 1 minute. Dilute quantitatively, and stepwise if necessary, to obtain solutions having known concentrations of about 500, 100, 50, 25, and 12.5 µg per mL. Pass through a membrane filter having a 0.45-µm or finer porosity.

Test solution—Accurately weigh approximately 750 mg of ground plant material, and place into a 20-mL polytef-capped centrifuge tube. Pipet 15 mL of methanol, mix, sonicate for 30 minutes, centrifuge, and transfer the supernatant to an evaporation flask. Repeat the extraction twice. Evaporate the combined extracts under vacuum at 45° to 50°. Dissolve the residue in methanol, and quantitatively transfer to a 10-mL volumetric flask. Dilute with methanol to volume, and pass through a membrane filter having a 0.45-µm or finer porosity.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with an evaporative light-scattering detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.6 mL per minute. The column temperature is maintained at 35°. The detector is set up according to the manufacturer's instruction in order to achieve a signal-to-noise ratio of not less than 10 for the 12.5 µg per mL *23-epi-26-Deoxyactein standard solution.* The chromatograph is programmed as follows.

Time (minutes)	Water (%)	*Solution A* (%)	*Solution B* (%)	Elution
0–8	0	80	20	isocratic
8–15	68	0	32	isocratic
15–55	68→36	0	32→64	linear gradient
55–65	36→5	0	64→95	linear gradient
65–70	5	0	95	isocratic
70–85	5→0	0→80	95→20	linear gradient

Chromatograph the *Standard solution,* the 100 µg per mL *23-epi-26-Deoxyactein standard solution*, and the *System suitability solution,* and record the peak responses as directed for *Procedure:* the chromatogram of the *Standard solution* is similar to the Reference Chromatogram provided with the lot of USP Powdered Black Cohosh Extract RS; the resolution, *R,* between the (26*S*)-actein and the 23-*epi*-26-deoxyactein peaks in the chromatogram of the *System suitability solution* is not less than 1.0; the tailing factor for the 23-*epi*-26-deoxyactein peak in the chromatogram of the 100 µg per mL *23-epi-26-Deoxyactein standard solution* is not more than 2.0; and the relative standard deviation of the logarithm of the area responses for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *System suitability solution, the 23-epi-26-Deoxyactein standard solutions*, the *Standard solution,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Using the chromatogram of the *Standard solution* and the Reference Chromatogram provided with the lot of USP Powdered Black Cohosh Extract RS, identify the retention times of the peaks

corresponding to the triterpene glycosides. The approximate relative retention times of the triterpene glycosides are provided in the following table.

Compound	Relative Retention Time
Cimicifugoside H-1	0.61
Cimiracemoside A	0.78
(26*R*)-Actein	0.94
26-Deoxycimicifugoside	0.96
(26*S*)-Actein	0.98
23-*epi*-26-Deoxyactein	1.00
Acetyl-shengmanol–xyloside	1.03
Cimigenol–arabinoside	1.08
Cimigenol–xyloside (cimicifugoside)	1.13
26-Deoxyactein	1.22
25-Acetyl-cimigenol–arabinoside	1.60
(24*S*)-25-Acetyl-cimigenol–xyloside	1.64
25-*O*-Methyl-cimigenol–arabinoside	1.90
25-*O*-Methyl-cimigenol–xyloside	1.93

Plot the logarithms of the peak area responses versus the logarithms of the concentrations, in µg per mL, of the *23-epi-26-Deoxyactein standard solutions,* and determine the regression line using a least-squares analysis. The correlation coefficient for the regression line is not less than 0.995. From the graphs so obtained, determine the concentration, *C*, in µg per mL, of the relevant analyte in the *Test solution*. Separately calculate the percentages of cimicifugoside H-1, cimiracemoside A, (26*R*)-actein, 26-deoxycimicifugoside, (26*S*)-actein, 23-*epi*-26-deoxyactein, acetyl-shengmanol–xyloside, cimigenol–arabinoside, cimigenol–xyloside (cimicifugoside), 26-deoxyactein, 25-acetyl-cimigenol–arabinoside, (24*S*)-25-acetyl-cimigenol–xyloside, 25-*O*-methyl-cimigenol–arabinoside, and 25-*O*-methyl-cimigenol–xyloside as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$) in the portion of Black Cohosh taken by the formula:

$$(C/W)$$

in which *C* is the concentration, in µg per mL, of the relevant analyte in the *Test solution,* as obtained above; and *W* is the weight, in mg, of Black Cohosh taken to prepare the *Test solution*. Calculate the content of triterpene glycosides, in percentage, in the portion of Black Cohosh taken by adding all of the percentages calculated for the individual analytes.■2S (*USP30*)

BRIEFING

Powdered Black Cohosh—See briefing under *Black Cohosh.*

(DSB: M. Sharaf) RTS—C39927

Add the following:

■Powdered Black Cohosh

» Powdered Black Cohosh is Black Cohosh reduced to a powder or a very fine powder. It contains not less than 0.4 percent of triterpene glycosides, calculated as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$) on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers, and protect from moisture.

Labeling—The label states the Latin binomial and, following the official name, the parts of the plant from which the article was derived.

In-Process Revision

USP Reference standards ⟨11⟩—*USP Powdered Black Cohosh Extract RS. USP 23-epi-26-Deoxyactein RS.*

Botanic characteristics—The material is a light to dark brown powder, is odorless or has a slight odor, and has an acrid and bitter taste. It shows numerous starch granules with concentric striations, simple or compound. The individual granules are spherical or more or less polygonal and are between 3 and 15 µm in diameter, each with a somewhat central slit-shaped hilum. Vessels with bordered pits occur, as do lignified fibers. Reddish to brown fragments of suberized epidermis with more or less tabular cells occur.

Other requirements—It meets the requirements of the tests for *Identification, Microbial enumeration, Loss on drying, Total ash, Acid-insoluble ash, Alcohol-soluble extractives, Pesticide residues, Heavy metals,* and *Content of triterpene glycosides* under *Black Cohosh*.■2S *(USP30)*

BRIEFING

Powdered Black Cohosh Extract—See briefing under *Black Cohosh.*

(DSB: M. Sharaf) RTS—C39927

Add the following:

■Powdered Black Cohosh Extract

» Powdered Black Cohosh Extract is prepared from Black Cohosh by extraction with hydroalcoholic mixtures or other suitable solvents. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of triterpene glycosides, calculated as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$) on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store in a cool place.

Labeling—It meets the requirements for *Labeling* under *Botanical Extracts* ⟨565⟩. Label it to indicate the content of triterpene glycosides, in percentage, calculated as 23-epi-26-deoxyactein.

USP Reference standards ⟨11⟩—*USP Actein RS. USP Powdered Black Cohosh Extract RS. USP 23-epi-26-Deoxyactein RS.*

Identification—

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

Test solution—Shake a quantity of Powdered Extract, equivalent to about 25 mg of triterpene glycosides, in 10 mL of methanol. Allow to stand for 15 minutes before use.

Standard solution 1, Standard solution 2, Developing solvent system, Spray reagent, and *Procedure*—Proceed as directed for *Identification* test *A* under *Black Cohosh*.

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

Test solution—Dilute 1 mL of the solution prepared in *Identification* test *A* with methanol to 10 mL.

Standard solution 1, Standard solution 2, Developing solvent system, Spray reagent, and *Procedure*—Proceed as directed for *Identification* test *B* under *Black Cohosh*.

C: The chromatogram of the *Test solution* exhibits peaks for cimiracemoside A, 26-deoxycimicifugoside, (26*S*) actein, 23-*epi*-26-deoxyactein, cimigenol–arabinoside, and cimigenol–xyloside at retention times corresponding to those compounds in the chromatogram of the *Standard solution,* as obtained in the test for *Content of triterpene glycosides*. The ratio of the peak areas of cimigenol–arabinoside to cimigenol–xyloside is not less than 0.4 (distinction from *Cimicifuga foetida*).

Microbial enumeration ⟨2021⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*. The total bacterial count does not exceed 10^4 cfu per g, and the total combined molds and yeasts count does not exceed 10^3 cfu per g.

Loss on drying ⟨731⟩**:** not more than 5.0%.

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

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

Content of triterpene glycosides—

Solution A, Solution B, Mobile phase, System suitability solution, Standard solution, 23-epi-26-Deoxyactein standard solutions, and *Chromatographic system*—Proceed as directed in the test for *Content of triterpene glycosides* under *Black Cohosh.*

Test solution—Transfer an accurately weighed quantity of Powdered Extract, equivalent to about 7.5 mg of triterpene glycosides, to a 10-mL volumetric flask, add 7 mL of methanol, and sonicate for 30 minutes. Dilute with methanol to volume, and mix. Centrifuge, or pass through a filter having a 0.45-µm or finer porosity.

Procedure—Proceed as directed in the test for *Content of triterpene glycosides* under *Black Cohosh*. Calculate the content of triterpene glycosides, in percentage, in the portion of Powdered Extract taken by adding all of the percentages calculated for individual analytes.

Other requirements—It meets the requirements for *Residual Solvents* and *Pesticide Residues* under *Botanical Extracts* ⟨565⟩.■2S (*USP30*)

BRIEFING

Black Cohosh Fluidextract. A new monograph is proposed for *Black Cohosh Fluidextract,* an article used in the manufacture of some black cohosh products. See also briefing under *Black Cohosh.*

(DSB: M. Sharaf) RTS—C45567

Add the following:

■Black Cohosh Fluidextract

» Black Cohosh Fluidextract is prepared from Black Cohosh by extraction with hydroalcoholic mixtures or isopropanol–water mixtures. Each mL contains the extracted constituents of 1 g of the plant material. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of triterpene glycosides, calculated as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$).

Packaging and storage—Preserve in tight, light-resistant containers, and store in a cool place.

Labeling—It meets the requirements for *Labeling* under *Botanical Extracts* ⟨565⟩. Label it to indicate the content, in percentage, of triterpene glycosides, calculated as 23-*epi*-26-deoxyactein.

USP Reference standards ⟨11⟩—*USP Actein RS. USP Powdered Black Cohosh Extract RS. USP 23*-epi-*26-Deoxyactein RS.*

Identification—

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

Test solution—Use the Fluidextract.

Standard solution 1, Standard solution 2, Developing solvent system, Spray reagent, and *Procedure*—Proceed as directed for *Identification* test *A* under *Black Cohosh*.

In-Process Revision

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

Test solution—Use the Fluidextract, diluting if necessary with a suitable solvent to obtain a solution containing about 0.25 mg per mL of triterpene glycosides.

Standard solution 1, Standard solution 2, Developing solvent system, Spray reagent, and *Procedure*—Proceed as directed for *Identification* test *B* under *Black Cohosh*.

C: The chromatogram of the *Test solution* exhibits peaks for cimiracemoside A, 26-deoxycimicifugoside, (26*S*)-actein, 23-*epi*-26-deoxyactein, cimigenol-arabinoside, and cimigenol-xyloside at retention times corresponding to those compounds in the chromatogram of the *Standard solution,* as obtained in the test for *Content of triterpene glycosides*. The ratio of the peak areas of cimigenol-arabinoside to cimigenol-xyloside is not less than 0.4 (in distinction from *Cimicifuga foetida*).

Microbial enumeration ⟨2021⟩—The total bacterial count does not exceed 10^4 per g, and the total combined molds and yeasts count does not exceed 10^3 per g.

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

Content of triterpene glycosides—

*Solution A, Solution B, Mobile phase, System suitability solution, Standard solution, 23-*epi*-26-Deoxyactein standard solutions,* and *Chromatographic system*—Proceed as directed in the test for *Content of triterpene glycosides* under *Black Cohosh.*

Test solution—Use the Fluidextract, diluting if necessary with a suitable solvent to obtain a solution containing about 0.75 mg per mL of triterpene glycosides. Centrifuge, or pass through a filter having a 0.45-µm or finer porosity.

Procedure—Proceed as directed in the test for *Content of triterpene glycosides* under *Black Cohosh*. Calculate the content of triterpene glycosides, in percentage, in the portion of Fluidextract taken by adding the percentages calculated for the individual analytes.

Other requirements—It meets the requirements for *Residual Solvents* and *Pesticide Residues* under *Botanical Extracts* ⟨565⟩.■2S (*USP30*)

BRIEFING

Black Cohosh Tablets—See briefing under *Black Cohosh.*

(DSB: M. Sharaf) RTS—C39927

Add the following:

■Black Cohosh Tablets

» Black Cohosh Tablets contain Powdered Black Cohosh Extract or Black Cohosh Fluidextract. Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Powdered Extract or Fluidextract, represented by the content of triterpene glycosides, calculated as 23-*epi*-26-deoxyactein ($C_{37}H_{56}O_{10}$).

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

Labeling—The label states the Latin binomial and, following the official name, the article from which the Tablets were prepared. The label also indicates the amount, in mg per Tablet, of Powdered Extract or Fluidextract; the solvents used to prepare the Powdered Extract or Fluidextract; and the ratio of starting crude plant material to Powdered Extract or Fluidextract. Label it to indicate the content, in percentage, of triterpene glycosides as 23-*epi*-26-deoxyactein in the Powdered Extract or Fluidextract used to prepare the Tablets.

USP Reference standards ⟨11⟩—*USP Actein RS. USP Powdered Black Cohosh Extract RS. USP 23-epi-26-Deoxyactein RS.*

Identification—

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

Test solution—Take 10 mL of the *Test solution* prepared for *Identification* test *B,* evaporate to dryness, and redissolve in 1 mL of methanol.

Standard solution 1, Standard solution 2, Developing solvent system, Spray reagent, and *Procedure*—Proceed as directed for *Identification* test *A* under *Black Cohosh.*

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Transfer a portion of powdered Tablets, equivalent to the labeled amount of Powdered Extract or Fluidextract containing about 25 mg of triterpene glycosides, to a suitable flask, add 25 mL of water, shake to disperse, and sonicate for 10 minutes. Add 75 mL of methanol, and sonicate for 10 minutes. Allow to stand for 15 minutes, and use the clear supernatant.

Standard solution 1, Standard solution 2, Developing solvent system, Spray reagent, and *Procedure*—Proceed as directed for *Identification* test *B* under *Black Cohosh.*

C: The chromatogram of the *Test solution* exhibits peaks for cimiracemoside A, 26-deoxycimicifugoside, (26*S*) actein, 23-*epi*-26-deoxyactein, cimigenol–arabinoside, and cimigenol–xyloside at retention times corresponding to those compounds in the chromatogram of the *Standard solution,* as obtained in the test for *Content of triterpene glycosides*. The ratio of the peak areas of cimigenol–arabinoside to cimigenol–xyloside is not less than 0.4 (distinction from *Cimicifuga foetida*).

Weight variation ⟨2091⟩: meet the requirements.

Disintegration ⟨2040⟩: meet the requirements under *Botanical Dosage Forms.*

Dissolution ⟨2040⟩—[To come.]

Microbial enumeration ⟨2021⟩—Tablets meet the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*. The total bacterial count does not exceed 10^4 cfu per g, and the total combined molds and yeasts count does not exceed 10^3 cfu per g.

Content of triterpene glycosides—

Solution A, Solution B, Mobile phase, System suitability solution, Standard solution, 23-epi-26-Deoxyactein standard solutions, and *Chromatographic system*—Proceed as directed in the test for *Content of triterpene glycosides* under *Black Cohosh.*

Test solution—Accurately weigh not fewer than 20 Tablets, and finely powder with a mortar and pestle. Transfer an accurately weighed quantity of the powder, equivalent to about 8 mg of triterpene glycosides, to a suitable polytef-capped centrifuge tube. Add 3 mL of water, shake to disperse, and sonicate for 10 minutes at 60°. Add 3 mL of methanol, and sonicate for 10 minutes. Centrifuge, and transfer the clear supernatant to a 10-mL volumetric flask. Wash the residue twice with 1.5 mL of a mixture of methanol and water (1 : 1), and transfer the washings to the volumetric flask. Dilute with a mixture of methanol and water (1 : 1) to volume, mix, and pass through a membrane filter having a 0.45-µm or finer porosity.

Procedure—Proceed as directed in the test for *Content of triterpene glycosides* under *Black Cohosh.* From the chromatogram obtained, determine the concentration, *C,* in µg per mL, of each triterpene glycoside. Calculate the quantity, in mg, of triterpene glycosides in the portion of Tablets taken by the formula:

$$C_T/100$$

in which C_T is the sum of the concentrations *C,* in µg per mL, of all the relevant triterpene glycosides, calculated as 23-*epi*-26-deoxyactein. ■2S (*USP30*)

In-Process Revision

BRIEFING

Glucosamine Tablets, *USP 29* page 2343. It is proposed to revise the test for *Disintegration and dissolution* to make the dissolution requirements for glucosamine consistent with those of *Glucosamine and Chondroitin Sulfate Sodium Tablets*.

(DS-BA: D. Cairatti) RTS—C44053

Change to read:

Disintegration and dissolution ⟨2040⟩: meet the requirements for *Dissolution.*

Medium: water; 900 mL.

Apparatus 2: ~~50 rpm.~~

■75 rpm.■2S (*USP30*)

Time: ~~45 minutes.~~

■60 minutes.■2S (*USP30*)

Determine the amount of $C_6H_{13}NO_5$ dissolved by employing the following method.

Phosphate buffer, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay* under *Glucosamine Hydrochloride.*

Standard solution—Dissolve an accurately weighed quantity of USP Glucosamine Hydrochloride RS in water to obtain a solution having a known concentration of about 1.0 mg per mL. Dilute with a suitable quantity of water, if necessary.

Test solution—Use the solution under test.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the glucosamine peaks. Calculate the amount, in mg, of $C_6H_{13}NO_5$ dissolved by the formula:

$$(179.17/215.63)(900C)(r_U/r_S)$$

in which 179.17 and 215.63 are the molecular weights of glucosamine and glucosamine hydrochloride, respectively; C is the concentration, in mg per mL, of USP Glucosamine Hydrochloride RS in the *Standard solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 75% of the labeled amount of $C_6H_{13}NO_5$ is dissolved in ~~45 minutes.~~

■60 minutes.■2S (*USP30*)

BRIEFING

Glucosamine and Methylsulfonylmethane Tablets—See briefing under *Glucosamine, Chondroitin Sulfate Sodium and Methylsulfonylmethane Tablets.*

(DSN: L. Evans; DS-BA: D. Cairatti) RTS—C45407

Add the following:

■Glucosamine and Methylsulfonylmethane Tablets

» Glucosamine and Methylsulfonylmethane Tablets are prepared from either Glucosamine Hydrochloride, Glucosamine Sulfate Sodium Chloride, Glucosamine Sulfate Potassium Chloride, or a mixture of any of them, with Methylsulfonylmethane. Tablets contain not less than 90.0 percent and not more than 120.0 percent of the labeled amount of glucosamine ($C_6H_{13}NO_5$) and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of methylsulfonylmethane ($C_2H_6O_2S$).

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—The label indicates the types of glucosamine salts contained in the article.

USP Reference standards ⟨11⟩—*USP Glucosamine Hydrochloride RS. USP Methylsulfonylmethane RS.*

Identification—

A: The retention times of the major peaks in the chromatogram of the *Test solution* correspond to those in the chromatogram of the *Standard solution,* as obtained in the test for *Content of glucosamine (presence of glucosamine)* under *Glucosamine and Chondroitin Sulfate Sodium Tablets.*

In-Process Revision

B: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the test for *Content of methylsulfonylmethane* under *Methylsulfonylmethane Tablets*.

Disintegration and dissolution ⟨2040⟩**:** meet the requirements for *Dissolution*.

Medium: water; 900 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Determine the amount of glucosamine ($C_6H_{13}NO_5$) dissolved by employing the following method.

Diluent, 0.2 M Borate buffer, Derivatizing reagent, Mobile phase, and *Chromatographic system*—Proceed as directed in the test for *Content of glucosamine.*

Standard solution—Prepare as directed in the test for *Content of glucosamine.* Dilute with a suitable quantity of water, if necessary.

Test solution—Use the solution under test.

Procedure—Proceed as directed in the test for *Content of glucosamine.* Calculate the quantity, in mg, of glucosamine ($C_6H_{13}NO_5$) dissolved by the formula:

$$(179.17/215.63)(900C)(r_U/r_S)$$

in which the terms are as defined therein.

Tolerances—Not less than 75% of the labeled amount of $C_6H_{13}NO_5$ is dissolved in 60 minutes.

Weight variation ⟨2091⟩**:** meet the requirements.

Content of glucosamine—

Diluent, 0.2 M Borate buffer, Derivatizing reagent, Mobile phase, Standard solution, Test solution, Chromatographic system, and *Procedure*—Proceed as directed in the test for *Content of glucosamine* under *Glucosamine and Chondroitin Sulfate Sodium Tablets*.

Content of methylsulfonylmethane—

Diluent, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Methylsulfonylmethane*.

Assay preparation and *Procedure*—Proceed as directed in the *Assay* under *Methylsulfonylmethane Tablets*.■2S (*USP30*)

BRIEFING

Glucosamine, Chondroitin Sulfate Sodium and Methylsulfonylmethane Tablets; Glucosamine and Methylsulfonylmethane Tablets. Because there are no existing *USP* monographs for these dietary supplements, new monographs, based on validated methods of analysis, are being proposed. The liquid chromatographic procedure in the test for *Content of glucosamine* is based on analyses performed with the Genesis brand of L1 column. Typical retention times are 4.5 minutes for the β-anomer and 8.1 minutes for the α-anomer. The gas chromatographic procedure in the test for *Content of methylsulfonylmethane* is based on analyses performed with the Zebron ZB-1 brand of G2 column. The typical retention time for the methylsulfonylmethane peak is about 4.4 minutes. The test for *Content of methylsulfonylmethane* references the *Assay* in the *Methylsulfonylmethane Tablets* monograph proposed in *PF* 32(3).

(DSN: L. Evans; DS-BA: D. Cairatti) RTS—C45407

Add the following:

■Glucosamine, Chondroitin Sulfate Sodium and Methylsulfonylmethane Tablets

» Glucosamine, Chondroitin Sulfate Sodium and Methylsulfonylmethane Tablets are prepared from either Glucosamine Hydrochloride, Glucosamine Sulfate Sodium Chloride, Glucosamine Sulfate Potassium Chloride, or a mixture of any of them, with Chondroitin Sulfate Sodium and Methylsulfonylmethane. Tablets contain not less than 90.0 percent and not more than 120.0 percent of the

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labeled amounts of chondroitin sulfate sodium and glucosamine ($C_6H_{13}NO_5$) and not less than 90.0 percent and not more than 110.0 percent of the labeled amount of methylsulfonylmethane ($C_2H_6O_2S$).

NOTE—Chondroitin Sulfate Sodium is extremely hygroscopic once dried. Avoid exposure to atmosphere, and weigh promptly.

Packaging and storage—Preserve in tight, light-resistant containers.

Labeling—The label indicates the types of glucosamine salts contained in the article and the species source from which chondroitin was derived. Label it to state the source(s) of chondroitin sulfate sodium, whether bovine, porcine, avian, or a mixture of any of them. The label states on the front panel the content of chondroitin sulfate sodium on the dried basis.

USP Reference standards ⟨11⟩*—USP Chondroitin Sulfate Sodium RS. USP Glucosamine Hydrochloride RS. USP Methylsulfonylmethane RS.*

Identification—

A: The retention times of the major peaks in the chromatogram of the *Test solution* correspond to those in the chromatogram of the *Standard solution,* as obtained in the test for *Content of glucosamine (presence of glucosamine)* under *Glucosamine and Chondroitin Sulfate Sodium Tablets.*

B:

Standard solutions—Prepare as directed in the test for *Content of chondroitin sulfate sodium* under *Chondroitin Sulfate Sodium.*

Test solution—Prepare as directed in the test for *Content of chondroitin sulfate sodium* under *Chondroitin Sulfate Sodium Tablets.*

Procedure (see *Electrophoresis* ⟨726⟩)—Proceed as directed for *Electrophoretic purity* under *Chondroitin Sulfate Sodium (presence of chondroitin sulfate).*

C: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the test for *Content of methylsulfonylmethane.*

Disintegration and dissolution ⟨2040⟩**:** meet the requirements for *Dissolution*.

Medium: water; 900 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Determine the amount of glucosamine ($C_6H_{13}NO_5$) dissolved by employing the following method.

Diluent, 0.2 M Borate buffer, Derivatizing reagent, Mobile phase, and *Chromatographic system*—Proceed as directed in the test for *Content of glucosamine.*

Standard solution—Prepare as directed in the test for *Content of glucosamine.* Dilute with a suitable quantity of water, if necessary.

Test solution—Use the solution under test.

Procedure—Proceed as directed in the test for *Content of glucosamine.* Calculate the quantity, in mg, of glucosamine ($C_6H_{13}NO_5$) dissolved by the formula:

$$(179.17/215.63)(900C)(r_U/r_S)$$

in which the terms are as defined therein.

Tolerances—Not less than 75% of the labeled amount of $C_6H_{13}NO_5$ is dissolved in 60 minutes.

Determine the amount of chondroitin sulfate sodium dissolved by employing the following method.

Cetylpyridinium chloride solution, Diluent, and *Test solution*—Prepare as directed in the test for *Content of chondroitin sulfate sodium* under *Chondroitin Sulfate Sodium Tablets.*

Standard solutions—Prepare as directed in the test for *Content of chondroitin sulfate sodium* under *Chondroitin Sulfate Sodium.*

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Procedure—Proceed as directed in the test for *Content of chondroitin sulfate sodium* under *Chondroitin Sulfate Sodium Tablets,* adjusting the volume of the sample and/or the concentrations of the standards, if necessary. Calculate the quantity, in mg, of chondroitin sulfate sodium dissolved by the formula:

$$900C$$

in which C is the concentration, in mg per mL, of chondroitin sulfate sodium in the solution under test.

Tolerances—Not less than 75% of the labeled amount of chondroitin sulfate sodium is dissolved in 60 minutes.

Weight variation ⟨2091⟩**:** meet the requirements.

Content of glucosamine—

Diluent, 0.2 M Borate buffer, Derivatizing reagent, Mobile phase, Standard solution, Test solution, Chromatographic system, and *Procedure*—Proceed as directed in the test for *Content of glucosamine* under *Glucosamine and Chondroitin Sulfate Sodium Tablets.*

Content of chondroitin sulfate sodium—

Cetylpyridinium chloride solution, Diluent, Test solution, and *Procedure*—Proceed as directed in the test for *Content of chondroitin sulfate sodium* under *Chondroitin Sulfate Sodium Tablets*.

Standard solutions—Prepare as directed in the test for *Content of chondroitin sulfate sodium* under *Chondroitin Sulfate Sodium.*

Content of methylsulfonylmethane—

Diluent, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Methylsulfonylmethane*.

Assay preparation and *Procedure*—Prepare as directed in the *Assay* under *Methylsulfonylmethane Tablets*.■2S (*USP30*)

BRIEFING

Maritime Pine, *USP 29* page 2359. In order to minimize analytical variability, it is proposed to use USP Maritime Pine Extract RS in the determination of the *Content of procyanidins* instead of the absorptivity value. The wavelength of the test has been changed from 546 nm to the wavelength of maximum absorption at 551 nm. In addition, editorial style changes have been made.

(DSB: M. Sharaf) RTS—C44237

Change to read:

Identification—

A: Pulverize 1 g of the dried Maritime Pine. Add 10 mg of the powdered material to 1 mL of methanol. Add 6 mL of a mixture of butanol and hydrochloric acid (95 : 5 v/v). Heat for 2 minutes in a water bath: the solution turns red.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Add 2 g of the powdered dried material to 20 mL of water. Place in a water bath for 20 minutes, and centrifuge. Extract the supernatant with 40 mL of ethyl acetate. Evaporate the ethyl acetate layer to dryness under a stream of nitrogen, with gentle heating. Dissolve the residue so obtained in 0.25 mL of alcohol.

Standard solution—Prepare a solution of USP Maritime Pine Extract RS in alcohol, having a concentration of about 25 mg per mL. [NOTE—Retain a portion of this solution for use in *Identification* test *C*.]

Application volume: 5 µL.

Developing solvent system: ~~a mixture of ethyl acetate, methanol, and water (100 : 10 : 6).~~

■a mixture of ethyl acetate, formic acid, and water (100 : 10 : 6).■2S (*USP30*)

Spray reagent: a mixture of alcohol and phosphoric acid (1 : 1), containing 1% of vanillin.

Procedure— ~~Proceed as directed in the chapter, except to dry the plate with the aid of a current of air, spray with the *Spray reagent,* and dry at 110° for 10 minutes. A red band appears in the upper part of the chromatogram of the *Test solution*, at an R_F value of about 0.82, corresponding to a similar band in the chromatogram of the *Standard solution (presence of catechin).* The lower part of the chromatogram of the *Test solution* also shows red bands, at an R_F value of about 0.45 *(presence of oligomeric and polymeric procyanidins).* Two other red bands in the chromatogram of the *Test solution* correspond to those at similar R_F values in the chromatogram of the *Standard solution (presence of dimeric procyanidins).* A blue band appears in the chromatogram of the *Test solution* between the bands for catechin and the dimeric procyanidins, corresponding in color and R_F value to a similar band in the chromatogram of the *Standard solution.*~~

■Proceed as directed in the chapter, except to dry the plate with the aid of a current of air, spray the plate with the *Spray reagent,* and heat at 115° for 15 minutes. Three red bands appear in the middle third of the chromatogram of the *Standard solution* corresponding to two dimeric procyanidins and catechin. The chromatogram of the *Standard solution* also exhibits a blue band between the upper band due to upper dimeric procyanidins and the band due to catechin. The

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chromatogram of the *Test solution* contains bands that correspond to those found in the chromatogram of the *Standard solution.*■2S *(USP30)*

C: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—
Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.
Test solution—Use the *Test solution* prepared as directed for *Identification* test *B*.
Standard solution 1—Use the *Standard solution* prepared as directed for *Identification* test *B.*
Standard solution 2—Prepare a solution of ferulic acid and protocatechuic acid containing 1 mg of each per mL.
Application volume: 10 µL.
Developing solvent system: a mixture of methylene chloride, methanol, glacial acetic acid, and water (80 : 15 : 2 : 2).
Spray reagent—Prepare a 5% ferric chloride solution in methanol.
Procedure— ~~Proceed as directed in the chapter, except to dry the plate at 110° and examine the plate under short-wavelength UV light. The upper third of the chromatogram of the *Test solution* exhibits three bands. The uppermost band is close to the solvent front. The middle third of the chromatogram of the *Test solution* exhibits a band corresponding in R_F value to the bands in the chromatograms of *Standard solution 1* and *Standard solution 2 (presence of ferulic acid).* The lower third of the chromatogram of the *Test solution* exhibits a band corresponding to bands of similar R_F value in the chromatograms of *Standard solution 1* and *Standard solution 2 (presence of protocatechuic acid).* A band near the origin is also visible in the chromatogram of the *Test solution.* Spray the plate with the *Spray reagent,* and dry at 110°. The bands due to ferulic acid and protocatechuic acid turn grayish green and orange, respectively. A grayish green band becomes visible in the chromatogram of the *Test solution* above the protocatechuic acid band *(presence of caffeic acid).* The band near the origin of the chromatogram of the *Test solution* turns orange.~~

■Proceed as directed in the chapter, except to dry the plate at 110° and to examine the plate under short-wavelength and long-wavelength UV light. The chromatograms of *Standard solution 1* and *Standard solution 2* exhibit bands in the middle third and upper third that correspond to protocatechuic acid and ferulic acid, respectively. Spray the plate with the *Spray reagent,* and heat at 115° for 15 minutes. The bands due to ferulic acid and protocatechuic acid turn grayish green. Grayish-green bands become visible in the chromatogram of *Standard solution 1* above and below protocatechuic acid indicating the presence of caffeic acid and catechin, respectively. The chromatogram of the *Test solution* exhibits bands due to catechin, protocatechuic acid, caffeic acid, and ferulic acid that correspond in color and R_F values to those in the chromatogram of *Standard solution 1* and *Standard solution 2.*■2S *(USP30)*

Change to read:

Content of procyanidins—
Reagent solution A—Prepare a mixture of butanol and hydrochloric acid (95 : 5). [NOTE—Prepare this solution on the day of use.]
Reagent solution B—Dissolve 2 g of ferric ammonium sulfate in a mixture of 100 mL of water and 17.5 mL of hydrochloric acid. [NOTE—This solution can be used within 15 days of preparation.]

■*Standard solution*—Prepare a solution of USP Maritime Pine Extract RS in methanol having a concentration of about 95 µg of procyanidins per mL.■2S *(USP30)*
Test solution—Dry crushed Maritime Pine at 110° for 3 hours. Place about 1.9 g of the crushed material, accurately weighed, in a 20-mL vial, and add 10 mL of methanol. Crimp the vial, and sonicate for 2 minutes. Heat in boiling water for 10 minutes. Cool to room temperature, allow the sediment to settle, and transfer the supernatant to a 100-mL volumetric flask, passing it through a filter having a 0.45-µm porosity. Wash the sediment two times with 10 mL of methanol, and transfer the solution into the same 100-mL volumetric flask, again passing it through a filter having a 0.45-µm porosity. Dilute with methanol to volume, and mix. Transfer 1.0 mL of that solution into a 20-mL volumetric flask, dilute with methanol to volume, and mix.
Procedure— ~~Transfer 1.0 mL of the *Test solution* and 1.0 mL of methanol to two separate 10-mL vials. To each flask add 6.0 mL of *Reagent solution A* and 0.25 mL of *Reagent solution B* to each flask.~~

■Transfer 1.0 mL of the *Standard solution,* 1.0 mL of the *Test solution,* and 1.0 mL of methanol to three separate 10-mL vials. To each vial add 6.0 mL of *Reagent solution A* and 0.25 mL of *Reagent solution B.*■2S *(USP30)*
Seal the vials with crimp caps. Mix, and heat in a water bath for 40 minutes. Quickly cool to room temperature in an ice bath. Quantitatively transfer these solutions, with the aid of *Reagent solution A,* to ~~two~~

■three■2S *(USP30)*
separate 10-mL volumetric flasks, dilute with *Reagent solution A* to volume, and mix. ~~Determine the absorbance of the solution obtained from the *Test solution* at 546 nm, using the methanol-containing solution as the blank. Calculate the percentage of total procyanidins in the portion of Maritime Pine taken by the formula:~~

~~$(2000A_U)/(36.7W)$,~~

~~in which A_U is the absorbance of the solution obtained from the *Test solution;* 36.7 is the absorptivity of the maritime pine procyanidins; and W is the weight, in g, of the Maritime Pine taken to prepare the *Test solution.*~~

■Determine the absorbance of the solutions obtained from the *Standard solution* and the *Test solution* at 551 nm, using the methanol-containing solution as the blank. Calculate the percentage of total procyanidins in the portion of Maritime Pine taken by the formula:

$$200(A_U/A_S)(C_S/W)$$

in which A_U and A_S are the absorbances of the solutions from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in µg per mL, of the *Standard solution;* and

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W is the weight, in mg, of Maritime Pine powder used to prepare the *Test solution,* corrected for the water content.■2S (*USP30*)

BRIEFING

Maritime Pine Extract, *USP 29* page 2360. In order to minimize analyst-to-analyst variations, it is proposed to use USP Maritime Pine Extract RS in the determination of the test for *Content of procyanidins* instead of the absorptivity value. The wavelength of the test has been changed from 546 nm to the wavelength of maximum absorption at 551 nm. An adsorbent of chromatographic silica gel mixture has been added to *Identification* tests *B* and *C*. In addition, editorial style changes have been made.

(DSB: M. Sharaf) RTS—C44243

Change to read:

Identification—

A: Dissolve 50 mg of Extract in 6 mL of a mixture of butanol and hydrochloric acid (95 : 5). Heat in a water bath for 2 minutes: the solution turns dark red.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

■*Adsorbent:* 0.25-mm layer of chromatographic silica gel mixture.■2S (*USP30*)

Test solution—Dissolve a quantity of Extract in methanol to obtain a solution having a concentration of about 25 mg per mL.

Standard solution 1—Prepare a solution of USP Maritime Pine Extract RS in methanol having a concentration of about 25 mg per mL.

Standard solution 2—~~Prepare a solution of ferulic acid in methanol having a concentration of about 1 mg per mL.~~

■Prepare a solution of ferulic acid and protocatechuic acid in methanol having a concentration of about 1 mg per mL of each.■2S (*USP30*)

Application volume: 5 µL.

Developing solvent system: a mixture of methylene chloride, methanol, glacial acetic acid, and water (80 : 15 : 2 : 2).

Spray reagent—Prepare a 5% ferric chloride solution in methanol.

Procedure—~~Proceed as directed in the chapter, except to dry the plate at 110° and to examine the plate under short-wavelength and long-wavelength UV light. The chromatogram of *Standard solution 1* exhibits bands in the middle third and upper third that correspond to protocatechuic acid and ferulic acid, respectively. Spray the plate with the *Spray reagent,* and dry at 110° for 10 minutes. The bands due to ferulic acid and protocatechuic acid turn grayish green and orange, respectively. Grayish-green bands become visible in the chromatogram of *Standard solution 1* above and below protocatechuic acid indicating the presence of caffeic acid and catechin, respectively. The chromatogram of the *Test solution* exhibits bands due to caffeic acid, protocatechuic acid, and ferulic acid that correspond in color and R_F value to those in the chromatogram of *Standard solution 1.*~~

■Proceed as directed in the chapter, except to dry the plate at 110° and to examine the plate under short-wavelength and long-wavelength UV light. The chromatograms of *Standard solution 1* and *Standard solution 2* exhibit bands in the middle third and upper third that correspond to protocatechuic acid and ferulic acid, respectively. Spray the plate with the *Spray reagent,* and heat at 115° for 15 minutes. The bands due to ferulic acid and protocatechuic acid turn grayish green. Grayish-green bands become visible in the chromatogram of *Standard solution 1* above and below protocatechuic acid indicating the presence of caffeic acid and catechin, respectively. The chromatogram of the *Test solution* exhibits bands due to catechin, protocatechuic acid, caffeic acid, and ferulic acid that correspond in color and R_F values to those in the chromatogram of *Standard solution 1* and *Standard solution 2.*■2S (*USP30*)

C: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

■*Adsorbent:* 0.25-mm layer of chromatographic silica gel mixture.■2S (*USP30*)

Test solution—Use the *Test solution* prepared as directed for *Identification* test *B.*

Standard solution—Use *Standard solution 1* prepared as directed for *Identification* test *B.*

Application volume: 5 µL.

Developing solvent system: a mixture of ethyl acetate, formic acid, and water (100 : 10 : 6).

Spray reagent: a mixture of phosphoric acid and alcohol (1 : 1), containing 1% of vanillin.

Procedure—Proceed as directed in the chapter, except to

■dry the plate with the aid of a current of air,■2S (*USP30*) spray the plate with the *Spray reagent,* and heat at ~~110° for 10 minutes.~~

■115° for 15 minutes.■2S (*USP30*) Three red bands appear in the middle third of the chromatogram of the *Standard solution* corresponding to two dimeric procyanidins and catechin. The chromatogram of the *Standard solution* also exhibits a blue band between the upper band due to upper dimeric procyanidins and the band due to catechin. The chromatogram of the *Test solution* contains bands that correspond to those found in the chromatogram of the *Standard solution.*

D: Proceed as directed in the following liquid chromatographic procedure.

Solution A—Use filtered and degassed methanol.

Solution B—Carefully weigh 1 g of phosphoric acid, and dilute with water. Transfer to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (*see System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Maritime Pine Extract RS in *Solution A* to obtain a solution having a known concentration of about 2 mg per mL. Pass through a membrane having a 0.45-µm or finer porosity.

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Test solution—Weigh about 20 mg of Extract. Add 10 mL of *Solution A,* and sonicate for 10 minutes. Pass through a membrane having a 0.45-µm or finer porosity, discarding the first 4 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains base-deactivated packing L7, having less than 5-µm particle size. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	8	92	equilibration
0–40	8→34	92→66	linear gradient
40–45	34→2	66→98	linear gradient
45–50	2	98	isocratic
50–52	2→8	98→92	linear gradient
52–57	8	92	isocratic

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the chromatogram obtained is similar to the Reference Chromatogram provided with the USP Maritime Pine Extract RS; the resolution, *R,* between taxifolin and ferulic acid is not less than 3.0; and the tailing factor for taxifolin is not more than 2.0.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and ~~measure the peak areas for catechin, caffeic acid, taxifolin, and ferulic acid, identifying the peaks~~

■identify the peaks for catechin, caffeic acid, taxifolin, and ferulic acid■2S (*USP30*)
by comparison of the chromatogram of the *Standard solution* with the Reference Chromatogram: the chromatogram of the *Test solution* exhibits peaks for catechin, caffeic acid, taxifolin, and ferulic acid at the retention times corresponding to those in the chromatogram of the *Standard solution*.

Change to read:

Microbial enumeration ⟨2021⟩—The total aerobic microbial count does not exceed 10^4 cfu per g, the total combined molds and yeasts count does not exceed ~~1000 cfu per g~~

■10^3 cfu per g,■2S (*USP30*)
and it meets the requirements of the tests for absence of *Salmonella* species, and *Escherichia coli.*

Change to read:

Content of procyanidins—

Reagent solution A—Prepare a mixture of butanol and hydrochloric acid (95 : 5). [NOTE—Prepare this solution on the day of use.]

Reagent solution B—Dissolve 2 g of ferric ammonium sulfate in a mixture of 100 mL of water and 17.5 mL of hydrochloric acid. [NOTE—This solution can be used within 15 days of preparation.]

■*Standard solution*—Prepare a solution of USP Maritime Pine Extract RS in methanol having a concentration of about 95 µg of procyanidins per mL.■2S (*USP30*)

Test solution—Transfer about ~~0.125 g~~

■0.25 g■2S (*USP30*)
of Extract, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Transfer 1.0 mL of this solution to a 20-mL volumetric flask, dilute with methanol to volume, and mix.

Procedure—~~Transfer 1.0 mL of the *Test solution* and 1.0 mL of methanol to two separate 10-mL vials. To each flask add 6.0 mL of *Reagent solution A* and 0.25 mL of *Reagent solution B.*~~

■Transfer 1.0 mL of the *Standard solution,* 1.0 mL of the *Test solution,* and 1.0 mL of methanol to three separate 10-mL vials. To each vial add 6.0 mL of *Reagent solution A* and 0.25 mL of *Reagent solution B.*■2S (*USP30*)
Seal the vials with crimp caps. Mix, and heat in a water bath for 40 minutes. Quickly cool to room temperature in an ice bath. Quantitatively transfer these solutions, with the aid of *Reagent solution A,* to ~~two~~

■three■2S (*USP30*)
separate 10-mL volumetric flasks, dilute with *Reagent solution A* to volume, and mix. ~~Determine the absorbance of the solution obtained from the *Test solution* at 546 nm, using the methanol-containing solution as the blank. Calculate the percentage of total procyanidins in the portion of Extract taken by the formula:~~

~~$(2000A_U)/(36.7W)$~~

~~in which A_U is the absorbance of the solution obtained from the *Test solution;* 36.7 is the absorptivity of the maritime pine procyanidins; and W is the weight, in g, of the Extract taken to prepare the *Test solution.*~~

■Determine the absorbance of the solutions obtained from the *Standard solution* and the *Test solution* at 551 nm, using the methanol-containing solution as the blank. Calculate the percentage of total procyanidins in the portion of Extract taken by the formula:

$$200(A_U/A_S)(C_S/W)$$

in which A_U and A_S are the absorbances of the solutions from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in µg per mL, of the *Standard solution;* and W is the weight, in mg, of Extract used to prepare the *Test solution,* corrected for loss on drying.■2S (*USP30*)

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 24* page 3257, page 3627 of the *First Supplement,* and page 390 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to add *Polydextrose* to the *Bulking Agent for Freeze-Drying* and *Humectant* categories to complement the proposed new monograph for *Polydextrose,* which appears elsewhere in this issue of *PF.*

(EM2) RTS—C44166

Change to read:

Bulking Agent for Freeze-Drying
Creatinine
Mannitol

■Polydextrose■2S *(NF25)*

Change to read:

Coating Agent

▲Amino Methacrylate Copolymer▲*NF25*
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose, Sodium
Cellaburate
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Cellulose Acetate Phthalate (see Cellacefate)

■Coconut Oil■1S *(NF25)*
Copovidone

▲Corn Syrup Solids▲*NF25*

▲Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion▲*NF25*
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Maltodextrin
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol

■Polyvinyl Acetate■1S *(NF25)*
Polyvinyl Acetate Phthalate
Shellac
Starch, Pregelatinized Modified
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Desiccant
Calcium Chloride
Calcium Sulfate

■Polyvinyl Acetate■1S *(NF25)*
Silicon Dioxide

Change to read:

Emollient
Alkyl (C12-15) Benzoate
Hydrogenated Soybean Oil

▲Oleyl Oleate▲*NF25*

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Carbomer Copolymer
Carbomer Interpolymer
Cholesterol

■Coconut Oil■1S *(NF25)*
Diethanolamine (Adjunct)
Diethylene Glycol Stearates
Ethylene Glycol Stearates
Glyceryl Distearate
Glyceryl Monolinoleate
Glyceryl Monooleate
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)

▲Oleyl Oleate▲*NF25*
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
Polyoxyl Lauryl Ether
Polyoxyl Stearyl Ether
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Cetostearyl Sulfate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Sorbitan Sesquioleate
Sorbitan Trioleate
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:

Humectant

▲Corn Syrup Solids▲*NF25*

▲Erythritol▲*NF25*
Glycerin
Hexylene Glycol

■Maltitol■2S (*NF24*)

■Polydextrose■2S (*NF25*)
Propylene Glycol
Sorbitol
Sorbitol Sorbitan Solution
■Tagatose■1S (*NF24*)

Change to read:

Polymer Membrane

▲Amino Methacrylate Copolymer▲*NF25*
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Cellaburate
Cellulose Acetate

▲Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion▲*NF25*

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

▲Gamma Cyclodextrin▲*NF25*
Sodium Tartrate

Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol

▲Canola Oil▲*NF25*
Caprylocaproyl Polyoxylglycerides
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
▲Lauroyl Polyoxylglycerides▲*NF24*
Linoleoyl Polyoxylglycerides
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Polyoxylglycerides
Peanut Oil
Polyethylene Glycol
Polyethylene Glycol Monomethyl Ether
Propylene Glycol
Sesame Oil
Stearoyl Polyoxylglycerides
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
Alamic Acid
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carbomer Copolymer
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

▲Corn Syrup Solids▲*NF25*
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate
Maltodextrin
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
Starch, Corn
Starch, Potato
Starch, Tapioca
Starch, Wheat
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent
Acesulfame Potassium
Aspartame
Aspartame Acesulfame

▲Corn Syrup Solids▲*NF25*
Dextrates
Dextrose
Dextrose Excipient

▲Erythritol▲*NF25*
Fructose
Galactose

■Maltitol■2S (*NF24*)
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup
■Tagatose■1S (*NF24*)

Change to read:

Tablet Binder
Acacia
Alginic Acid

▲Amino Methacrylate Copolymer▲*NF25*
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
Copovidone

▲Corn Syrup Solids▲*NF25*
Dextrin

▲Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion▲*NF25*
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Low-Substituted Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Maltodextrin
Maltose
Methylcellulose
Polyethylene Oxide

■Polyvinyl Acetate■1S (*NF25*)
Povidone
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Syrup

Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered

▲Corn Syrup Solids▲*NF25*
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose, Monohydrate

■Maltitol■2S (*NF24*)
Maltodextrin
Maltose
Mannitol
Sorbitol
Starch
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tonicity Agent

▲Corn Syrup Solids▲*NF25*
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

▲Corn Syrup Solids▲*NF25*
Dextrose
Peppermint Water
Sorbitol Solution
Syrup
OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil

▲Canola Oil▲*NF25*
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

MONOGRAPHS (NF)

BRIEFING

Almond Oil, *NF 24* page 3270. On the basis of data, validation, and comments received as well as on the monograph *Almond Oil, Refined* in the *European Pharmacopoeia, Fifth Edition,* page 3893, it is proposed to make significant changes to this monograph. The following changes have been proposed.

1. Revise the Definition of this article to reflect the latest classification.
2. Add a *Labeling* section to include the use of the suitable antioxidants.
3. Revise the *Packaging and storage* section.
4. Add a test for *Identification.*
5. Delete the tests for *Foreign kernel oils, Cottonseed oil, Sesame oil, Mineral oil and foreign fatty oils,* and *Foreign oils*.
6. Delete the tests for *Free fatty acid, Iodine value,* and *Saponification value*.
7. Add the test for *Fatty acid composition* as an *Identification* test.
8. Add the tests for *Acid value, Peroxide value,* and *Unsaponifiable matter.*
9. Add a test for *Sterol composition*.
10. Delete the test for *Residual solvents*.

(EM2: H. Wang) RTS—C42256

Change to read:

» Almond Oil is the

■refined■2S (*NF25*)
fixed oil obtained by expression from the kernels of varieties of ~~*Prunus amygdalus* Batsch~~

■*Prunus dulcis* (Miller) D.A. Webb■2S (*NF25*)
(Fam. Rosaceae).

■It may contain suitable antioxidants.■2S (*NF25*)

Change to read:

Packaging and storage~~— Preserve in tight containers.~~

■Preserve in tight, light-resistant, and well-filled containers. No storage requirements specified.■2S (*NF25*)

Add the following:

■**Labeling**—Label it to indicate the name and quantity of any added antioxidants.■2S (*NF25*)

Add the following:

■**Identification**—It meets the requirements of the test for *Fatty acid composition*.■2S (*NF25*)

Delete the following:

■~~**Foreign kernel oils**— Shake vigorously 2 mL with a mixture of 1 mL of fuming nitric acid and 1 mL of water for 5 minutes: the mixture is not more than slightly colored.~~■2S (*NF25*)

Delete the following:

■~~**Cottonseed oil**— Mix 5 mL in a test tube with 5 mL of a mixture of equal volumes of amyl alcohol and a 1 in 100 solution of sulfur in carbon disulfide, warm the mixture carefully until the carbon disulfide is expelled, and immerse the test tube to one third of its length in a boiling, saturated solution of sodium chloride: the mixture develops no reddish color within 2 hours.~~■2S (*NF25*)

Delete the following:

■~~**Sesame oil**— Mix 10 mL with 10 mL of hydrochloric acid, add 0.1 mL of a 1 in 50 solution of furfural in alcohol, and shake the mixture vigorously for 15 seconds: no pink to crimson color appears in the acid layer when separate layers form. Should any color appear in the acid layer, add 10 mL of water, and again shake the mixture vigorously. In the absence of sesame oil the pink color is fugitive.~~■2S (*NF25*)

Delete the following:

■~~**Mineral oil and foreign fatty oils**— Heat 10 mL on a steam bath with 15 mL of 4 N sodium hydroxide and 30 mL of alcohol in a flask that has a small, short-stem funnel inserted in the neck, and occasionally agitate the mixture until it becomes clear. Transfer the solution to a shallow dish, evaporate the alcohol on a steam bath, and mix the residue with 100 mL of water: a clear solution results (*absence of mineral oil*). Add an excess of hydrochloric acid to this solution, remove the layer of fatty acids that rises to the surface, wash it with warm water, clarify it by heating on a steam bath, and allow it to cool to 15° without stirring: the fatty acids remain clear for 30 minutes at this temperature (*absence of foreign fatty oils*).~~■2S (*NF25*)

Delete the following:

■~~**Foreign oils**— One volume of the mixed fatty acids obtained in the test for *Mineral oil and foreign fatty oils,* when mixed with 1 volume of alcohol, yields a clear solution, which at 15° does not deposit any fatty acid or become turbid upon the further addition of 1 volume of alcohol (*absence of olive, peanut, or other fixed oils*).~~■2S (*NF25*)

Delete the following:

■~~**Free fatty acids** ⟨401⟩— The free fatty acids in 10 g require for neutralization not more than 5.0 mL of 0.10 N sodium hydroxide.~~■2S (*NF25*)

Delete the following:

■~~**Iodine value** ⟨401⟩: between 95 and 105.~~■2S (*NF25*)

In-Process Revision

Delete the following:

■~~**Saponification value** ⟨401⟩: between 190 and 200.~~■2S (*NF25*)

Add the following:

■**Acid value** ⟨401⟩**:** not more than 0.5.■2S (*NF25*)

Add the following:

■**Peroxide value** ⟨401⟩**:** not more than 5.0.■2S (*NF25*)

Add the following:

■**Unsaponifiable matter** ⟨401⟩**:** not more than 0.9%.■2S (*NF25*)

Add the following:

■**Fatty acid composition**—Almond Oil exhibits the following composition profiles of fatty acids, as determined in the section *Fatty Acid Composition* under *Fats and Fixed Oils* ⟨401⟩:

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
<16	0	≤0.1
16	0	4.0–9.0
17	0	≤0.2
18	0	≤3.0
20	0	≤0.2
22	0	≤0.2
16	1	≤0.8
18	1	62.0–86.0
18	2	10.0–30.0
18	3	≤0.4
20	1	≤0.3
22	1	≤0.1

■2S (*NF25*)

Add the following:

■**Sterol composition**—

SEPARATION OF THE STEROLS FRACTION—

Reference solution A—Dissolve an accurately weighed quantity of cholesterol in chloroform to obtain a solution of 5% (w/v).

Developing solvent system: a mixture of toluene and acetone (95 : 5) or a mixture of hexane and ether (65 : 35).

Test solution A—Weigh accurately 5 g of Almond Oil into a 250-mL flask. Add 50 mL of 2 N alcoholic potassium hydroxide, and heat to gentle boiling with continuous vigorous stirring until saponification takes place (the solution becomes clear). Continue heating for a further 20 minutes, and add 50 mL of water from the top of the condenser. Cool the flask to approximately 30°. Transfer the contents of the flask to a 500-mL separating funnel with several rinses of water, amounting in all to about 50 mL. Add approximately 80 mL of ether, shake vigorously for approximately 30 seconds, and allow to settle. [NOTE—Any emulsion can be destroyed by adding small quantities of ethyl or methyl alcohol by means of a spray.] Separate the lower aqueous phase, and collect it into a second separating funnel. Perform two further extractions on the water–alcohol phase in the same way using 60 to 70 mL of ether on each occasion. Pool the ether extracts into a single separating funnel, and wash with water, 50 mL at a time, until the wash water is no longer alkaline to phenolphthalein. Dry the ether phase with anhydrous sodium sulfate, and filter on anhydrous sodium sulfate into a previously weighed 250-mL flask, washing the funnel and filter with small quantities of ether. Distill the ether down to a few mL, and bring to dryness under a slight vacuum or in a stream of nitrogen. Complete drying at 100° for approximately 15 minutes, and then weigh after cooling in a desiccator. Dissolve the unsaponifiables so obtained in chloroform to prepare a solution having a concentration of approximately 5%.

Test solution B—Treat 5 g of canola oil in the same way as prescribed for Almond Oil in *Test solution A*, beginning with "Add 50 mL of 2 N alcoholic potassium hydroxide".

Test solution C—Treat 5 g of sunflower oil in the same way as prescribed for Almond Oil in *Test solution A*, beginning with "Add 50 mL of 2 N alcoholic potassium hydroxide".

Procedure—Immerse the thin-layer chromatographic plate (see *Chromatography* ⟨621⟩), 20-cm × 20-cm silica gel on polyester with a layer thickness of 200 µm and particle size of 5–17 µm, completely in the 0.2 N alcoholic potassium hydroxide for 10 seconds, then allow to dry in a fume cupboard for 2 hours and finally place at 100° for 1 hour. [NOTE—Remove from the validated heating device, and keep the plate in a desiccator until required for use. The plates must be used within 15 days. Thin-layer chromatographic plates without requiring the preconditioning are also commercially available.] Use a separate plate for each test solution.

Place a mixture of toluene and acetone (95 : 5) or a mixture of hexane and ether (65 : 35) to a depth of approximately 1 cm. Close the chamber with the appropriate cover, and leave for at least 30 minutes. Strips of filter paper dipping into the eluent may be placed on the internal surfaces of the chamber. [NOTE—The developing mixture should be replaced for every test to ensure reproducible elution conditions.] Apply 0.3 mL of *Test solution A* approximately 2 cm from the lower edge in a streak which is as thin and as uniform as possible. In line with the streak place 2 to 3 µL of *Reference solution A* at one end of the plate. Develop the chromatograms in an equilibrated chamber with a *Developing solvent system* until the solvent front reaches approximately 1 cm from the upper edge of the plate. Remove the plate from the developing chamber, and evaporate the solvent under a current of hot air [NOTE—Avoid excessive heat.] or by leaving the plate for a short while under a hood. Spray the plate with a 0.2% alcoholic solution of 2,7-dichlorofluorescein, and examine in UV light at 254 nm [NOTE—The plates pretreated with UV indicator are also commercially available and used equivalently.] In each of the plates, mark the limits of the sterol band identified through being aligned with the stain obtained from *Reference solution A* along the edges of the fluorescence, and additionally the area of the zones 2 to 3 mm above and below the visible zones corresponding to *Reference solution A* is included. Remove the silica gel in the marked area into a filter funnel with a G3 porous septum. Add 10 mL of hot chloroform, mix carefully with the metal spatula and filter under vacuum, and collect the filtrate in the conical flask attached to the filter funnel. Wash the residue in the funnel three times with ether, about 10 mL each time, and collect the filtrate in the same flask attached to the funnel. Evaporate the filtrate to a volume of 4 to 5 mL, transfer the residual solution to a previously weighed 10-mL test tube with a tapering bottom and a sealing stopper, and evaporate to dryness by mild heating in a gentle stream of nitrogen. Make up again using a few drops of acetone, and evaporate again to dryness. Place at 105° for approximately 10 minutes, and allow to cool in a desiccator, and weigh.

Treat *Test solution B* and *Test solution C* the same way as prescribed for *Test solution A*.

DETERMINATION OF THE STEROLS—

Test solution D—To the test tube containing the sterol fraction separated from Almond Oil by thin-layer chromatography add a freshly prepared mixture of anhydrous pyridine, hexamethyldisilazane, and chlorotrimethylsilane (9 : 3 : 1) [NOTE—This reagent is also commercially available and used equivalently.] in the ratio of 50 µL for every mg of sterols, avoiding any uptake of moisture. Stopper the test tube, and shake carefully until the sterols are completely dissolved. Allow it to stand for at least 15 minutes at ambient temperature, and centrifuge for a few minutes if necessary. Use the supernatant. [NOTE—The slight opalescence which may form is normal and does not cause an anomaly. However, the formation of a white floc or the appearance of a pink color is indicative of the presence of moisture or deterioration of the reagent. If these occur the test must be repeated.]

Reference solution E—To 9 parts of the sterols separated from canola oil by thin-layer chromatography add 1 part of cholesterol. Treat the mixture in the same way as prescribed under the *Test solution D*.

Reference solution F—Treat the sterols separated from sunflower oil by thin-layer chromatography in the same way as prescribed under the *Test solution D*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a glass or fused-silica capillary column of length 20 to 30 m, internal diameter 0.25 to 0.32 mm, entirely coated with a 0.10 to 0.30-µm layer of stationary phase G27 or G36. The injection port temperature is maintained at 280°, the detector temperature is maintained at 290°, and the column temperature is maintained at 260 ± 5°. The carrier gas is either helium with a linear velocity of 20 to 35 cm per second or hydrogen with a linear velocity of 30 to 50 cm per second. A split ratio of 1 : 50 to 1 : 100 is used. Chromatograph *Reference solution E* and *Reference solution F*, and record the peak responses as directed for *Procedure:* the retention time should be 20 ± 5 minutes for β-sitosterol, all the sterols present must be separated. [NOTE—For peak identification purposes, the chromatogram obtained with *Reference solution E* shows four principal peaks corresponding to cholesterol, brassicasterol, campesterol, and β-sitosterol; and the chromatogram obtained with *Reference solution F* shows four principal peaks corresponding to campesterol, stigmasterol, β-sitosterol and Δ7-stigmastenol. The retention times of the sterols with reference to β-sitosterol are given in *Table 1*.]

Table 1. Relative Retention Times of Sterols for Two Different Columns

Identification	G36 column	G27 column
Cholesterol	0.67	0.63
Brassicasterol	0.73	0.71
24-Methylene -cholesterol	0.82	0.80
Campesterol	0.83	0.81
Campestanol	0.85	0.82
Stigmasterol	0.88	0.87
Δ7-Campesterol	0.93	0.92
Δ5,23-Stigmasta-dienol	0.95	0.95
Clerosterol	0.96	0.96
β-Sitosterol	1.00	1.00
Sitostanol	1.02	1.02
Δ5-Avenasterol	1.03	1.03
Δ5,24-Stigmasta-dienol	1.08	1.08
Δ7-Stigmastenol	1.12	1.12
Δ7-Avenasterol	1.16	1.16

Procedure—Separately inject equal volumes (about 1 µL) of *Test solution D, Reference solution E,* and *Reference solution F* into the chromatograph, record the chromatograms, and measure the peak areas for the sterols. Calculate the percentage of each individual sterol in the sterol fraction of Almond Oil taken by the formula:

$$100(A / S)$$

in which A is the area of the peak due to the sterol component to be determined, and S is the sum of the areas of the peaks due to the components indicated in *Table 1*. Almond Oil exhibits the following composition profiles of sterols.

Component	Percentage (%)
Cholesterol	≤0.7
Brassicasterol	≤0.3
Campesterol	≤5.0
Stigmasterol	≤4.0
β-Sitosterol	73.0–87.0
Δ5-Avenasterol	≥5.0
Δ7-Stigmastenol	≤3.0
Δ7-Avenasterol	≤3.0

■2S (*NF25*)

Delete the following:

■**~~Residual solvents~~** ~~⟨467⟩: meets the requirements.~~
~~(Official January 1, 2007)~~■2S (*NF25*)

BRIEFING

High Fructose Corn Syrup. The proposal on page 408 of *PF* 28(2) [Mar.–Apr. 2002] is canceled and a new proposal is presented in this *PF* for this new monograph. The references to the monograph for *Corn Syrup* are deleted; and detailed procedures in the tests for *Limit of sulfur dioxide* and *Limit of lead* are provided. In addition, minor editorial changes have been made.

(EM2: H. Wang; NOM: W. Paul) RTS—C45813

Add the following:

■High Fructose Corn Syrup

» High Fructose Corn Syrup is a sweet, nutritive saccharide mixture prepared as a clear, aqueous solution from high-dextrose-equivalent corn starch hydrolysate by the partial enzymatic conversion of dextrose to fructose, using an insoluble glucose isomerase enzyme preparation that complies with 21 CFR 184.1372. It is available in two types, 42% and 55%, based on fructose content. High Fructose Corn Syrup 42% contains not less than 97.0 percent of total saccharides, expressed as a percentage of total solids, of which not less than 92.0 percent consists of monosaccharides (fructose and dextrose), including not less than 41.5 percent and not more than 44.8 percent of fructose, and not more than 8.0 percent consists of other saccharides. High Fructose Corn Syrup 55% contains not less than 95.0 percent of total saccharides, expressed as a percentage of total solids, of which not less than 95.0 percent consists of monosaccharides (fructose and dextrose), including not less than 54.5 percent and not more than 56.5 percent of fructose, and not more than 5.0 percent consists of other saccharides.

Packaging and storage—Preserve in tight containers. No storage requirement specified.

Labeling—Label it to state, as part of the official title, the nominal percentage of fructose, based on the specified minimum percentage concentration of total saccharides. Label it to indicate the presence of sulfur dioxide if the residual sulfur dioxide concentration is greater than 10 μg per g.

USP Reference standards ⟨11⟩—*USP Dextrose RS. USP Fructose RS. USP Maltose Monohydrate RS.*

Identification—Add a few drops of a solution (1 in 10) of Syrup to 5 mL of hot, alkaline cupric tartrate TS: a copious, red precipitate of cuprous oxide is formed *(distinction from sucrose).*

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

Residue on ignition ⟨281⟩**:** not more than 0.05%.

Heavy metals, *Method II* ⟨231⟩**:** not more than 5 µg per g, an ignition temperature of 500° being used.

Total solids—Determine the refractive index of Syrup at 20° or 45° (see *Refractive Index* ⟨831⟩). Use the table below for calculating the percentage of dry substance (percentage of total solids).

Fructose Content	% Dry Substance	Refractive Index at 20°	Refractive Index at 45°
42%	70.5	1.4632	1.4577
	71.0	1.4643	1.4589
	72.0	1.4667	1.4612
	73.0	1.4691	1.4635
55%	76.5	1.4774	1.4716
	77.0	1.4786	1.4728
	78.0	1.4811	1.4752
	79.0	1.4835	1.4776

Limit of sulfur dioxide—Transfer about 100 g of Syrup, accurately weighed, to a 250-mL conical flask, add 100 mL of water, and mix. Cool to between 5° and 10°. While stirring with a magnetic stirrer, add 10 mL of cold 1.5 N sodium hydroxide (at a temperature between 5° and 10°). Stir for an additional 20 seconds, and add 10 mL of starch indicator solution prepared as follows. Mix 10 g of soluble starch with 50 mL of cold water, transfer to 1000 mL of boiling water, stir until completely dissolved, cool, and add 1 g of salicylic acid preservative. [NOTE—Discard the solution after 1 month.] Add 10 mL of 2.0 N sulfuric acid (at a temperature between 5° and 10°), and titrate immediately with 0.005 N iodine VS until a light blue color persists for 1 minute (see *Titrimetry* ⟨541⟩). Perform a blank determination, using 200 mL of water treated similarly to the solution under test, and make any necessary correction. Each mL of 0.005 N iodine is equivalent to 0.16 mg of SO_2: not more than 30 µg per g is found.

Limit of lead—[NOTE—For the preparation of all aqueous solutions and for the rinsing of glassware before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. For digestion, use acid-cleaned, high-density polyethylene, polypropylene, polytef, or quartz tubes. Select all reagents to have as low a content of lead as practicable, and store all reagent solutions in borosilicate glass containers. Cleanse glassware before use by soaking in warm 8 N nitric acid for 30 minutes, and rinsing with deionized water. Store final diluted solutions in acid-cleaned plastic or polytef tubes or bottles.]

Modifier solution—Prepare a solution of magnesium nitrate in water containing about 200 mg per mL. Just before use, transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with 5% nitric acid to volume, and mix.

Standard solutions—Transfer 10.0 mL of *Lead Nitrate Stock Solution,* prepared as directed under *Heavy Metals* ⟨231⟩, to a 100-mL volumetric flask, add 40 mL of water and 5 mL of nitric acid, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a second 100-mL volumetric flask, dilute with 5% nitric acid to volume, and mix. This solution contains 0.1 µg of lead per mL. Transfer portions of this solution to four suitable containers, and dilute quantitatively, and stepwise if necessary, with 5% nitric acid to obtain *Standard solutions* having lead concentrations of 100 ng per mL, 50 ng per mL, 25 ng per mL, and 10 ng per mL, respectively.

Test solution—[NOTE—Perform this procedure in a fume hood.] Transfer about 1.5 g of Syrup, accurately weighed, to two digestion tubes, labeled "Test solution" and "Temper-

ature monitor solution", and add 0.75 mL of nitric acid to each tube. Warm both solutions slowly to between 90° and 95° to avoid spattering. Heat until all brown vapors have dissipated and any rust-colored tint is gone from the tube labeled "Test solution" (20 to 30 minutes). Cool, add 0.5 mL of 50% hydrogen peroxide dropwise to both solutions, heat to between 90° and 95° for 5 minutes, and cool. Add a second 0.5-mL portion of 50% hydrogen peroxide dropwise to each solution, and heat to between 90° and 100° for 5 to 10 minutes until the tube labeled "Test solution" is clear. Cool, and transfer the *Test solution* to a 10-mL volumetric flask. Rinse the tube labeled "Test solution" with 5% nitric acid, add the rinsing to the volumetric flask, dilute with 5% nitric acid to volume, and mix.

Standard blank—Use 5% nitric acid.

Test blank—Transfer 1.5 g of water to a digestion tube, and proceed as directed for the *Test solution,* beginning with "add 0.75 mL of nitric acid."

Procedure—[NOTE—Use peak area measurements for all quantitations.] Add 5 µL of the *Modifier solution* to 20 µL each of the *Standard solutions,* the *Test solution,* the *Standard blank,* and the *Test blank,* and mix. Separately inject equal volumes (about 20 µL) of the *Standard solutions,* the *Test solution,* the *Standard blank,* and the *Test blank* into a suitable graphite furnace atomic absorption spectrophotometer equipped with pyrolytically coated graphite tubes and adequate means of background correction. The temperature is programmed as follows. Maintain the drying temperature of the furnace at 200° for 30 seconds after a 20-second ramp time using an argon gas flow of about 300 mL per minute; maintain the ashing temperature at 750° for 40 seconds after a 40-second ramp time using an airflow of about 300 mL per minute; cool down and purge the air from the furnace for 60 seconds using a 20° set temperature and an argon gas flow of about 300 mL per minute; and maintain the atomization temperature at 1800° for 10 seconds after a 0-second ramp time with the argon gas flow stopped. [NOTE—The temperature program may be modified to obtain optimum furnace temperatures.] Using the *Standard blank* to set the instrument to zero, determine the integrated absorbances of the *Standard solutions* at the lead emission line at 283.3 nm. Plot the integrated absorbances of the *Standard solutions* versus their contents of lead, in ng per mL, and draw the line best fitting the four points to determine the calibration curve. Similarly determine the integrated absorbances of the *Test solution* and the *Test blank* at the lead emission line at 283.3 nm. Correct the absorbance value of the *Test solution* by subtracting from it the absorbance value obtained from the *Test blank*. Calculate the concentration, in µg per g, of lead in the portion of Syrup taken by the formula:

$$0.01(C/W)$$

in which C is the concentration, in ng per mL, of lead in the *Test solution,* as determined from the calibration curve; and W is the weight, in g, of Syrup taken to prepare the *Test solution:* the limit is 0.1 µg per g.

Assay—

Mobile phase—Use filtered and degassed water.

Standard preparation—Prepare a solution in water containing a total of about 10% saccharide solids of USP Dextrose RS, USP Fructose RS, and USP Maltose Monohydrate RS, in which the USP Dextrose RS and USP Fructose RS percentage concentrations are in the same ratio as those in the *Assay preparation,* based on the labeled nominal fructose percentage for the Syrup under test. Calculate the percentage of USP Maltose Monohydrate RS by the formula:

$$100 - (F + D)$$

in which F is the labeled nominal fructose percentage for the Syrup under test; and D is the difference between the specified minimum percentage concentration of total monosaccharides for the Syrup and *F.*

Assay preparation—Dilute a known volume of Syrup, determined from the results of the test for *Total solids* and on the nominal total saccharides content, with water to a total saccharides concentration of about 10% (w/v), and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector maintained at 45° and a 7.8-mm × 30-cm column that contains packing L19. The column is maintained at a constant temperature of about 85°. The flow rate is about 0.6 mL per minute. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.83, 1.0, and 1.32 for maltose, dextrose, and fructose, respectively; and the resolution, *R,* between maltose and dextrose is not less than 1.2.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of fructose and of dextrose in the portion of Syrup taken by the formula:

$$100C(V_A/V_S S_1 S_2)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Fructose RS or USP Dextrose RS in the *Standard preparation;* V_A is the volume, in mL, of the *Assay preparation;* V_S is the volume, in mL, of Syrup taken to prepare the *Assay preparation;* S_1 is the percentage of total saccharides in the *Standard preparation* (corresponding to 97 for High Fructose Corn Syrup 42% and to 95 for High Fructose Corn Syrup 55%); S_2 is the percentage of total solids in the Syrup as determined in the test for *Total solids;* and r_U and r_S are the peak areas of fructose or dextrose obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the percentage of other saccharides, expressed in terms of maltose, in the portion of Syrup taken by the formula:

$$C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Maltose Monohydrate RS in the *Standard preparation;* r_U is the sum of all peak areas obtained from the *Assay preparation,* except those of fructose and dextrose; and r_S is the peak area of maltose obtained from the *Standard preparation.* ■2S (*NF25*)

BRIEFING

Isomalt, *NF 24* page 3354. On the basis of comments received, it is proposed to revise *Identification* test *A* as well as the formula in the test for *Related compounds.*

(EM1: C. Sheehan) RTS—C43794

Change to read:

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture containing a fluorescent indicator having optimal intensity at 254 nm.

Test solution: 5000 µg per mL in water.

Application volume: 1 µL.

Developing solvent system: a mixture of ethyl acetate, pyridine, water, acetic acid, and propionic acid (50 : 50 : 10 : 5 : 5).

Procedure—Separately apply 1 µL each of the Standard solution and the *Test solution* to the thin-layer chromatographic plate, and thoroughly dry the starting points in warm air. Develop over 10 cm using the *Developing solvent system,* dry the plate in a current of hot air, and dip for 3 seconds in a 1 g per L solution of sodium periodate. Dip the plate for 3 seconds in a mixture of dehydrated alcohol, sulfuric acid, acetic acid, and anisaldehyde (90 : 5 : 1 : 1). Dry the plate in a current of hot air until colored spots become visible. The background color may be brightened by exposure to warm steam. Examine in daylight. ~~The chromatogram obtained from the Standard solution shows two blue-grey spots with R_F values of about 0.13 (1,6-GPS) and 0.16 (1,1-GPM). The chromatogram obtained from the *Test solution* shows principal spots similar in position and color to the chromatogram obtained from the Standard solution.~~

■The chromatograms obtained from the Standard solution and the *Test solution* show principal spot(s) similar in position and color. ■2S (*NF25*)

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B: The retention times of the two principal peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Change to read:

Related compounds—

Mobile phase—Prepare as directed in the *Assay.*

Resolution solution—Dissolve accurately weighed quantities of USP Isomalt RS, USP Mannitol RS, and USP Sorbitol RS, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 20 mg per mL, 0.1 mg per mL, and 0.1 mg per mL, respectively.

Standard solution—Dissolve an accurately weighed quantity of USP Sorbitol RS and USP Mannitol RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg of each per mL.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the typical retention time of 1,1-GPM is about 12.3 minutes; the relative retention times are about 1.2 for 1,6-GPS, about 1.6 for mannitol, about 2.0 for sorbitol, and 1.0 for 1,1-GPM; and the resolution, *R,* between 1,1-GPM and 1,6-GPS is not less than 2.0.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of mannitol or sorbitol in the portion of Isomalt taken by the formula:

$$5000C/W(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Mannitol RS or USP Sorbitol RS in the *Standard solution; W* is the weight, in mg, of Isomalt used to prepare the *Test solution;* and r_U and r_S are the individual peak responses of mannitol or sorbitol obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.5% of mannitol and not more than 0.5% of sorbitol is found. Calculate the percentage of any ~~other~~

■unknown■2S (*NF25*)
impurity in the portion of Isomalt taken by the formula:

~~$100(r_i/r_u)$~~

~~in which r_i is the peak response for each impurity, and r_u is the sum of the responses of all the peaks obtained from the *Test solution.*~~

■$5000C/W(r_i/r_S)$

in which C is the concentration, in mg per mL, of USP Sorbitol RS in the *Standard solution; W* is the weight, in mg, of Isomalt used to prepare the *Test solution;* r_i is the peak response of each unknown impurity; and r_S is the peak response of Sorbitol in the *Standard solution:*■2S (*NF25*)
not more than 0.5% of any individual impurity is found; and not more than 2.0% of total impurities, including mannitol and sorbitol, is found. Disregard any impurity peak that is less than 0.1%.

BRIEFING

Polydextrose. Because there is no existing *NF* monograph for this article, it is proposed to add a new monograph based on the Polydextrose monograph in the *Food Chemicals Codex, Fifth Edition,* pages 336–339 and also on the Polydextroses monograph in the *51st Joint FAO/WHO Expert Committee on Food Additives (JECFA),* 1998.

(EM2: H. Wang; NOM: W. Paul) RTS—C44166

Add the following:

■Polydextrose

Modified polydextrose [*68424-04-4*].

» Polydextrose is a randomly bonded polymer prepared by melting and subsequent condensation of the ingredients, which consist of approximately 90 parts dextrose, 10 parts sorbitol, and up to 1 part citric acid or 0.1 part phosphoric acid. The 1,6-glycosidic linkage predominates in the polymer but other linkages are present. It contains not less than 90.0 percent of dextrose polymer units, calculated on the anhydrous and ash-free basis. It contains small quantities of free dextrose, sorbitol, and 1,6-anhydro-D-glucose (levoglucosan), with traces of citric acid or phosphoric acid. It may be untreated, or neutralized with potassium hydroxide and decolorized and deionized for further purification. It may be partially reduced by transition metal catalytic hydrogenation in an aqueous solution.

Packaging and storage—Preserve in tight, light-resistant containers. No storage requirements specified.

USP Reference standards ⟨11⟩—*USP 1,6-Anhydro-D-glucose RS. USP Dextrose RS. USP Sorbitol RS.*

Identification—

A: To 1 drop of a solution (1 in 10), add 4 drops of 5% phenol solution, then rapidly add 15 drops of sulfuric acid TS: a deep yellow to orange color is produced.

B: With vigorous swirling, add 1 mL of acetone to 1 mL of a solution (1 in 10): the solution remains clear.

C: With vigorous swirling, add 2 mL of acetone to the solution obtained in *Identification* test *B:* a heavy, milky turbidity develops immediately.

D: To 1 mL of a solution (1 in 50), add 4 mL of alkaline cupric citrate TS. Boil vigorously for 2 to 4 minutes. Remove from heat, and allow the precipitate (if any) to settle: the supernatant is blue or blue-green.

pH ⟨791⟩**:** between 2.5 and 7.0, in a solution (1 in 10) for untreated Polydextrose; between 5.0 and 6.0, in a solution (1 in 10) for neutralized and/or decolorized Polydextrose.

Water, *Method I* ⟨921⟩**:** not more than 4.0%, anhydrous pyridine being used in place of methanol in the titration vessel.

Residue on ignition ⟨281⟩**:** not more than 0.3% for untreated Polydextrose; not more than 2.0% for neutralized and/or decolorized Polydextrose.

Limit of lead—[NOTE—Use reagent-grade chemicals with as low a lead content as is practicable, as well as high-purity water and gases. Before use in this analysis, rinse all glassware and plasticware twice with 10% nitric acid and twice with 10% hydrochloric acid, and then rinse them thoroughly with *Purified Water*.]

Matrix modifier solution—Prepare a solution in water containing 100.0 mg of dibasic ammonium phosphate per 10 mL of solution.

Lead nitrate stock solution—Dissolve 159.8 mg of lead nitrate in 100 mL of water to which has been added 1 mL of nitric acid, then dilute with water to 1000 mL. Prepare and store this solution in glass containers free from soluble lead salts.

Standard lead solution—On the day of use, dilute 10.0 mL of *Lead nitrate stock solution* with water to 100.0 mL, and mix. Each mL of *Standard lead solution* contains the equivalent of 10 µg of lead.

Standard solutions—Into five separate 100-mL volumetric flasks, pipet 0.2, 0.5, 1, 2, and 5 mL, respectively, of *Standard lead solution*, dilute with water, and mix. The *Standard solutions* contain 0.02, 0.05, 0.1, 0.2, and 0.5 µg of lead per mL, respectively.

Test solution—Transfer about 1.0 g of Polydextrose, accurately weighed and calculated on the anhydrous and ash-free basis, into a 10-mL volumetric flask, dissolve in water, dilute with water to volume, and mix.

Spiked test solution—Transfer about 1.0 g of Polydextrose, accurately weighed and calculated on the anhydrous and ash-free basis, into a 10-mL volumetric flask, and dissolve in water. Add 100 µL of the *Standard lead solution,* dilute with water to volume, and mix. This solution contains 0.1 µg of added lead per mL.

Procedure—Concomitantly determine the absorbances of 10-µL aliquots of the five *Standard solutions,* a mixture of 10 µL of the *Matrix modifier solution* and 10 µL of the *Test solution,* and a mixture of 10 µL of the *Matrix modifier solution* and 10 µL of the *Spiked test solution* at the lead emission line at 283.3 nm, with a suitable graphite furnace atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩). The spectrophotometer is equipped with a pyrolytic tube with a platform and a lead hollow-cathode lamp, using a slit width of 0.7 mm (set low) and a deuterium arc lamp for background correction. The drying temperature of the furnace is maintained at 130° for 40 seconds after a 20-second ramp time using an argon flow rate of 300 mL per minute; the ashing temperature is maintained at 800° for 40 seconds after a 20-second ramp time using an argon flow rate of 300 mL per minute; and the atomization temperature is maintained at 2400° for 6 seconds using an argon flow rate of 50 mL per minute. Clean the graphite furnace at 2600° for 5 seconds after a 1-second ramp time

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using an argon flow rate of 300 mL per minute, and recharge the graphite furnace at 20° for 20 seconds after a 2-second ramp time using an argon flow rate of 300 mL per minute. Plot the absorbance of each *Standard solution,* compensated for background correction, versus its content of lead, in µg per mL, and draw the best straight line fitting the five points. From this plot, determine the concentrations, C_T and C_{ST}, in µg per mL, of lead in the *Test solution* and the *Spiked test solution*, respectively. Calculate the percentage recovery taken by the formula:

$$100[(C_{ST} - C_T)/0.1]$$

in which 0.1 is the amount of lead, in µg per mL, added to the *Spiked test solution*. Calculate the content, in µg per g, of lead in Polydextrose taken by the formula:

$$10C_T/W$$

in which W is the weight, in g, of Polydextrose taken to prepare the *Test solution:* not more than 0.5 µg of lead per g is found.

Limit of 5-hydroxymethylfurfural and related compounds—

Test solution—Transfer about 1.0 g of Polydextrose, accurately weighed and calculated on the anhydrous and ash-free basis, into a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Procedure—Determine the absorbance of the *Test solution* in a 1-cm quartz cell at 283 nm, with a suitable spectrophotometer, using water as the blank. Calculate the percentage of 5-hydroxymethylfurfural and related compounds in the Polydextrose taken by the formula:

$$100[(0.1)(126)A]/(16{,}830LW)$$

in which 0.1 is the volume, in L, of the *Test solution;* 126 is the molecular weight, in g per mol, of 5-hydromethylfurfural; A is the absorbance of the *Test solution;* 16,830 is the molar extinction coefficient, in L per mol per cm, of 5-hydromethylfurfural at a wavelength of 283 nm; L is the path length, in cm, of the spectrophotometer cell; and W is the weight, in g, of Polydextrose taken to prepare the *Test solution:* not more than 0.1% is found.

Molecular weight limit—

Mobile phase—Dissolve 35.0 g of sodium nitrate and 1.0 g of sodium azide in 100 mL of water. Dilute with water to 4 L, and mix. Pass through a 0.45-µm filter or finer porosity, and degas by applying an aspirator vacuum for 30 minutes. The resulting *Mobile phase* is 0.1 N sodium nitrate containing 0.025% sodium azide.

Standard solution—Transfer about 20 mg each of USP Dextrose RS, stachyose, and 5800-, 23,700-, and 100,000-molecular weight (MW) pullulan standards, accurately weighed, into a 10-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix. Pass through a syringe filter having a 0.45-µm or finer porosity into a suitable autosampler vial, and seal.

Test solution—Transfer about 50 mg of Polydextrose, accurately weighed, into a 10-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix. Pass through a syringe filter having a 0.45-µm or finer porosity into a suitable autosampler vial, and seal.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector set at a sensitivity of 4×10^{-6} refractive index units full scale and is maintained at a temperature of $35 \pm 0.1°$ and a 7.8-mm × 30-cm column that contains packing L25 and is maintained at a temperature of 45°. The flow rate is about 0.8 mL per minute. [NOTE—After installation of a new column, pump *Mobile phase* through the column overnight at a rate of about 0.3 mL per minute. Before calibration or analysis, increase the flow slowly over a 1-minute period to 0.8 mL per minute. Continue to pump *Mobile phase* through the column at this flow rate for at least 1 hour before the first injection. Check the flow gravimetrically, and adjust it if necessary. Reduce the flow rate to about 0.1 mL per minute when the

system is not in use.] Chromatograph replicate injections of the *Standard solution*, allowing 15 minutes between injections, and record the retention times of the components of the *Standard solution* as directed for *Procedure:* the retention times for each component determined on replicate injections agree within ±2 seconds; and dextrose and stachyose are baseline resolved from one another and from the 5800-MW pullulan standard. [NOTE—Elevated valleys are usually observed between the peaks for the three pullulan standards.]

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the retention times for the major peaks. Plot the average retention time, in seconds, of each component in the *Standard solution,* versus its molecular weight, in g per mol, of each component, draw the best cubic line fitting the five points, and calculate the correlation coefficient for the line. A suitable system is one that yields a line having a correlation coefficient of not less than 0.99. From the molecular weight distribution graph, generate a MW distribution profile of Polydextrose: no measurable peak above a molecular weight of 22,000 is found.

Limit of monomers—

Internal standard solution—Transfer about 50 mg of *n*-octadecane, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with pyridine to volume, and mix.

Standard stock solution—Dissolve accurately weighed quantities of USP Dextrose RS, USP Sorbitol RS, and USP 1,6-Anhydro-D-glucose RS in pyridine to obtain a solution having a known concentration of about 0.5 mg of dextrose, about 0.4 mg of sorbitol, and about 0.35 mg of 1,6-anhydro-D-glucose per mL.

Standard solution—Transfer 1.0 mL of *Standard stock solution* to a reaction vial equipped with a screw cap. Add 1.0 mL of *Internal standard solution* and 0.5 mL of *N*-(trimethylsilyl)imidazole to the reaction vial, seal the vial with the screw cap, and mix. Place the vial in an ultrasonic bath at 70° for 60 minutes, remove, and allow the contents to cool.

Test solution—Transfer 20 mg of Polydextrose, accurately weighed and calculated on the anhydrous and ash-free basis, into a reaction vial equipped with a screw cap. Add 1.0 mL of *Internal standard solution,* 1.0 mL of pyridine, and 0.5 mL of *N*-(trimethylsilyl)imidazole to the reaction vial, seal the vial with the screw cap, and mix. Place the vial in an ultrasonic bath at 70° for 60 minutes, remove, and allow the contents to cool.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and 2-mm × 250-cm glass column packed with 3% phase G2 on support S1AB. The detector temperature is maintained at about 230°. The column temperature is maintained at about 175°, and the injection port temperature is maintained at about 210°. Chromatograph the *Standard solution,* and record the peak response as directed for *Procedure*. [NOTE—For peak identification purposes, relative retention times are 0.3, 0.4, 0.45, 0.8, 1.0, and 1.2 for D-anhydroglucose (levoglucosan) pyranose form, D-anhydroglucose furanose form (not present in standard), *n*-octadecane, alpha-D-glucose; D-sorbitol, beta-D-glucose, respectively.]

Procedure—Separately inject equal volumes (about 3 µL) of the *Standard solution* and the *Test solution* into the chromatograph. Record the chromatograms and measure the responses for the major peaks. Calculate the percentage of each monomer in Polydextrose taken by the formula:

$$(100C / W) / (R_U / R_S)$$

in which C is the concentration, in mg per mL, of the respective monomer in the *Standard stock solution; W* is the weight, in mg, of Polydextrose taken to prepare the *Test solution;* R_U and R_S are the ratios of the peak of the respective monomer silyl derivative peak to the peak area of the internal standard peak obtained from the *Test solution* and the

Standard solution, respectively: not more than 4.0% of 1,6-anhydrous-D-glucose is found, and not more than 6.0% of dextrose and sorbitol is found. [NOTE—In the case of glucose, the peak areas for the alpha- and beta-epimers are combined, and in the case of 1,6-anhydro-D-glucose, the peak areas for the pyranose and furanose forms are combined.]

Limit of nickel—[NOTE—This test is required only for hydrogenated Polydextrose.]

Blank solution—Add 2.0 mL of a saturated solution of ammonium pyrrolidinedithiocarbamate TS, into 150.0 mL of strong acetic acid TS, and mix. Add 10.0 mL of methyl isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer.

Standard solutions—Into three identical 250-mL volumetric flasks, dissolve about 20.0 g of hydrogenated Polydextrose, accurately weighed, in strong acetic acid TS, and dilute with strong acetic acid TS to 150.0 mL. Into these three volumetric flasks, introduce respectively 0.5, 1.0, and 1.5 mL of nickel standard solution TS, and mix. To each flask, add 2.0 mL of a saturated solution of ammonium pyrrolidinedithiocarbamate TS, and 10.0 mL of methyl isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer. These *Standard solutions* are fortified with the equivalent of 0.5, 1.0, and 1.5 µg per g of nickel from the nickel standard solution TS.

Test solution—Dissolve about 20.0 g of hydrogenated Polydextrose, accurately weighed, in strong acetic acid TS, and dilute with strong acetic acid TS to 150.0 mL. Add 2.0 mL of a saturated solution of ammonium pyrrolidinedithiocarbamate TS, and 10.0 mL of methyl isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at least three times each, at the wavelength of maximum absorbance at 232.0 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with an air–acetylene flame and a nickel hollow-cathode lamp using the *Blank solution* to zero the instrument. Record the average of the steady readings for each of the *Standard solutions* and the *Test solution*. Between each measurement, aspirate the *Blank solution,* and ascertain that the reading returns to its initial blank value. Plot the absorbances of the *Standard solutions* and the *Test solution* versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel in the *Test solution*: not more than 2 µg per g is found.

Assay—

Phenol solution—Add 20 mL of water to 80 g of phenol, and mix.

Dextrose stock standard solution—Transfer 100 mg of USP Dextrose RS, accurately weighed, to a 500-mL volumetric flask, dilute with water to volume, and mix.

Standard preparations—Quantitatively dilute the *Dextrose stock standard solution* with water to obtain five *Standard preparations* containing 5, 10, 20, 40, and 50 µg of dextrose per mL, respectively.

Assay preparation—Transfer approximately 10 mg of Polydextrose, accurately weighed and calculated on the anhydrous and ash-free basis, to a 250-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Freshly pipet 2.0 mL of each of the *Standard preparations* into a separate acetone-free, 15-mL vial equipped with a screw-cap. Transfer 2.0 mL of the *Assay preparation* to a separate acetone-free, 15-mL vial equipped with a screw-cap, and transfer 2.0 mL of water to a separate acetone-free, 15-mL vial equipped with a screw-cap to provide a blank. To each vial, add 0.12 mL of the *Phenol solution,* cap the vial, and mix gently. Uncap each vial, and rapidly add 5.0 mL of sulfuric acid. Immediately recap each vial, and shake vigorously. *[Caution—Wear rubber gloves and a safety shield while adding sulfuric acid.]* Allow the

vials to stand at room temperature for 45 minutes. Concomitantly determine the absorbances of the solutions in 1-cm cells at 490 nm with a suitable spectrophotometer, using the blank to set the instrument. Prepare a standard curve by plotting the absorbances of the solutions from the *Standard preparations* versus their contents of dextrose, in µg per mL. Draw the straight line best fitting the five points, and extrapolate the line until it intercepts the absorbance axis (*y* axis). From the curve, determine the concentration C_D, in µg per mL, of dextrose in the *Assay preparation*. Calculate the percentage of dextrose polymer units in the Polydextrose taken by the formula:

$$1.05(25C_D / W_T - P_G - 1.11P_L)$$

in which 1.05 is an experimentally derived correction factor to account for the polymer (which also contains a small amount of sorbitol) not giving the exact amount of color given by an equivalent amount of glucose monomers; W_T is the weight, in mg, of the Polydextrose taken to prepare the *Assay preparation;* P_G and P_L are the percentages of dextrose and 1,6-anhydrous-D-glucose (levoglucosan) determined, respectively, in the test for *Limit of monomers;* and 1.11 is a conversion factor from 1,6-anhydrous-D-glucose, which gives an equivalent amount of color to an equivalent weight of glucose.■2S (*NF25*)

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**11**〉 **USP Reference Standards,** *USP 29* page 2458, page 3591 of the *First Supplement,* page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 1601 of *PF* 29(5) [Sept.–Oct. 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], page 1154 of *PF* 31(4) [July–Aug. 2005], page 1433 of *PF* 31(5) [Sept.–Oct. 2005], page 1680 of *PF* 31(6) [Nov.–Dec. 2005], page 181 of *PF* 32(1) [Jan.–Feb. 2006], page 407 of *PF* 32(2) [Mar.–Apr. 2006], and page 829 of *PF* 32(3) [May–June 2006].

(HDQ) RTS—C30631; C39733; C41734; C41770; C43102; C43837; C43862; C44166; C44223; C45484; C45811

Add the following:

■**USP Actein RS—**[To come.]■2S (*USP30*)

Add the following:

■**USP 1,6-Anhydro-D-glucose RS.**■2S (*USP30*)

Add the following:

■**USP Bemotrizinol RS.**■2S (*USP30*)

Add the following:

■**USP Capecitabine RS.**■2S (*USP30*)

Add the following:

■**USP Capecitabine Related Compound A RS—**[To come.]■2S (*USP30*)

Add the following:

■**USP Capecitabine Related Compound B RS—**[To come.]■2S (*USP30*)

Add the following:

■**USP Capecitabine Related Compound C RS—**[To come.]■2S (*USP30*)

Add the following:

■**USP Carvedilol RS.**■2S (*USP30*)

Add the following:

■**USP Carvedilol Related Compound A RS [**1-[[9-[2-hydroxy-3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]-9*H*-carbazol-4-yl]oxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol**]**—[To come.]■2S (*USP30*)

Add the following:

■**USP Carvedilol Related Compound B RS [**1,1′-[[2-(2-methoxyphenoxy)ethyl]nitrilo]bis[3-(9*H*-carbazol-4-yloxy)-propan-2-ol**]**—[To come.]■2S (*USP30*)

Add the following:

■**USP Carvedilol Related Compound C RS [**(2*RS*)-1-[benzyl[2-(2-methoxyphenoxyethyl]amino]-3-(9*H*-cabazol-4-yloxy)propan-2-ol**]**—[To come.]■2S (*USP30*)

Add the following:

■**USP Carvedilol Related Compound D RS [**4-(2,3-epoxy-propoxy)carbazole**]**—[To come.]■2S (*USP30*)

Add the following:

■**USP Carvedilol Related Compound E RS [**2-(2-methoxy-phenoxy)ethylamine**]**—[To come.]■2S (*USP30*)

Add the following:

■**USP Powdered Cat's Claw Extract RS.** ■2S (*USP30*)

Add the following:

■**USP Citalopram Related Compound G RS [**1-(4-fluoro-phenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane hydrobromide**]** ($C_{19}H_{21}ClFNO \cdot HBr$ ✧ 414.5).■2S (*USP30*)

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Add the following:

■**USP Citalopram Related Compound H RS** [1-4-fluorophenyl-1-(3-dimethylaminopropyl)-5-bromophthalane hydrobromide] $C_{19}H_{21}BrFNO \cdot HBr$ ✧ 459.1.■2S (*USP30*)

Add the following:

■**USP Deacetylnorgestimate RS** [mixture of *syn*-17-deacetylnorgestimate and *anti*-17-deacetylnorgestimate]—[To come.]■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound D RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound E RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound F RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound G RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound H RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound I RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Isopteropodine RS**—[To come.]■2S (*USP30*)

Change to read:

USP Norgestimate Oxime Mixture RS ~~[mixture of *syn*-17-deacetyl norgestimate and *anti*-17-deacetyl norgestimate]~~ —■(NAME CHANGE) See *USP Deacetylnorgestimate RS.*■2S (*USP30*)

Add the following:

■**USP Pancuronium Bromide Related Compound A RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Pancuronium Bromide Related Compound B RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Pancuronium Bromide Related Compound C RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Pancuronium Internal Standard RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Permethrin RS.**■2S (*USP30*)

Add the following:

■**USP Permethrin Related Compound A RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Permethrin Related Compound B RS**—[To come.]■2S (*USP30*)

Add the following:

■**USP Phenothiazine RS**—[To come.]■2S (*USP30*)

Add the following:

~~■USP Promethazine Related Compound A RS■ —[To come.] ■1S (*USP30*)~~■2S (*USP30*)

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Physical Tests and Determinations

BRIEFING

⟨**621**⟩ **Chromatography,** *USP 29* page 2639, page 3595 of the *First Supplement,* the *Second Interim Revision Announcement* on page 265 of *PF* 32(2) [Mar.–Apr. 2006], and page 831 of *PF* 32(3) [May–June 2006]. On the basis of comments received, the General Chapters Expert Committee has introduced changes in the *System Suitability* section. It is proposed to eliminate the reference to chapter ⟨1226⟩ and give to the user the reponsibility of verifying the impact of the changes made on the official method.

In order to avoid unnecessary republishing of this chapter each time a chromatographic reagent is modified or new chromatographic reagents are added to the existing lists, the Expert Committee has proposed to move the lists of *Packings, Phases,* and *Supports* under *Chromatographic Reagents* to a new section called *Chromatographic Reagents* under *Reagents, Indicators, and Solutions.*

In addition, minor revisions are proposed in the sections *Introduction, Thin-Layer Chromatography,* and *Interpretation of Chromatograms.*

(GC: H. Pappa) RTS—C43823; C43930

Change to read:

INTRODUCTION

This chapter defines the terms and procedures used in chromatography and provides general information. Specific requirements for chromatographic procedures for drug substances and dosage forms, including adsorbent and developing solvents, are given in the individual monographs.

Chromatography is defined as a procedure by which solutes are separated by a dynamic differential migration process in a system consisting of two or more phases, one of which moves continuously in a given direction and in which the individual substances exhibit different mobilities by reason of differences in adsorption, partition, solubility, vapor pressure, molecular size, or ionic charge density. The individual substances thus separated can be identified or determined by analytical procedures.

The general chromatographic technique requires that a solute undergo distribution between two phases, one of them fixed (stationary phase), the other moving (mobile phase). It is the mobile phase that transfers the solute through the medium until it eventually emerges separated from other solutes that are eluted earlier or later. Generally, the solute is transported through the separation medium by means of a flowing stream of a liquid or a gaseous solvent known as the ''eluant.'' The stationary phase may act through adsorption, as in the case of adsorbents such as activated alumina and silica gel, or it may act by dissolving the solute, thus partitioning the latter between the stationary and mobile phases. In the latter process, a liquid coated onto an inert support, or chemically bonded onto silica gel, or directly onto the wall of a fused silica capillary, serves as the stationary phase. Partitioning is the predominant mechanism of separation in gas–liquid chromatography, paper chromatography, in forms of column chromatography, and in thin-layer chromatography designated as liquid-liquid ~~separation~~

■chromatography.■2S (*USP30*)

In practice, separations frequently result from a combination of adsorption and partitioning effects. Other separation principles include ion exchange, ion-pair formation, size exclusion, hydrophobic interaction, and chiral recognition.

The types of chromatography useful in qualitative and quantitative analysis that are employed in the *USP* procedures are column, gas, paper, thin-layer, (including high-performance thin-layer chromatography), and pressurized liquid chromatography (commonly called high-pressure or high-performance liquid chromatography). Paper and thin-layer chromatography are ordinarily more useful for purposes of identification because of their convenience and simplicity. Column chromatography offers a wider choice of stationary phases and is useful for the separation of individual compounds, in quantity, from mixtures. Modern high-performance thin-layer chromatography, gas chromatography, and pressurized liquid chromatography require more elaborate apparatus but usually provide high resolution and identify and quantitate very small amounts of material.

Use of Reference Substances in Identity Tests—In paper and thin-layer chromatography, the ratio of the distance (this distance being measured to the point of maximum intensity of the spot or zone) traveled on the medium by a given compound to the distance traveled by the front of the mobile phase, from the point of application of the test substance, is designated as the R_F value of the compound. The ratio between the distances traveled by a given compound and a reference substance is the R_R value. R_F values vary with the experimental conditions, and thus identification is best accomplished where an authentic specimen of the compound in question is used as a reference substance on the same chromatogram.

For this purpose, chromatograms are prepared by applying on the thin-layer adsorbent or on the paper in a straight line, parallel to the edge of the chromatographic plate or paper, solutions of the substance to be identified, the authentic specimen, and a mixture of nearly equal amounts of the substance to be identified and the authentic specimen. Each sample application contains approximately the same quantity by weight of material to be chromatographed. If the substance to be identified and the authentic specimen are identical, all chromatograms agree in color and R_F value and the mixed chromatogram yields a single spot; i.e., R_R is 1.0.

Location

■**and Identification**■2S (*USP30*)
of Components—The spots produced by paper or thin-layer chromatography may be located by: (1) direct inspection if the compounds are visible under white or either short-wavelength (254 nm) or long-wavelength (360 nm) UV light, (2) inspection in white or UV light after treatment with reagents that will make the spots visible (reagents are most conveniently applied with an atomizer), (3) use of a Geiger-Müller counter or autoradiographic techniques in the case of the presence of radioactive substances, or (4) evidence resulting from stimulation or inhibition of bacterial growth by the placing of removed portions of the adsorbent and substance on inoculated media.

In open-column chromatography, in pressurized liquid chromatography performed under conditions of constant flow rate, and in gas chromatography, the retention time, *t,* defined as the time elapsed between sample injection and appearance of the peak concentration of the eluted sample zone, may be used as a parameter of identification. Solutions of the substance to be identified or derivatives thereof, of the reference compound, and of a mixture of equal amounts of these two are chromatographed successively on the same column under the same chromatographic conditions. Only one peak should be observed for the mixture. The ratio of the retention times of the test substance, the reference compound, and a mixture of these, to the retention time of an internal standard is called the relative retention time R_R and is also used frequently as a parameter of identification.

The deviations of R_R, R_F, or t values measured for the test substance from the values obtained for the reference compound and mixture should not exceed the reliability estimates determined statistically from replicate assays of the reference compound.

Chromatographic identification by these methods under given conditions strongly indicates identity but does not constitute definitive identification. Coincidence of identity parameters under three to six different sets of chromatographic conditions (temperatures, column packings, adsorbents, eluants, developing solvents, various chemical derivatives, etc.) increases the probability that the test and reference substances are identical. However, many isomeric compounds cannot be separated. Specific and pertinent chemical, spectroscopic, or phys-

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icochemical identification of the eluted component combined with chromatographic identity is the most valid criterion of identification. For this purpose, the individual components separated by chromatography may be collected for further identification.

Change to read:

THIN-LAYER CHROMATOGRAPHY

In thin-layer chromatography, the adsorbent is a relatively thin, uniform layer of dry, finely powdered material applied to a glass, plastic, or metal sheet or plate, glass plates being most commonly employed. The coated plate can be considered an ''open chromatographic column'' and the separations achieved may be based upon adsorption, partition, or a combination of both effects, depending on the particular type of stationary phase, its preparation, and its use with different solvents. Thin-layer chromatography on ion-exchange layers can be used for the fractionation of polar compounds. Presumptive identification can be effected by observation of spots or zones of identical R_F value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size or intensity of the spots or zones may serve for semiquantitative estimation. Quantitative measurements are possible by means of densitometry (absorbance or fluorescence measurements), or the spots may be carefully removed from the plate, followed by elution with a suitable solvent and spectrophotometric measurement. For two-dimensional thin-layer chromatography, the chromatographed plate is turned at a right angle and again chromatographed, usually in another chamber equilibrated with a different solvent system.

Apparatus—Acceptable apparatus and materials for thin-layer chromatography consist of the following.

A *TLC or HPTLC plate.* The chromatography is generally carried out using *precoated plates* or *sheets* (on glass, aluminum, or polyester support) of suitable size. It may be necessary to clean the plates prior to separation. This can be done by migration of, or immersion in, an appropriate solvent. The plates may also be impregnated by procedures such as development, immersion, or spraying. At the time of use, the plates may be activated, if necessary, by heating in an oven at 120° for 20 minutes. The *stationary phase* of TLC plates has an average particle size of 10–15 µm, and that of HPTLC plates an average particle size of 5 µm. Commercial plates with a preadsorbant zone can be used if they are specified in a monograph. Sample applied to the preabsorbant region develops into sharp, narrow bands at the preabsorbant-sorbent interface. Alternatively, flat *glass plates* of convenient size, typically 20 cm × 20 cm, can be coated as described under *Preparation of Chromatographic Plates.*

A suitable *manual, semiautomatic, or automatic application device* can be used to ensure proper positioning of the plate and proper transfer of the sample, with respect to volume and position, onto the plate. Alternatively, a *template* can be used to guide in manually placing the test spots at definite intervals, to mark distances as needed, and to aid in labeling the plates. For the proper application of the solutions, *micropipets, microsyringes, or calibrated disposable capillaries* are recommended.

For ascending development, a *chromatographic chamber* made of inert, transparent material and having the following specifications is used: a flat bottom or twin trough, a tightly fitted lid, and a size suitable for the plates. For horizontal development, the chamber is provided with a reservoir for the mobile phase, and it also contains a device for directing the mobile phase to the stationary phase.

Devices for transfer of reagents onto the plate by spraying, immersion, or exposure to vapor and devices to facilitate any necessary heating for visualization of the separated spots or zones.

A *UV light source* suitable for observations under short (254 nm) and long (365 nm) wavelength UV light.

A suitable *device for documentation* of the visualized chromatographic result.

Procedure—Apply the prescribed volume of the test solution and the standard solution in sufficiently small portions to obtain circular spots of 2 to 5 mm in diameter (1 to 2 mm on HPTLC plates) or bands of 10 to 20 mm by 1 to 2 mm (5 to 10 mm by 0.5 to 1 mm on HPTLC plates) at an appropriate distance from the lower edge—during chromatography the application position must be

■at least■2S (*USP30*)
3 mm (HPTLC) ~~to~~

■or■2S (*USP30*)
5 mm (TLC) above the level of the developing solvent—and from the sides of the plate. Apply the solutions on a line parallel to the lower edge of the plate with an interval of at least 10 mm (5 mm on HPTLC plates) between the centers of spots or 4 mm (2 mm on HPTLC plates) between the edges of bands, and allow to dry.

Ascending Development—Line at least one wall of the chromatographic chamber with filter paper. Pour into the chromatographic chamber a quantity of the mobile phase sufficient for the size of the chamber to give, after impregnation of the filter paper, a level of depth appropriate to the dimension of the plate used. For saturation of the chromatographic chamber, close the lid, and allow the system to equilibrate. Unless otherwise indicated, the chromatographic separation is performed in a saturated chamber.

Place the plate in the chamber, ensuring that the plate is as vertical as possible and that the spots or bands are above the surface of the mobile phase, and close the chamber. The stationary phase faces the inside of the chamber. Remove the plate when the mobile phase has moved over the prescribed distance. Dry the plate, and visualize the chromatograms as prescribed. For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Horizontal Development—Introduce a sufficient quantity of the developing solvent into the reservoir of the chamber using a syringe or pipet. Place the plate horizontally in the chamber, connect the mobile phase direction device according to the manufacturer's instructions, and close the chamber. If prescribed, develop the plate starting simultaneously at both ends. Remove the plate when the mobile phase has moved over the distance prescribed in the monograph. Dry the plate, and visualize the chromatograms as prescribed.

For two-dimensional chromatography, dry the plates after the first development, and carry out a second development in a direction perpendicular to that of the first development.

Detection—Observe the dry plate first under short-wavelength UV light (254 nm) and then under long-wavelength UV light (365 nm) or as stated in the monograph. If further directed, spray, immerse, or expose the plate to vapors of the specified reagent, heat the plate when required, observe, and compare the test chromatogram with the standard chromatogram. Document the plate after each observation. Measure and record the distance of each spot or zone from the point of origin, and indicate for each spot or zone the wavelength under which it was observed. Determine the R_F values for the principal spots or zones (see *Glossary of Symbols*).

Quantitative Measurement—Using appropriate instrumentation, substances separated by TLC and responding to ultraviolet-visible (UV-Vis) irradiation prior to or after derivatization can be determined directly on the plate. While moving the plate or the measuring device, the plate is examined by measuring the reflectance of the incident light. Similarly, fluorescence may be measured using an appropriate optical system. Substances containing radionuclides can be quantified in three ways: (1) directly by moving the plate alongside a suitable counter or vice versa; (2) by cutting the plates into strips and measuring the radioactivity on each individual strip using a suitable counter; or (3) by scraping off the stationary phase, dissolving it in a suitable scintillation cocktail, and measuring the radioactivity using a liquid scintillation counter (see *Radioactivity* ⟨821⟩).

The apparatus for direct quantitative measurement on the plate is a densitometer that is composed of a mechanical device to move the plate or the measuring device along the *x*-axis and the *y*-axis, a recorder, a suitable integrator or a computer; and, for substances responding to UV-Vis irradiation, a photometer with a source of light, an optical device capable of generating monochromatic light, and a photo cell of adequate sensitivity, all of which are used for the measurement of reflectance. In the case where fluorescence is measured, a suitable filter is also required to prevent the light used

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for excitation from reaching the photo cell while permitting the emitted light or specific portions thereof to pass. The linearity range of the counting device must be verified.

For quantitative tests, it is necessary to apply to the plate not fewer than three standard solutions of the substance to be examined, the concentrations of which span the expected value in the test solution (e.g., 80%, 100%, and 120%). Derivatize with the prescribed reagent, if necessary, and record the reflectance or fluorescence in the chromatograms obtained. Use the measured results for the calculation of the amount of substance in the test solution.

Preparation of Chromatographic Plates—

Apparatus—

Flat *glass plates* of convenient size, typically 20 cm × 20 cm.

An *aligning tray* or a flat surface upon which to align and rest the plates during the application of the adsorbent.

A *storage rack* to hold the prepared plates during drying and transportation. The rack holding the plates should be kept in a desiccator or be capable of being sealed in order to protect the plates from the environment after removal from the drying oven.

The *adsorbent* consists of finely divided adsorbent materials, normally 5 to 40 µm in diameter, suitable for chromatography. It can be applied directly to the glass plate or can be bonded to the plate by means of plaster of Paris [calcium sulfate hemihydrate (at a ratio of 5% to 15%)] or with starch paste or other binders. The plaster of Paris will not yield as hard a surface as will the starch, but it is not affected by strongly oxidizing spray reagents. The adsorbent may contain fluorescing material to aid in the visualization of spots that absorb UV light.

A *spreader,* which, when moved over the glass plate, will apply a uniform layer of adsorbent of desired thickness over the entire surface of the plate.

Procedure—[NOTE—In this procedure, use Purified Water that is obtained by distillation.] Clean the glass plates scrupulously, using an appropriate cleaning solution (see *Cleaning Glass Apparatus* ⟨1051⟩), rinsing them with copious quantities of water until the water runs off the plates without leaving any visible water or oily spots, then dry. It is important that the plates be completely free from lint and dust when the adsorbent is applied.

Arrange the plate or plates on the aligning tray, place a 5- × 20-cm plate adjacent to the front edge of the first square plate and another 5- × 20-cm plate adjacent to the rear edge of the last square, and secure all of the plates so that they will not slip during the application of the adsorbent. Position the spreader on the end plate opposite the raised end of the aligning tray. Mix 1 part of adsorbent with 2 parts of water (or in the ratio suggested by the supplier) by shaking vigorously for 30 seconds in a glass-stoppered conical flask, and transfer the slurry to the spreader. Usually 30 g of adsorbent and 60 mL of water are sufficient for five 20- × 20-cm plates. Complete the application of adsorbents using plaster of Paris binder within 2 minutes of the addition of the water, because thereafter the mixture begins to harden. Draw the spreader smoothly over the plates toward the raised end of the aligning tray, and remove the spreader when it is on the end plate next to the raised end of the aligning tray. (Wash away all traces of adsorbent from the spreader immediately after use.) Allow the plates to remain undisturbed for 5 minutes, then transfer the square plates, layer side up, to the storage rack, and dry at 105° for 30 minutes. Preferably place the rack at an angle in the drying oven to prevent the condensation of moisture on the back sides of plates in the rack. When the plates are dry, allow them to cool to room temperature, and inspect the uniformity of the distribution and the texture of the adsorbent layer; transmitted light will show uniformity of distribution, and reflected light will show uniformity of texture. Store the satisfactory plates over silica gel in a suitable chamber.

Change to read:

INTERPRETATION OF CHROMATOGRAMS

Figure 1 represents a typical chromatographic separation of two substances, 1 and 2, where t_1 and t_2 are the respective retention times; and h, $h/2$, and $W_{h/2}$ are the height, the half-height, and the width at half-height, respectively, for peak 1. W_1 and W_2 are the respective widths of peaks 1 and 2 at the baseline. Air peaks are a feature of gas chromatograms and correspond to the solvent front in liquid chromatography.

■The retention time of these unretained components is designated as t_{M}.■2S *(USP30)*

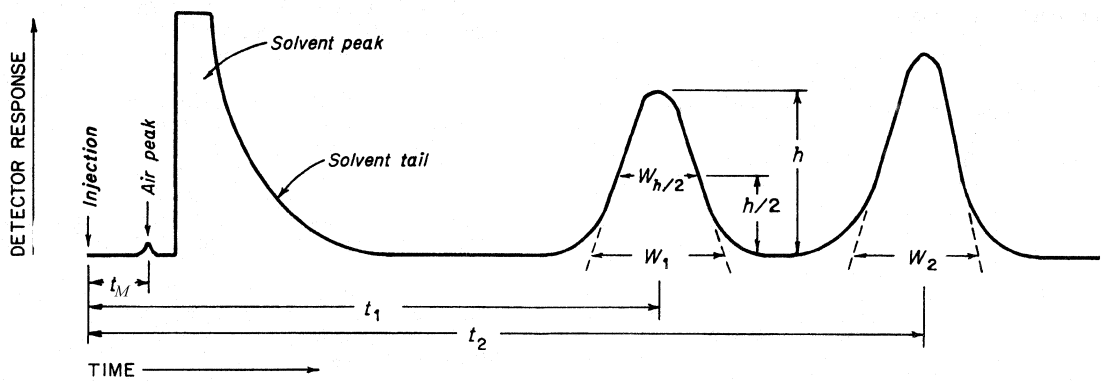

Figure 1. Chromatographic separation of two substances

Chromatographic retention times are characteristic of the compounds they represent but are not unique. Coincidence of retention times of a test and a reference substance can be used as a feature in construction of an identity profile but is insufficient on its own to establish identity. Absolute retention times of a given compound vary from one chromatogram to the next.

■Because in most procedures there is no need to identify an unretained peak, comparisons are normally made in terms of relative retention times, R_r:

$$R_r = \frac{t_2}{t_1}$$

where t_2 and t_1 are the retention times, measured from the point of injection, of the test and the reference substances, respectively, determined under identical experimental conditions on the same column.

Other procedures may identify the peak position using the relative retention, r:

$$r = \frac{t_2 - t_M}{t_1 - t_M}$$

where t_M is the retention time of a nonretained marker, which needs to be defined in the procedure.■1S (*USP29*)

The number of theoretical plates, N, is a measure of column efficiency. For Gaussian peaks, it is calculated by the equation:

■$$N = 16\left(\frac{t}{W}\right)^2$$ ■1S (*USP29*)

where t is the retention time of the substance and W is the width of the peak at its base, obtained by extrapolating the relatively straight sides of the peak to the baseline. ■■1S (*USP29*) The value of N depends upon the substance being chromatographed as well as the operating conditions such as mobile phase or carrier gas flow rates and temperature, the quality of the packing, the uniformity of the packing within the column and, for capillary columns, the thickness of the stationary phase film, and the internal diameter and length of the column.

The separation of two components in a mixture, the resolution, R, is determined by the equation:

$$R = \frac{2(t_2 - t_1)}{W_2 + W_1}$$

in which t_2 and t_1 are the retention times of the two components, and W_2 and W_1 are the corresponding widths at the bases of the peaks obtained by extrapolating the relatively straight sides of the peaks to the baseline.

Where electronic integrators are used, it may be convenient to determine the resolution, R, by the equation:

$$R = \frac{2(t_2 - t_1)}{1.70(W_{1,h/2} + W_{2,h/2})}$$

and to determine the number of theoretical plates, N, by the equation:

$$N = 5.54(t/W_{h/2})^2$$

■where $W_{h/2}$ is the peak width at half-height, obtained directly by electronic integrators.■1S (*USP29*) However, in the event of dispute, only equations based on peak width at baseline are to be used.

Peak areas and peak heights are usually proportional to the quantity of compound eluting. These are commonly measured by electronic integrators but may be determined by more classical approaches. Peak areas are generally used but may be less accurate if peak interference occurs. For manual measurements, the chart should be run faster than usual, or a comparator should be used to measure the width at half-height and the width at the base of the peak, to minimize error in these measurements. For accurate quantitative work, the components to be measured should be separated from any interfering components. Peak tailing and fronting and the measurement of peaks on solvent tails are to be avoided.

Chromatographic purity tests for drug raw materials are sometimes based on the determination of peaks due to impurities, expressed as a percentage of the area due to the drug peak. It is preferable, however, to compare impurity peaks with those in the chromatogram of a standard at a similar concentration. The standard may be the drug itself at a level corresponding to, for example, 0.5% impurity, or in the case of toxic or signal impurities, a standard of the impurity itself.

Change to read:

SYSTEM SUITABILITY

System suitability tests are an integral part of gas and liquid chromatographic methods. They are used to verify that the ▲detection sensitivity,▲*USP29* ●(Postponed indefinitely)●2 resolution, and reproducibility of the chromatographic system are adequate for the analysis to be done. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such.

▲The detection sensitivity is a measure used to ensure the suitability of a given chromatographic procedure for the complete detection of the impurities in the *Chromatographic purity* or *Related compounds* tests by injecting a volume of a quantitation limit solution equal to that of the *Test solution*. Unless otherwise specified in the individual monograph, the quantitation limit solution may be prepared by dissolving the drug substance Reference Standard in the same solvent as that used for the *Test solution* at a 0.05% concentration level relative to the amount of drug substance in the *Test solution* for drug substances, and a 0.1% level relative to the amount of drug substance in the *Test solution* for drug products. The signal-to-noise ratio for the drug substance peak obtained with the quantitation limit solution should be not less than 10.▲*USP29* ●(Postponed indefinitely)●2

The resolution, R, [NOTE—All terms and symbols are defined in the *Glossary of Symbols*] is a function of column efficiency, N, and is specified to ensure that closely eluting compounds are resolved from each other, to establish the general resolving power of the system, and to ensure that internal standards are resolved from the drug. Column efficiency may be specified also as a system suitability requirement, especially if there is only one peak of interest in the chromatogram; however, it is a less reliable means to ensure resolution than direct measurement. Column efficiency is a measure of peak sharpness, which is important for the detection of trace components.

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Replicate injections of a standard preparation used in the assay or other standard solution are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, S_R, if the requirement is 2.0% or less; data from six replicate injections are used if the relative standard deviation requirement is more than 2.0%.

The tailing factor, *T,* a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced (see *Figure 2*). In some cases, values less than unity may be observed. As peak asymmetry increases, integration, and hence precision, becomes less reliable.

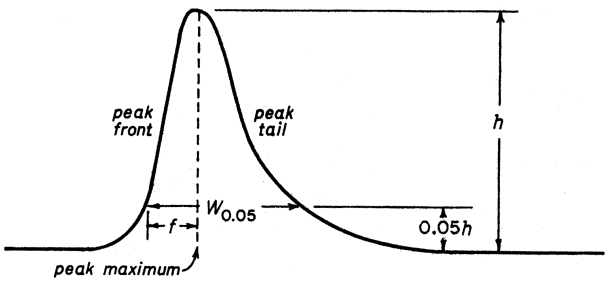

Figure 2. Asymmetrical chromatographic peak

These tests are performed by collecting data from replicate injections of standard or other solutions as specified in the individual monograph. The specification of definitive parameters in a monograph does not preclude the use of other suitable operating conditions (see *Procedures* under *Tests and Assays* in the *General Notices*). ~~Adjustments of operating conditions to meet system suitability requirements may be necessary.~~

■If adjustments of operating conditions to meet system suitability requirements are necessary, each of the following is the maximum ~~specification~~ variation that can be considered, unless otherwise directed in the monograph. Adjustments are permitted only when ~~Reference Standards~~ suitable standards (including Reference Standards) are available for all ~~analytes~~ compounds used in the suitability test and only when those standards are used to show that the adjustments have improved the quality of the chromatography in meeting system suitability requirements. Adjustments to chromatographic systems performed in order to comply with system suitability requirements are not to be made to compensate for column failure ~~or to circumvent replacing a deteriorated column~~ or system malfunction. ~~The changes described below may require additional validation data unless the user can verify the suitability of the method under the new conditions. This verification consists of assessing the analytical performance characteristics that can be affected by the change (e.g., specificity, linearity, precision, accuracy) to ensure the adequacy of the method. Multiple adjustments that may have a cumulative effect in the performance of the system are to be avoided.~~ The changes described below may require additional validation data. The user should verify the suitability of the method under the new conditions by assessing the relevant analytical performance characteristics potentially affected by the change. ~~*Tables 1* and *2* in the general information chapter *Verification of Compendial Procedures* ⟨1226⟩ provide lists of analytical performance validation characteristics that may require assessment.~~ Multiple adjustments can have a cumulative effect in the performance of the system and should be considered carefully before implementation.

pH of Mobile Phase (HPLC)—The pH of the aqueous buffer used in the preparation of the mobile phase can be adjusted to within ~~0.2~~ ±0.2 units of the value or range specified.

Concentration of Salts in Buffer (HPLC)—The concentration of the salts used in the preparation of the aqueous buffer used in the mobile phase can be adjusted to within ±10%, provided the permitted pH variation (see above) is met.

Ratio of Components in Mobile Phase (HPLC)—~~The amount of the minor~~ The following adjustment limits apply to minor components of the mobile phase (specified at 50% or less). The amount(s) of these component(s) can be adjusted by ±30% relative. ~~or ±2% absolute (i.e., in relation to the total mobile phase), whichever is larger.~~ However, the change in any component cannot exceed ±10% absolute (i.e., in relation to the total mobile phase). ~~nor can the final concentration of any component be reduced to zero.~~ Adjustment can be made to one minor component in a ternary mixture. Examples of adjustments for binary and ternary mixtures are given below.

Binary Mixtures—

SPECIFIED RATIO OF 50 : 50—Thirty percent of 50 is 15% absolute, but this exceeds the maximum permitted change of ±10% absolute in either component. Therefore, the mobile phase ratio may be adjusted only within the range of 40 : 60 to 60 : 40.

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~~SPECIFIED RATIO OF 95 : 5—Thirty percent of 5 is 1.5% absolute. However, because adjustments up to ±2% absolute are allowed, the ratio may be adjusted within the range of 93 : 7 to 97 : 3.~~

SPECIFIED RATIO OF 2 : 98—Thirty percent of 2 is 0.6% absolute. ~~In this case an absolute adjustment of ±2% is not allowed because it would reduce the amount of the first component to zero.~~ Therefore the maximum allowed adjustment is within the range of 1.4 : 98.6 to 2.6 : 97.4.

Ternary Mixtures—

SPECIFIED RATIO OF 60 : 35 : 5—For the second component, 30% of 35 is 10.5% absolute, which exceeds the maximum permitted change of ±10% absolute in any component. Therefore the second component may be adjusted only within the range of 25% to 45% absolute. For the third component, 30% of 5 is 1.5% absolute. ~~Since ±2% absolute is permitted and provides more flexibility, the third component may be adjusted within the range of 3% to 7% absolute.~~ In all cases, a sufficient quantity of the first component is used to give a total of 100%. Therefore, mixture ranges of 50 : 45 : 5 to 70 : 25 : 5 or ~~58 : 35 : 7 to 62 : 35 : 3~~ 58.5 : 35 : 6.5 to 61.5 : 35 : 3.5 would meet the requirement.

~~Detector~~ Wavelength of UV-Visible Detector (HPLC)— Deviations from the wavelengths specified in the method are not permitted. The procedure specified by the detector manufacturer, or another validated procedure, is to be used to verify that error in the detector wavelength is, at most, ±3 nm.

Column Length (GC, HPLC): can be adjusted by as much as ~~70%.~~ ±70%.

Column Inner Diameter (GC, HPLC): can be adjusted by as much as ~~±25% 50%.~~ ±25% for HPLC and ±50% for GC.

Film Thickness (Capillary GC): can be adjusted by as much as –50% to 100%.

Particle Size (HPLC): can be reduced by as much as 50%.

Particle Size (GC): going from a larger to a smaller or a smaller to a larger (if it is the same "Range Ratio", which is the diameter of the largest particle divided by the diameter of the smallest particle) particle size GC mesh support is acceptable, provided the chromatography meets the requirements of the system suitability.

Flow Rate (GC, HPLC): can be adjusted by as much as ±50%.

Injection Volume (GC, HPLC): can be reduced as far as is consistent with accepted precision and detection limits. ~~It may be increased to as much as twice the volume specified, provided there are no adverse effects on factors such as baseline, peak shapes, resolution, linearity, and retention times.~~

Column Temperature (HPLC): can be adjusted by as much as ~~±20°.~~ ±10°. Column thermostating is recommended to improve control and reproducibility of retention time.

~~Column~~ Oven Temperature (GC): can be adjusted by as much as ~~±2%, in terms of absolute temperature.~~ ±10%.

Oven Temperature Program (GC)—Adjustment of temperatures is permitted as stated above. For the times specified for the temperature to be maintained or for the temperature to be changed from one value to another, an adjustment of up to ±20% is permitted.

~~**Gradient Elution (HPLC)**—The configuration of the equipment employed may significantly alter the resolution, retention time, and relative retentions described in the method. Should this occur, it may be due to excess dwell time, which is the volume between the point at which the two eluants meet and the top of the column.~~ ■2S (*USP30*)

Unless otherwise directed in the monograph, system suitability parameters are determined from the analyte peak.

■Relative retention times may be provided in monographs for informational purposes only, to aid in peak identification. There are no acceptance criteria applied to relative retention times.■2S (*USP30*)

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To ascertain the effectiveness of the final operating system, it should be subjected to suitability testing. Replicate injections of the standard preparation required to demonstrate adequate system precision may be made before the injection of samples or may be interspersed among sample injections. System suitability must be demonstrated throughout the run by injection of an appropriate control preparation at appropriate intervals. The control preparation can be a standard preparation or a solution containing a known amount of analyte and any additional materials useful in the control of the analytical system, such as excipients or impurities. Whenever there is a significant change in equipment or in a critical reagent, suitability testing should be performed before the injection of samples. No sample analysis is acceptable unless the requirements of system suitability have been met. Sample analyses obtained while the system fails

■system suitability■2S *(USP30)* requirements are unacceptable.

Change to read:

CHROMATOGRAPHIC REAGENTS

~~The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer.~~

■A complete list of *Packings* (L), *Phases* (G), and *Supports* (S) used in *USP–NF* tests and assays is located under *Chromatographic Reagents* in the *Reagents, Indicators, and Solutions* section. This list is intended to be a convenient reference for the chromatographer to identify the pertinent chromatographic reagent specified in the individual monograph.■2S *(USP30)*

[NOTE—Particle sizes given in ~~this~~

■the■2S *(USP30)* listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed ~~below~~

■■2S *(USP30)* there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

~~Packings~~

~~L1 Octadecyl silane chemically bonded to porous silica or ceramic micro particles, 3■1.5■1S *(USP30)* to 10 µm in diameter, ■or a monolithic silica rod.■1S *(USP29)*~~

~~L2 Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to 50 µm in diameter.~~

~~L3 Porous silica particles, 5 to 10 µm in diameter.~~

~~L4 Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.~~

~~L5 Alumina of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.~~

~~L6 Strong cation exchange packing sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to 50 µm in diameter.~~

~~L7 Octylsilane chemically bonded to totally porous silica particles, 3■1.5■1S *(USP29)* to 10 µm in diameter.~~

~~L8 An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, 3 to 10 µm in diameter.~~

~~L9 ■■1S *(USP29)* Irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation exchange coating, ■3 to 10 µm in diameter.■1S *(USP29)*~~

~~L10 Nitrile groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.~~

~~L11 Phenyl groups chemically bonded to porous silica particles, 5■1.5■1S *(USP30)* to 10 µm in diameter.~~

~~L12 A strong anion exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to 50 µm in diameter.~~

~~L13 Trimethylsilane chemically bonded to porous silica particles, 3 to 10 µm in diameter.~~

~~L14 Silica gel having a chemically bonded, strongly basic quaternary ammonium anion exchange coating, 5 to 10 µm in diameter.~~

~~L15 Hexylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.~~

~~L16 Dimethylsilane chemically bonded to porous silica particles, 5 to 10 µm in diameter.~~

~~L17 Strong cation exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to 11 µm in diameter.~~

~~L18 Amino and cyano groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.~~

~~L19 Strong cation exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about 9 µm in diameter.~~

~~L20 Dihydroxypropane groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.~~

~~L21 A rigid, spherical styrene-divinylbenzene copolymer, 5 to 10 µm in diameter.~~

~~L22 A cation exchange resin made of porous polystyrene gel with sulfonic acid groups, about 10 µm in size.~~

~~L23 An anion exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about 10 µm in size.~~

~~L24 A semi rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to 63 µm in diameter.~~

~~■[NOTE—Available as YMC-Pack PVA-SIL manufactured by YMC Co., Ltd. and distributed by Waters Corp. (www.waters.com).]■1S *(USP29)*~~

~~L25 Packing having the capacity to separate compounds with a molecular weight range from 100–5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.~~

~~L26 Butyl silane chemically bonded to totally porous silica particles, ■3■1S *(USP29)* to 10 µm in diameter.~~

~~L27 Porous silica particles, 30 to 50 µm in diameter.~~

~~L28 A multifunctional support, which consists of a high purity, 100-Å, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.~~

~~L29 Gamma alumina, reverse phase, low carbon percentage by weight, alumina based polybutadiene spherical particles, 5 µm in diameter with a pore volume of 80 Å.~~

~~L30 Ethyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.~~

~~L31 A ■hydroxide selective,■1S *(USP29)* strong anion exchange resin quaternary amine bonded on latex particles attached to a core of 8.5-µm macroporous particles having a pore size of 2000 Å and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene.~~

~~L32 A chiral ligand exchange packing L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to 10 µm in diameter.~~

~~L33 Packing having the capacity to separate dextrans by molecular size over a range of 4000 to 500,000 Da. It is spherical, silica-based, and processed to provide pH stability.~~

~~■[NOTE—Available as TSKgel G4000 SWXL from Tosoh Biosep (www.tosohbiosep.com).]■1S *(USP29)*~~

~~L34 Strong cation exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about 9 µm in diameter.~~

L35—A zirconium stabilized spherical silica packing with a hydrophilic (diol type) molecular monolayer bonded phase having a pore size of 150 Å.

L36—A 3,5 dinitrobenzoyl derivative of L phenylglycine covalently bonded to 5-µm aminopropyl silica.

L37—Packing having the capacity to separate proteins by molecular size over a range of 2,000 to 40,000 Da. It is a polymethacrylate gel.

L38—A methacrylate-based size-exclusion packing for water-soluble samples.

L39—A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40—Cellulose tris 3,5-dimethylphenylcarbamate coated porous silica particles, 5 to 20 µm in diameter.

L41—Immobilized α_1-acid glycoprotein on spherical silica particles, 5 µm in diameter.

L42—Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, 5 µm in diameter.

L43—Pentafluorophenyl groups chemically bonded to silica particles by a propyl spacer, 5 to 10 µm in diameter.

L44—A multifunctional support, which consists of a high purity, 60-Å, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed-phase C8 functionality.

L45—Beta cyclodextrin bonded to porous silica particles, 5 to 10 µm in diameter.

L46—Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, about 10 µm in diameter.

L47—High capacity anion exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.

■[NOTE—Available as CarboPac MA1 and distributed by Dionex Corp. (www.dionex.com).]■*1S (USP29)*

L48—Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion exchange microbeads, 15 µm in diameter.

L49—A reversed phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to 10 µm in diameter.

■[NOTE—Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.]■*1S (USP29)*

L50—Multifunction resin with reversed-phase retention and strong anion exchange functionalities. The resin consists of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm in diameter, and a surface area not less than 350 m^2 per g. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene.

■[NOTE—Available as OmniPac PAX-500 and distributed by Dionex Corp. (www.dionex.com).]■*1S (USP29)*

L51—Amylose tris 3,5-dimethylphenylcarbamate coated, porous, spherical, silica particles, 5 to 10 µm in diameter.

■[NOTE—Available as Chiralpak AD from Chiral Technologies, Inc., (www.chiraltech.com).]■*1S (USP29)*

L52—A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.

■[NOTE—Available as TSK-IC-SW Cation from Tosoh Biosep (www.tosohbiosep.com).]■*1S (USP29)*

L53—Weak cation exchange resin consisting of ethylvinylbenzene, 55% cross linked with divinylbenzene copolymer, 3 to 15 µm diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than 500 µEq/column.

■[NOTE—Available as IonPac CS14 distributed by Dionex Corp. (www.dionex.com).]■*1S (USP29)*

L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter.

■[NOTE—Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).]■*1S (USP29)*

L55—A strong cation exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.

■[NOTE—Available as IC-Pak C M/D from Waters Corp. (www.waters.com).]■*1S (USP29)*

L56—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

■[NOTE—Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem).]■*1S (USP29)*

L57—A chiral recognition protein, ovomucoid, chemically bonded to silica particles, about 5 µm in diameter, with a pore size of 120 Å.

■[NOTE—Available as Ultron ES-OVM from Agilent Technologies (www.agilent.com/chem).]■*1S (USP29)*

L58—Strong cation exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.

■[NOTE—Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143) www.bio-rad.com.]■*1S (USP29)*

L59—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa. It is spherical (10 µm), silica based, and processed to provide hydrophilic characteristics and pH stability.

■[NOTE—Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively) (www.tosohbiosep.com).]■*1S (USP29)*

L60—Spherical, porous silica gel, 3 or 5 µm■10 µm or less■*1S (USP29)*, in diameter, the surface of which has been covalently modified with palmitamidopropyl■alkyl amide■*1S (USP30)*, groups and end capped.

■[NOTE—Available as Supelcosil ABZ from Supelco (http://www.sigmaaldrich.com/Brands/Supelco_Home.html).]■*1S (USP29)*

L61—A hydroxide selective strong anion exchange resin consisting of a highly cross-linked core of 13 µm microporous particles having a pore size less than 10 Å units and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene with a latex coating composed of 85 nm diameter microbeads bonded with alkanol quaternary ammonium ions (6%).

■[NOTE—Available as Ion Pac AS-11 and AG-11 from Dionex (www.dionex.com).]■*1S (USP29)*

L62—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter.

L## (Enoxaparin Sodium, Dowex 1X8)—[To come.]

L## (Enoxaparin Sodium, Dowex 50WX2)—[To come.]

■L## (Dalteparin Sodium, anion exchange Dowex 1X8)—[To come.]

L## (Dalteparin Sodium, cation exchange Dowex 50WX2)—[To come.]■*2S (USP29)*

■L## (Glucosamine, Shodex NH2P-50)—Polyamine chemically bonded to cross-linked polyvinyl alcohol polymer, 5 µm in diameter. [NOTE—Available as Shodex NH2P-50 from Shodex (www.shodex.com).]

L## [Valganciclovir Hydrochloride, Crownpak CR(+)]—A crown ether coated on a 5 µm particle size silica gel substrate. The active site is *(S)*-18-crown-6-ether.

[NOTE—Available as Crownpak CR(+) from Daicel (www.daicel.com).]

L## (Trehalose, Sugar KS-801)—Strong cation exchange resin consisting of sulfonated cross-linked styrene divinylbenzene copolymer in the sodium form, 6 to 17 µm in diameter.

[NOTE—Available as Sugar KS-801 from Shodex (www.shodex.com).]

L## (Levalbuterol, Chirobiotic T)—Glycopeptide teicoplanin linked through multiple covalent bonds to a 100-Å units spherical silica.

[NOTE—Available as Chirobiotic T from Astec (www.asteceusa.com).]■*1S (USP30)*

Phases

G1—Dimethylpolysiloxane oil.

G2—Dimethylpolysiloxane gum.

G3—50% Phenyl 50% methylpolysiloxane.

G4—Diethylene glycol succinate polyester.

G5—3-Cyanopropylpolysiloxane.

G6—Trifluoropropylmethylpolysiloxane.

G7—50% 3-Cyanopropyl 50% phenylmethylsilicone.

G8—80% Bis(3-cyanopropyl) 20% 3-cyanopropylphenylpolysiloxane (percentages refer to molar substitution).

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~~G9 Methylvinylpolysiloxane.~~
~~G10 Polyamide formed by reacting a C_{36} dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00 : 0.90 : 0.20.~~
~~G11 Bis(2-ethylhexyl) sebacate polyester.~~
~~G12 Phenyldiethanolamine succinate polyester.~~
~~G13 Sorbitol.~~
~~G14 Polyethylene glycol (av. mol. wt. of 950 to 1050).~~
~~G15 Polyethylene glycol (av. mol. wt. of 3000 to 3700).~~
~~G16 Polyethylene glycol compound (av. mol. wt. about 15,000). A high-molecular-weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.~~
~~G17 75% Phenyl 25% methylpolysiloxane.~~
~~G18 Polyalkylene glycol.~~
~~G19 25% Phenyl 25% cyanopropyl 50% methylsilicone.~~
~~G20 Polyethylene glycol (av. mol. wt. of 380 to 420).~~
~~G21 Neopentyl glycol succinate.~~
~~G22 Bis(2-ethylhexyl) phthalate.~~
~~G23 Polyethylene glycol adipate.~~
~~G24 Diisodecyl phthalate.~~
~~G25 Polyethylene glycol compound TPA. A high-molecular-weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid.~~ ■~~[NOTE—Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.]~~■ ~~1S (*USP30*)~~
~~G26 25% 2-Cyanoethyl 75% methylpolysiloxane.~~
~~G27 5% Phenyl 95% methylpolysiloxane.~~
~~G28 25% Phenyl 75% methylpolysiloxane.~~
~~G29 3,3′-Thiodipropionitrile.~~
~~G30 Tetraethylene glycol dimethyl ether.~~
~~G31 Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol-30.~~
~~G32 20% Phenylmethyl 80% dimethylpolysiloxane.~~
~~G33 20% Carborane 80% methylsilicone.~~
~~G34 Diethylene glycol succinate polyester stabilized with phosphoric acid.~~
~~G35 A high-molecular-weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.~~
~~G36 1% Vinyl 5% phenylmethylpolysiloxane.~~
~~G37 Polyimide.~~
~~G38 Phase G1 containing a small percentage of a tailing inhibitor.~~
■~~[NOTE—A suitable grade is available commercially as "SP2100/0.1% Carbowax 1500" from Supelco, Inc. (http://www.sigmaaldrich.com/Brands/Supelco_Home.html).]~~■ ~~1S (*USP30*)~~
~~G39 Polyethylene glycol (av. mol. wt. about 1500).~~
~~G40 Ethylene glycol adipate.~~
~~G41 Phenylmethyldimethylsilicone (10% phenyl substituted).~~
~~G42 35% phenyl 65% dimethylpolysiloxane (percentages refer to molar substitution).~~
~~G43 6% cyanopropylphenyl 94% dimethylpolysiloxane (percentages refer to molar substitution).~~
~~G44 2% low-molecular-weight petrolatum hydrocarbon grease and 1% solution of potassium hydroxide.~~
~~G45 Divinylbenzene ethylene glycol dimethylacrylate.~~
~~G46 14% Cyanopropylphenyl 86% methylpolysiloxane.~~
~~G47 Polyethylene glycol (av. mol. wt. of about 8000).~~
~~G48 Highly polar, partially cross-linked cyanopolysiloxane.~~■ ~~1S (*USP29*)~~

~~Supports~~

~~NOTE—Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.~~

~~S1A Siliceous earth for gas chromatography has been flux calcined by mixing diatomite with Na_2CO_3 flux and calcining above 900°. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane.~~ ■~~[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]~~■ ~~1S (*USP30*)~~ ~~to mask surface silanol groups.~~
~~S1AB The siliceous earth as described above is both acid- and base-washed.~~ ■~~[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]~~■ ~~1S (*USP30*)~~
~~S1C A support prepared from crushed firebrick and calcined or burned with a clay binder above 900° with subsequent acid wash. It may be silanized.~~
~~S1NS The siliceous earth is untreated.~~
~~S2 Styrene-divinylbenzene copolymer having a nominal surface area of less than 50 m^2 per g and an average pore diameter of 0.3 to 0.4 μm.~~
~~S3 Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to 600 m^2 per g and an average pore diameter of 0.0075 μm.~~
~~S4 Styrene-divinylbenzene copolymer with aromatic O and N groups, having a nominal surface area of 400 to 600 m^2 per g and an average pore diameter of 0.0076 μm.~~
~~S5 40- to 60-mesh, high-molecular-weight tetrafluorethylene polymer.~~
~~S6 Styrene-divinylbenzene copolymer having a nominal surface area of 250 to 350 m^2 per g and an average pore diameter of 0.0091 μm.~~
~~S7 Graphitized carbon having a nominal surface area of 12 m^2 per g.~~
~~S8 Copolymer of 4-vinyl pyridine and styrene-divinylbenzene.~~
~~S9 A porous polymer based on 2,6-diphenyl *p*-phenylene oxide.~~
~~S10 A highly polar cross-linked copolymer of acrylonitrile and divinylbenzene.~~
~~S11 Graphitized carbon having a nominal surface area of 100 m^2 per g modified with small amounts of petrolatum and polyethylene glycol compound.~~ ■~~[NOTE—Commercially available as SP1500 on Carbopack B from Supelco (www.sigmaaldrich.com/Brands/Supelco_Home.html).]~~■ ~~1S (*USP29*)~~
~~S12 Graphitized carbon having a nominal surface area of 100 m^2 per g.~~

■■ 2S (*USP30*)

BRIEFING

⟨**660**⟩ **Containers—Glass.** It is proposed to remove the sections pertaining to glass that are currently under *Containers* ⟨661⟩ in order to create this proposed new chapter. In addition, the Type NP glass section has been deleted because it is no longer an industry practice, and a *Surface Glass Test* has been added to this new chapter to reflect a widely used test in industry. The sections pertaining to plastic will remain in general chapter ⟨661⟩. These proposed changes are intended to better organize the information on containers.

(P&S: D. Hunt) RTS—C44239

Add the following:

■⟨660⟩ CONTAINERS—GLASS

Glass containers for pharmaceutical use are intended to come into direct contact with pharmaceutical preparations. Glass used for pharmaceutical containers is either a borosilicate (neutral) glass or a soda-lime glass. Borosilicate glass

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contains a significant amount of boric oxide, aluminum oxide, and alkali and/or alkaline earth oxides. Borosilicate glass has a high hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Soda-lime glass is a silica glass containing alkali metal oxides. Soda-lime glass has a moderate hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type III glass. The inner surface of glass containers may be treated, for example, to improve hydrolytic resistance. The treatment of Type III soda-lime glass containers will raise their hydrolytic resistance from a moderate to a high level, changing the classification of the glass to Type II.

The outer surface of glass containers may be treated to reduce friction or for protection against abrasion or breakage. The treatment of the outer surface does not come into contact with the inner surface of the container. Glass may be colored to provide protection from light or may have a coating applied to the outer surface. Such containers will meet the requirements for *Light Transmission* under *Containers—Permeation* ⟨671⟩. A clear and colorless or a translucent container that is made light-resistant by means of an opaque enclosure (see *Light-Resistant Container* in *Preservation, Packaging, Storage, and Labeling* under the *General Notices*) is exempt from the requirements for *Light Transmission.*

The quality of glass containers is defined by measuring their resistance to chemical attack. In addition, containers for aqueous parenteral preparations are tested for arsenic release, and colored glass containers are tested for light transmission.

CHEMICAL RESISTANCE

The following tests are designed to determine the resistance to water attack of new (not previously used) glass containers. The degree of attack is determined by the amount of alkali released from the glass under the influence of the attacking medium under the conditions specified. This quantity of alkali is extremely small in the case of the more resistant glasses, thus calling for particular attention to all details of the tests and the use of apparatus of high quality and precision. The tests should be conducted in an area relatively free from fumes and excessive dust.

Glass Types—Glass containers suitable for packaging Pharmacopeial preparations may be classified as in *Table 1* on the basis of the tests set forth in this section. Containers of Type I borosilicate glass are generally used for preparations that are intended for parenteral administration. Containers of Type I glass, or of Type II glass (i.e., soda-lime glass that is suitably dealkalized) are usually used for packaging acidic and neutral parenteral preparations. Type I glass containers, or Type II glass containers (where stability data demonstrate their suitability), are used for alkaline parenteral preparations. Type III soda-lime glass containers usually are not used for parenteral preparations, except where suitable stability test data indicate that Type III glass is satisfactory for the parenteral preparations that are packaged therein.

Table 1. Glass Types and Test Limits

			Limits	
Type	General Description[a]	Type of Test	Size,[b] mL	mL of 0.020 N Acid
I	Highly resistant, borosilicate glass	*Powdered Glass*	All	1.0
II	Treated soda-lime glass	*Water Attack*	100 or less	0.7
			Over 100	0.2
III	Soda-lime glass	*Powdered Glass*	All	8.5

[a] The description applies to containers of this type of glass usually available.
[b] Size indicates the overflow capacity of the container.

Apparatus—

Autoclave—For these tests, use an autoclave capable of maintaining a temperature of 121 ± 2.0°, equipped with a thermometer, a pressure gauge, a vent cock, and a rack adequate to accommodate at least 12 test containers above the water level.

Mortar and Pestle—Use a hardened-steel mortar and pestle, made according to the specifications in *Figure 1*.

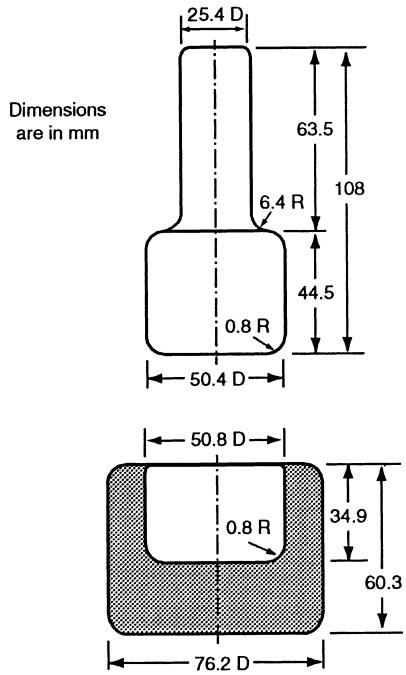

Figure 1. Special Mortar and Pestle for Pulverizing Glass[1]

Other Equipment—Also required are 20.3-cm (8-inch) sieves made of stainless steel including the Nos. 20, 40, and 50 sieves along with the pan and cover (see *Sizes of Standard Sieve Series in Range of Interest* under *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩), 250-mL conical flasks made of resistant glass aged as specified, a 900-g (2-lb) hammer, a permanent magnet, a desiccator, and an adequate volumetric apparatus.

Reagents—

High-Purity Water—The water used in these tests has a conductivity at 25°, as measured in an in-line cell just prior to dispensing, of not greater than 0.15 µS per cm (6.67 Megohm-cm). There must also be an assurance that this water is not contaminated by copper or its products (e.g., copper pipes, stills, or receivers). The water may be prepared by passing distilled water through a deionizer cartridge packed with a mixed bed of nuclear-grade resin, then through a cellulose ester membrane having openings not exceeding 0.45 µm.[2] Do not use copper tubing. Flush the discharge lines before water is dispensed into test vessels. When the low conductivity specification can no longer be met, replace the deionizer cartridge.

Methyl Red Solution—Dissolve 24 mg of methyl red sodium in *Purified Water* to make 100 mL. If necessary, neutralize the solution with 0.02 N sodium hydroxide, or acidify it with 0.02 N sulfuric acid so that the titration of 100 mL of *High-Purity Water,* containing 5 drops of indicator, does not require more than 0.020 mL of 0.020 N sodium hydroxide to effect the color change of the indicator, which should occur at a pH of 5.6.

Powdered Glass Test

Rinse thoroughly with *Purified Water* 6 or more containers selected at random, and dry them with a current of clean, dry air. Crush the containers into fragments about 25 mm in size, divide about 100 g of the coarsely crushed glass into three approximately equal portions, and place one of the portions in the special mortar. With the pestle in place, crush the glass further by striking 3 or 4 blows with the hammer. Nest the sieves, and empty the mortar into the No. 20 sieve. Repeat the operation on each of the two remaining portions of glass, emptying the mortar each time into the No. 20 sieve. Shake the sieves for a short time, then remove the glass from the Nos. 20 and 40 sieves, and again crush and sieve as before. Repeat again this crushing and sieving operation. Empty the receiving pan, re-

[1] A suitable mortar and pestle is available (catalog No. H-17280) from Humboldt Manufacturing Co., 7300 West Agatite, Norridge, Chicago, IL 60656.

[2] A suitable nuclear-grade resin mixture of the strong acid cation exchanger in the hydrogen form and the strong base anion exchanger in the hydroxide form, with a one-to-one cation to anion equivalence ratio, is available from the Millipore Corp., Bedford, MA 01730; Barnstead Co., 225 Rivermoor St., Boston, MA 02132; Illinois Water Treatment Co., 840 Cedar St., Rockford, IL 61105; and Vaponics, Inc., 200 Cordage Park, Plymouth, MA 02360. A suitable in-line filter is available from the Millipore Corp.; Gelman Instrument Co., 600 S. Wagner Rd., Ann Arbor, MI 48106; and Schleicher and Schuell, Inc., 540 Washington St., Keene, NH 10003.

assemble the nest of sieves, and shake by mechanical means for 5 minutes or by hand for an equivalent length of time. Transfer the portion retained on the No. 50 sieve, which should weigh in excess of 10 g, to a closed container, and store in a desiccator until used for the test.

Spread the specimen on a piece of glazed paper, and pass a magnet through it to remove particles of iron that may be introduced during the crushing. Transfer the specimen to a 250-mL conical flask of resistant glass, and wash it with six 30-mL portions of acetone, swirling each time for about 30 seconds, and carefully decanting the acetone. After washing, the specimen should be free from agglomerations of glass powder, and the surface of the grains should be practically free from adhering fine particles. Dry the flask and contents for 20 minutes at 140°, transfer the grains to a weighing bottle, and cool in a desiccator. Use the test specimen within 48 hours after drying.

Procedure—Transfer 10.00 g of the prepared specimen, accurately weighed, to a 250-mL conical flask that has been digested (aged) previously with *High-Purity Water* in a bath at 90° for at least 24 hours or at 121° for 1 hour. Add 50.0 mL of *High-Purity Water* to this flask and to one similarly prepared to provide a blank. Cap all flasks with borosilicate glass beakers that previously have been treated as described for the flasks and that are of such size that the bottoms of the beakers fit snugly down on the top rims of the containers. Place the containers in the autoclave, and close it securely, leaving the vent cock open. Heat until steam issues vigorously from the vent cock, and continue heating for 10 minutes. Close the vent cock, and adjust the temperature to 121°, taking 19 to 23 minutes to reach the desired temperature. Hold the temperature at 121 ± 2.0° for 30 minutes, counting from the time this temperature is reached. Reduce the heat so that the autoclave cools and comes to atmospheric pressure in 38 to 46 minutes, being vented as necessary to prevent the formation of a vacuum. Cool the flask at once in running water, decant the water from the flask into a suitably cleansed vessel, and wash the residual powdered glass with four 15-mL portions of *High-Purity Water,* adding the decanted washings to the main portion. Add 5 drops of *Methyl Red Solution,* and titrate immediately with 0.020 N sulfuric acid. If the volume of titrating solution is expected to be less than 10 mL, use a microburet. Record the volume of 0.020 N sulfuric acid used to neutralize the extract from 10 g of the prepared specimen of glass, corrected for a blank. The volume does not exceed that indicated in *Table 2* for the type of glass concerned.

Water Attack at 121°

Rinse thoroughly 3 or more containers, selected at random, twice with *High-Purity Water.*

Procedure—Fill each container to 90% of its overflow capacity with *High-Purity Water*, and proceed as directed for *Procedure* under *Powdered Glass Test,* beginning with "Cap all flasks," except that the time of autoclaving shall be 60 minutes instead of 30 minutes, and ending with "to prevent the formation of a vacuum." Empty the contents from 1 or more containers into a 100-mL graduated cylinder, combining, in the case of smaller containers, the contents of several containers to obtain a volume of 100 mL. Place the pooled specimen in a 250-mL conical flask of resistant glass, add 5 drops of *Methyl Red Solution,* and titrate, while warm, with 0.020 N sulfuric acid. Complete the titration within 60 minutes after opening the autoclave. Record the volume of 0.020 N sulfuric acid used, corrected for a blank obtained by titrating 100 mL of *High-Purity Water* at the same temperature and with the same amount of indicator. The volume does not exceed that indicated in *Table 2* for the type of glass concerned.

Arsenic

Arsenic ⟨211⟩—Use as the *Test Preparation* 35 mL of the water from one Type I glass container or, in the case of smaller containers, 35 mL of the combined contents of several Type I glass containers, prepared as directed for *Procedure* under *Water Attack at 121°:* the limit is 0.1 µg per g.

In-Process Revision

Surface Glass Test

Determination of the Filling Volume—The filling volume is the volume to be filled with *Purified Water* in the container for the purpose of the test. For vials and bottles the filling volume is 90% of the brimful capacity. For ampules it is the volume up to the height of the shoulder.

Vials and Bottle—Select, at random, 6 containers from the sample lot, or 3 if their capacity exceeds 100 mL, and remove any dirt or debris. Weigh the empty containers with an accuracy of 0.1 g. Place the containers on a horizontal surface, and fill them with *Purified Water* to about the rim edge, avoiding overflow and introduction of air bubbles. Adjust the liquid levels to the brimful line. Weigh the filled containers to obtain the mass of the water, expressed to 2 decimal places, for containers having a nominal volume less or equal to 30 mL, and expressed to 1 decimal place for containers having a nominal volume greater than 30 mL. Calculate the mean value of the brimful capacity in mL, and multiply it by 0.9. This volume, expressed to 1 decimal place, is the filling volume for the particular container lot.

Ampules—Place at least 6 dry ampules on a flat, horizontal surface, and fill them with *Purified Water* from a buret until the water reaches point A, where the body of the ampule decreases to the shoulder of the ampule (see *Figure 2*). Read the capacities, expressed to 2 decimal places, and calculate the mean value. This volume, expressed to 1 decimal place, is the filling volume for the particular ampule lot. The filling volume may also be determined by weighing.

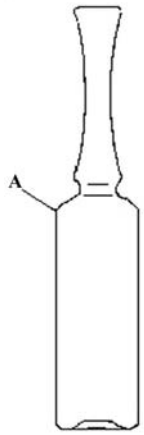

Figure 2. Filling Volumes of Ampules (up to point A)

Test—The determination is carried out on unused containers. The volumes of the test liquid necessary for the final determination are indicated in *Table 2*.

Table 2. Volume of Test Liquid and Number of Titrations

Filling Volume (mL)	Volume of Test Liquid for One Titration (mL)	Number of Titrations
Up to 3	25.0	1.0
Above 3 and up to 30	50.0	2.0
Above 30 and up to 100	100.0	2.0
Above 100	100.0	3.0

Cleaning—Remove any debris or dust. Shortly before the test, rinse each container carefully at least twice with *Purified Water,* and allow to stand. Immediately before testing, empty the containers, rinse once with *Purified Water,* then with carbon dioxide-free water, and allow to drain. Complete the cleaning procedure from the first rinsing in not less than 20 minutes and not more than 25 minutes. Heat closed ampules in a water bath or in an air-oven at about 50° for approximately 2 minutes before opening. Do not rinse before testing.

Filling and Heating—The containers are filled with carbon dioxide-free water up to the filling volume. Containers in the form of cartridges or prefilled syringes are closed in a suitable

manner with material that does not interfere with the test. Each container, including ampules, shall be loosely capped with an inert material such as a dish of neutral glass or aluminum foil previously rinsed with *Purified Water.* Place the containers on the tray of the autoclave.

Place the tray in the autoclave containing a quantity of water such that the tray remains clear of the water. Close the autoclave, and carry out the following operations:

(1) heat the autoclave to 100° and allow the steam to issue from the vent cock for 10 minutes;

(2) close the vent cock and raise the temperature from 100° to 121° at a rate of 1° per minute;

(3) maintain the temperature at 121 ± 1° for 60 ± 1 minutes;

(4) lower the temperature from 121° to 100° at a rate of 0.5° per minute, venting to prevent a vacuum;

(5) do not open the autoclave before it has cooled down to 95°;

(6) remove the containers from the autoclave using normal precautions, place them in a water bath at 80°, and run cold tap water, taking care that the water does not contact the loose foil caps to avoid contamination of the extraction solution;

(7) cooling time does not exceed 30 minutes.

The extraction solutions are analyzed by titration according to the method described below.

Method—Carry out the titration within 1 hour of removal of the containers from the autoclave.

Combine the liquids obtained from the containers, and mix. Introduce the prescribed volume indicated in *Table 3* into a conical flask. Place the same volume of carbon dioxide-free water into a second similar flask as a blank. Add 0.05 mL of *Methyl Red Solution* to each flask for each 25 mL of liquid. Titrate the blank with 0.01 M hydrochloric acid. Titrate the test liquid with the same acid until the color of the resulting solution is the same as that obtained for the blank. Subtract the value found for the blank titration from that found for the test liquid, and express the results in mL of 0.01 M hydrochloric acid per 100 mL. Express titration values of less than 1.0 mL to 2 decimal places and titration values of more than or equal to 1.0 mL to 1 decimal place.

Limits—The results, or the average of the results if more than one titration is performed, are not greater than the values stated in *Table 3.*

Table 3. Limit Values in the Test for Surface Hydrolytic Resistance

	Maximum Volume of 0.01 M HCl per 100 mL of Test Liquid (mL)	
Filling Volume (mL)	Types I and II	Type III
Up to 1	2.0	20.0
Above 1 and Up to 2	1.8	17.6
Above 2 and Up to 5	1.3	13.2
Above 5 and Up to 10	1.0	10.2
Above 10 and Up to 20	0.80	8.1
Above 20 and Up to 50	0.60	6.1
Above 50 and Up to 100	0.50	4.8
Above 100 and Up to 200	0.40	3.8
Above 200 and Up to 500	0.30	12.9
Above 500	0.20	2.2

■2S (*USP30*)

BRIEFING

⟨**661**⟩ **Containers,** *USP 29* page 2655. To clarify the specialized content of this chapter, it is proposed to separate the chapter into three new chapters: sections relevant to plastics will remain in this chapter but the title will be changed to *Containers—Plastics* ⟨661⟩; sections relevant to glass will be included in a new chapter *Containers—Glass* ⟨660⟩; and those sections relative to repackaging will be included in a new chapter *Repackaging into Single-Unit Containers and Unit-Dose Containers from Nonsterile Solid and Liquid Dosage Forms* ⟨681⟩. The plastics content will also be reorganized to eliminate redundancy, and the standards and tests used to determine the functional properties of plastic containers (permeation test for polyethylene and polypropylene containers and the light transmission test) will be placed in General Chapter *Containers—Permeation* ⟨671⟩, which is being renamed *Containers—Performance Testing* ⟨671⟩.

(P&S: D. Hunt) RTS—C44573

In-Process Revision

Change to read:

⟨661⟩ CONTAINERS

■—PLASTICS■ 2S (*USP30*)

Many Pharmacopeial articles are of such nature as to require the greatest attention to the containers in which they are stored or maintained even for short periods of time. While the needs vary widely and some of them are not fully met by the containers available, objective standards are essential. It is the purpose of this chapter to provide such standards as have been developed for the materials of which pharmaceutical containers principally are made, i.e., glass and plastic.

A container intended to provide protection from light or offered as a "light resistant" container meets the requirements for *Light Transmission*, where such protection or resistance is by virtue of the specific properties of the material of which the container is composed, including any coating applied thereto. A clear and colorless or a translucent container that is made light resistant by means of an opaque enclosure (see *General Notices*) is exempt from the requirements for *Light Transmission*.

Containers composed of glass meet the requirements for *Chemical Resistance—Glass Containers*, and containers composed of plastic and intended for packaging products prepared for parenteral use meet the requirements under *Biological Tests—Plastics* and *Physicochemical Tests—Plastics*.

Where dry oral dosage forms, not meant for constitution into solution, are intended to be packaged in a container defined in the section *Polyethylene Containers*, the requirements given in that section are to be met.

Guidelines and requirements under *Repacking into Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms* apply to official dosage forms that are repackaged into single-unit or unit-dose containers or mnemonic packs for dispensing pursuant to prescription.

LIGHT TRANSMISSION

Apparatus[1]**—** Use a spectrophotometer of suitable sensitivity and accuracy, adapted for measuring the amount of light transmitted by either transparent or translucent glass or plastic materials used for pharmaceutical containers. For transparent glass or plastic pharmaceutical containers, use a spectrophotometer of suitable sensitivity and accuracy for measuring and recording the amount of light transmitted. For translucent glass or plastic pharmaceutical containers, use a spectrophotometer as described above that, in addition, is capable of measuring and recording light transmitted in diffused as well as parallel rays.

Preparation of Specimen—

Glass—Break the container or cut it with a circular saw fitted with a wet abrasive wheel, such as a carborundum or a bonded diamond wheel. Select sections to represent the average wall thickness in the case of blown glass containers, and trim them as necessary to give segments of a size convenient for mounting in the spectrophotometer. After cutting, wash and dry each specimen, taking care to avoid scratching the surfaces. If the specimen is too small to cover the opening in the specimen holder, mask the uncovered portion of the opening with opaque paper or masking tape, provided that the length of the specimen is greater than that of the slit in the spectrophotometer. Immediately before mounting in the specimen holder, wipe the specimen with lens tissue. Mount the specimen with the aid of a tacky wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks on the surfaces through which light must pass.

Plastic—Cut circular sections from two or more areas of the container, and wash and dry them, taking care to avoid scratching the surfaces. Mount in the apparatus as described for *GlassC*.

Procedure— Place the section in the spectrophotometer with its cylindrical axis parallel to the plane of the slit and approximately centered with respect to the slit. When properly placed, the light beam is normal to the surface of the section and reflection losses are at a minimum.

Measure the transmittance of the section with reference to air in the spectral region of interest, continuously with a recording instrument or at intervals of about 20 nm with a manual instrument, in the region of 290 to 450 nm.

Limits— The observed light transmission does not exceed the limits given in *Table 1* for containers intended for parenteral use.

Table 1. Limits for Glass Types I, II, and III and Plastic Classes I–VI

	Maximum Percentage of Light Transmission at Any Wavelength Between 290 and 450 nm	
Nominal Size (in mL)	Flame-sealed Containers	Closure-sealed Containers
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50	15	10

NOTE—Any container of a size intermediate to those listed above exhibits a transmission not greater than that of the next larger size container listed in the table. For containers larger than 50 mL, the limits for 50 mL apply.

The observed light transmission for containers of Type NP glass and for plastic containers for products intended for oral or topical administration does not exceed 10% at any wavelength in the range from 290 to 450 nm.

CHEMICAL RESISTANCE—GLASS CONTAINERS

The following tests are designed to determine the resistance to water attack of new (not previously used) glass containers. The degree of attack is determined by the amount of alkali released from the glass under the influence of the attacking medium under the conditions specified. This quantity of alkali is extremely small in the case of the more resistant glasses, thus calling for particular attention to all details of the tests and the use of apparatus of high quality and precision. The tests should be conducted in an area relatively free from fumes and excessive dust.

Glass Types— Glass containers suitable for packaging Pharmacopeial preparations may be classified as in *Table 2* on the basis of the tests set forth in this section. Containers of Type I borosilicate glass are generally used for preparations that are intended for parenteral administration. Containers of Type I glass, or of Type II glass (i.e., soda-lime glass that is suitably dealkalized) are usually used for packaging acidic and neutral parenteral preparations. Type I glass containers, or Type II glass containers (where stability data demonstrate their suitability), are used for alkaline parenteral preparations. Type III soda-lime glass containers usually are not used for parenteral preparations, except where suitable stability test data indicate that Type III glass is satisfactory for the parenteral preparations that

[1] For further detail regarding apparatus and procedures, reference may be made to the following publications of the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19428-2959: "Standard Method of Test for Haze and Luminous Transmittance of Transparent Plastics," ASTM Designation D 1003-61; "Tentative Method of Test for Luminous Reflectance, Transmittance, and Color of Materials," ASTM E 308-66.

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are packaged therein. Containers of Type NP glass are intended for packaging nonparenteral articles, i.e., those intended for oral or topical use.

Table 2. Glass Types and Test Limits

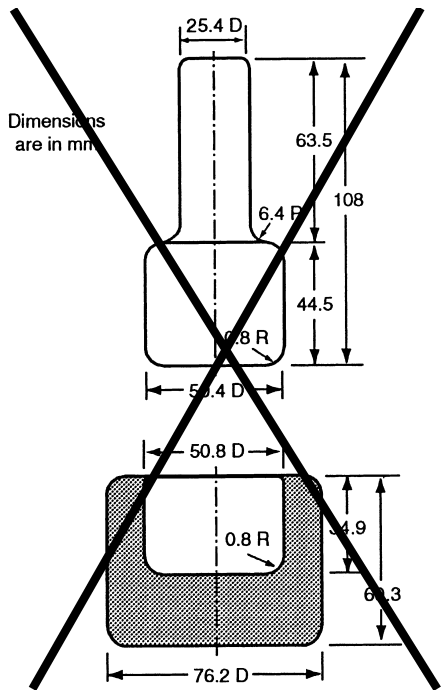
Type	General Description[1]	Type of Test	Limits: Size,[2] mL	Limits: mL of 0.020 N Acid
I	Highly resistant, borosilicate glass	*Powdered Glass*	All	1.0
II	Treated soda-lime glass		100 or less	0.7
		Water Attack	Over 100	0.2
III	Soda-lime glass	*Powdered Glass*	All	8.5
NP	General-purpose soda-lime glass	*Powdered Glass*	All	15.0

[1] The description applies to containers of this type of glass usually available.
[2] Size indicates the overflow capacity of the container.

Apparatus

Autoclave—For these tests, use an autoclave capable of maintaining a temperature of 121 ± 2.0°, equipped with a thermometer, a pressure gauge, a vent cock, and a rack adequate to accommodate at least 12 test containers above the water level.

Mortar and *Pestle*—Use a hardened steel mortar and pestle, made according to the specifications in the accompanying illustration.



Special Mortar and Pestle for Pulverizing Glass[3]

Other Equipment—Also required are 20.3-cm (8-inch) sieves made of stainless steel including the Nos. 20, 40, and 50 sieves along with the pan and cover (see *Sizes of Standard Sieve Series in Range of Interest* under *Particle-Size Distribution Estimation by Analytical Sieving* ⟨786⟩), 250-mL conical flasks made of resistant glass aged as specified, a 900-g (2-lb) hammer, a permanent magnet, a desiccator, and an adequate volumetric apparatus.

[3] A suitable mortar and pestle is available (catalog No. H 17280) from Humboldt Manufacturing Co., 7300 West Agatite, Norridge, Chicago, IL 60656.

Reagents

High-Purity Water—The water used in these tests has a conductivity at 25°, as measured in an in-line cell just prior to dispensing, of not greater than 0.15 µS per cm (6.67 Megohm-cm). There must also be an assurance that this water is not contaminated by copper or its products (e.g., copper pipes, stills, or receivers). The water may be prepared by passing distilled water through a deionizer cartridge packed with a mixed bed of nuclear-grade resin, then through a cellulose ester membrane having openings not exceeding 0.45 µm.[3] Do not use copper tubing. Flush the discharge lines before water is dispensed into test vessels. When the low-conductivity specification can no longer be met, replace the deionizer cartridge.

Methyl Red Solution—Dissolve 24 mg of methyl red sodium in *Purified Water* to make 100 mL. If necessary, neutralize the solution with 0.02 N sodium hydroxide or acidify it with 0.02 N sulfuric acid so that the titration of 100 mL of *High-Purity Water*, containing 5 drops of indicator, does not require more than 0.020 mL of 0.020 N sodium hydroxide to effect the color change of the indicator, which should occur at a pH of 5.6.

Powdered-Glass Test

Rinse thoroughly with *Purified Water* 6 or more containers selected at random, and dry them with a current of clean, dry air. Crush the containers into fragments about 25 mm in size, divide about 100 g of the coarsely crushed glass into three approximately equal portions, and place one of the portions in the special mortar. With the pestle in place, crush the glass further by striking 3 or 4 blows with the hammer. Nest the sieves, and empty the mortar into the No. 20 sieve. Repeat the operation on each of the two remaining portions of glass, emptying the mortar each time into the No. 20 sieve. Shake the sieves for a short time, then remove the glass from the Nos. 20 and 40 sieves, and again crush and sieve as before. Repeat again this crushing and sieving operation. Empty the receiving pan, reassemble the nest of sieves, and shake by mechanical means for 5 minutes or by hand for an equivalent length of time. Transfer the portion retained on the No. 50 sieve, which should weigh in excess of 10 g, to a closed container, and store in a desiccator until used for the test.

Spread the specimen on a piece of glazed paper, and pass a magnet through it to remove particles of iron that may be introduced during the crushing. Transfer the specimen to a 250-mL conical flask of resistant glass, and wash it with six 30-mL portions of acetone, swirling each time for about 30 seconds and carefully decanting the acetone. After washing, the specimen should be free from agglomerations of glass powder, and the surface of the grains should be practically free from adhering fine particles. Dry the flask and contents for 20 minutes at 140°, transfer the grains to a weighing bottle, and cool in a desiccator. Use the test specimen within 48 hours after drying.

Procedure—Transfer 10.00 g of the prepared specimen, accurately weighed, to a 250-mL conical flask that has been digested (aged) previously with *High-Purity Water* in a bath at 90° for at least 24 hours or at 121° for 1 hour. Add 50.0 mL of *High-Purity Water* to this flask and to one similarly prepared to provide a blank. Cap all flasks with borosilicate glass beakers that previously have been treated as described for the flasks and that are of such size that the bottoms of the beakers fit snugly down on the top rims of the containers. Place the containers in the autoclave, and close it securely, leaving the vent cock open. Heat until steam issues vigorously from the vent cock, and continue heating for 10 minutes. Close the vent cock, and adjust the temperature to 121°, taking 19 to 23 minutes to reach the desired temperature. Hold the temperature at 121 ± 2.0° for 30 minutes, counting from the time this temperature is reached. Reduce the heat so that the autoclave cools and comes to atmospheric pressure in 38 to 46 minutes, being vented as necessary to prevent the formation of a vacuum. Cool the flask at once in running water, decant the water from

[3] A suitable nuclear-grade resin mixture of the strong acid cation exchanger in the hydrogen form and the strong base anion exchanger in the hydroxide form, with a one-to-one cation to anion equivalence ratio, is available from the Millipore Corp., Bedford, MA 01730; Barnstead Co., 225 Rivermoor St., Boston, MA 02132; Illinois Water Treatment Co., 840 Cedar St., Rockford, IL 61105; and Vaponics, Inc., 200 Cordage Park, Plymouth, MA 02360. A suitable in-line filter is available from the Millipore Corp.; Gelman Instrument Co., 600 S. Wagner Rd., Ann Arbor, MI 48106; and Schleicher and Schuell, Inc., 540 Washington St., Keene, NH 10003.

the flask into a suitably cleansed vessel, and wash the residual powdered glass with four 15-mL portions of *High Purity Water*, adding the decanted washings to the main portion. Add 5 drops of *Methyl Red Solution*, and titrate immediately with 0.020 N sulfuric acid. If the volume of titrating solution is expected to be less than 10 mL, use a microburet. Record the volume of 0.020 N sulfuric acid used to neutralize the extract from 10 g of the prepared specimen of glass, corrected for a blank. The volume does not exceed that indicated in *Table 2* for the type of glass concerned.

Water Attack at 121°

Rinse thoroughly 3 or more containers, selected at random, twice with *High-Purity Water*.

Procedure— Fill each container to 90% of its overflow capacity with *High-Purity Water*, and proceed as directed for *Procedure* under *Powdered Glass Test*, beginning with "Cap all flasks," except that the time of autoclaving shall be 60 minutes instead of 30 minutes, and ending with "to prevent the formation of a vacuum." Empty the contents from 1 or more containers into a 100-mL graduated cylinder, combining, in the case of smaller containers, the contents of several containers to obtain a volume of 100 mL. Place the pooled specimen in a 250-mL conical flask of resistant glass, add 5 drops of *Methyl Red Solution*, and titrate, while warm, with 0.020 N sulfuric acid. Complete the titration within 60 minutes after opening the autoclave. Record the volume of 0.020 N sulfuric acid used, corrected for a blank obtained by titrating 100 mL of *High-Purity Water* at the same temperature and with the same amount of indicator. The volume does not exceed that indicated in *Table 2* for the type of glass concerned.

Arsenic

Arsenic ⟨211⟩— Use as the *Test Preparation* 35 mL of the water from one Type I glass container or, in the case of smaller containers, 35 mL of the combined contents of several Type I glass containers, prepared as directed for *Procedure* under *Water Attack at 121°*: the limit is 0.1 µg per g.

BIOLOGICAL TESTS—PLASTICS AND OTHER POLYMERS

Perform the in vitro biological tests according to the procedures set forth under *Biological Reactivity Tests, In Vitro* ⟨87⟩. Materials that meet the requirements of the in vitro tests are not required to undergo further testing. No plastic class designation is assigned to these materials. Materials that do not meet the requirements of the in vitro tests are not suitable for containers for drug products

If a plastic class designation is needed for plastics and other polymers that meet the requirements under *Biological Reactivity Tests, In Vitro* ⟨87⟩, perform the appropriate in vivo tests specified for *Classification of Plastics* under *Biological Reactivity Tests, In Vivo* ⟨88⟩.

PHSYSICOCHEMICAL TESTS—PLASTIC

The following tests, designed to determine physical and chemical properties of plastics and their extracts, are based on the extraction of the plastic material, and it is essential that the designated amount of the plastic be used. Also, the specified surface area must be available for extraction at the designated temperature.

Extracting Medium— Unless otherwise directed in a specific test below, use *Purified Water* (see monograph) as the extracting medium, maintained at a temperature of 70° during the extraction of the prepared *Sample*.

Apparatus— Use a water bath and the *Extraction Containers* as described under *Biological Reactivity Tests, In Vivo* ⟨88⟩.

Preparation of Apparatus— Proceed as directed in the first paragraph of *Preparation of Apparatus* under *Biological Reactivity Tests, In Vivo* ⟨88⟩. [NOTE—The containers and equipment need not be sterile.]

Procedure—

Preparation of Sample— From a homogeneous plastic specimen, use a portion, for each 20.0 mL of extracting medium, equivalent to 120 cm² total surface area (both sides combined), and subdivide into strips approximately 3 mm in width and as near to 5 cm in length as is practical. Transfer the subdivided *Sample* to a glass-stoppered, 250-mL graduated cylinder of Type I glass, and add about 150 mL of *Purified Water*. Agitate for about 30 seconds, drain off and discard the liquid, and repeat with a second washing.

Transfer the prepared *Sample* to a suitable extraction flask, and add the required amount of *Extracting Medium*. Extract by heating in a water bath at the temperature specified for the *Extracting Medium* for 24 hours. Cool, but not below 20°. Pipet 20 mL of the extract of the prepared *Sample* into a suitable container. Use this portion in the test for *Buffering Capacity*. Immediately decant the remaining extract into a suitably cleansed container, and seal.

Blank— Use *Purified Water* where a blank is specified in the following tests.

NONVOLATILE RESIDUE— Transfer, in suitable portions, 50.0 mL of the extract of the prepared *Sample* to a suitable, tared crucible (preferably a fused-silica crucible that has been acid-cleaned), and evaporate the volatile matter on a steam bath. Similarly evaporate 50.0 mL of the *Blank* in a second crucible. [NOTE—If an oily residue is expected, inspect the crucible repeatedly during the evaporation and drying period, and reduce the amount of heat if the oil tends to creep along the walls of the crucible.] Dry at 105° for 1 hour: the difference between the amounts obtained from the *Sample* and the *Blank* does not exceed 15 mg.

RESIDUE ON IGNITION ⟨**281**⟩— []It is not necessary to perform this test when the *Nonvolatile Residue* test result does not *Nonvolatile Residue* obtained from the *Sample* and from the *Blank*, using, if necessary, additional sulfuric acid but adding the same amount of sulfuric acid to each crucible: the difference between the amounts of residue on ignition obtained from the *Sample* and the *Blank* does not exceed 5 mg.

HEAVY METALS— Pipet 20 mL of the extract of the prepared *Sample*, filtered if necessary, into one of two matched 50-mL color-comparison tubes. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as external indicator, dilute with water to about 35 mL, and mix.

Into the second color-comparison tube pipet 2 mL of *Standard Lead Solution* (see *Heavy Metals* ⟨231⟩), and add 20 mL of the *Blank*. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as external indicator, dilute with water to about 35 mL, and mix. To each tube add 1.2 mL of thioacetamide-glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer* (see *Heavy Metals* ⟨231⟩), dilute with water to 50 mL, and mix: any brown color produced within 10 minutes in the tube containing the extract of the prepared *Sample* does not exceed that in the tube containing the *Standard Lead Solution*, both tubes being viewed downward over a white surface (1 ppm in extract).

BUFFERING CAPACITY— Titrate the previously collected 20-mL portion of the extract of the prepared *Sample* potentiometrically to a pH of 7.0, using either 0.010 N hydrochloric acid or 0.010 N sodium hydroxide, as required. Treat a 20.0-mL portion of the *Blank* similarly: if the same titrant was required for both *Sample* and *Blank*, the difference between the two volumes is not greater than 10.0 mL; and if acid was required for either the *Sample* or the *Blank* and alkali for the other, the total of the two volumes required is not greater than 10.0 mL.

CONTAINERS FOR OPHTHALMICS—PLASTICS

Plastics for ophthalmics are composed of a mixture of homologous compounds, having a range of molecular weights. Such plastics frequently contain other substances such as residues from the polymerization process, plasticizers, stabilizers, antioxidants, pigments, and lubricants. Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use.

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Definition— For the purposes of this chapter, a *container* is that which holds the drug and is or may be in direct contact with the drug.

Biological Tests— Plastics and other polymers used for containers for ophthalmics meet the requirements set forth in the section *Biological Tests—Plastics and Other Polymers*.

POLYETHYLENE CONTAINERS

The standards and tests provided in this section characterize high-density and low-density polyethylene containers that are interchangeably suitable for packaging dry oral dosage forms not meant for constitution into solution.

Where stability studies have been performed to establish the expiration date of a particular dry oral dosage form not meant for constitution into solution in a container meeting the requirements set forth herein for either high- or low-density polyethylene containers, then any other polyethylene container meeting the same sections of these requirements may be similarly used to package such dosage form, provided that the appropriate stability programs are expanded to include the alternative container, in order to assure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Both high- and low-density polyethylene are long-chain polymers synthesized under controlled conditions of heat and pressure, with the aid of catalysts from not less than 85.0% ethylene and not less than 95.0% total olefins. The other olefin ingredients most frequently used are butene, hexene, and propylene. The ingredients used to manufacture the polyethylene, and those used in the fabrication of the containers, conform to the requirements in the applicable sections of the *Code of Federal Regulations*, Title 21.

High-density polyethylene and low-density polyethylene both have an IR absorption spectrum that is distinctive for polyethylene, and each possesses characteristic thermal properties. High-density polyethylene has a density between 0.941 and 0.965 g per cm^3. Low-density polyethylene has a density between 0.850 and 0.940 g per cm^3. The permeation properties of molded polyethylene containers may be altered when re-ground polymer is incorporated, depending upon the proportion of re-ground material in the final product. Other properties that may affect the suitability of polyethylene used in containers for packaging drugs are: oxygen and moisture permeability, modulus of elasticity, melt index, environmental stress crack resistance, and degree of crystallinity after molding. The requirements in this section are to be met when dry oral dosage forms, not meant for constitution into solution, are intended to be packaged in a container defined by this section.

Multiple Internal Reflectance—

APPARATUS— Use an IR spectrophotometer capable of correcting for the blank spectrum and equipped with a multiple internal reflectance accessory and a KRS-5 internal reflection plate.[4] A KRS-5 crystal 2 mm thick having an angle of incidence of 45° provides a sufficient number of reflections.

PREPARATION OF SPECIMEN— Cut 2 flat sections representative of the average wall thickness of the container, and trim them as necessary to obtain segments that are convenient for mounting in the multiple internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimens with dry paper or, if necessary, clean them with a soft cloth dampened with methanol, and permit them to dry. Securely mount the specimens on both sides of the KRS-5 internal reflection plate, ensuring adequate surface contact. Prior to mounting the specimens on the plate, they may be compressed to thin uniform films by exposing them to temperatures of about 177° under high pressures (15,000 psi or more).

PROCEDURE— Place the mounted specimen sections within the multiple internal reflectance accessory, and place the assembly in the specimen beam of the IR spectrophotometer. Adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, upon completing the adjustments in the accessory, attenuate the reference beam to permit full scale deflection during the scanning of the specimen.) Determine the IR spectrum from 3500 to 600 cm^{-1}: the corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP High-density Polyethylene RS or USP Low-density Polyethylene RS, similarly determined.

Thermal Analysis— Cut a section weighing about 12 mg, and place it in the test specimen pan. Determine the thermogram under nitrogen at temperatures between 40° and 200° at a heating rate between 2° and 10° per minute followed by cooling at a rate between 2° and 10° per minute to 40°, using equipment capable of performing the determinations described under *Thermal Analysis* ⟨891⟩.

High-Density Polyethylene— The thermogram of the specimen is similar to the thermogram of USP High-Density Polyethylene RS, similarly determined, and the temperatures of the endotherms and exotherms in the thermogram of the specimen do not differ from those of the standard by more than 6.0°.

Low-Density Polyethylene— The thermogram of the specimen is similar to the thermogram of USP Low-Density Polyethylene RS, similarly determined, and the temperatures of the endotherms and exotherms in the thermogram of the specimen do not differ from those of the standard by more than 8.0°.

Light Transmission— Polyethylene containers intended to provide protection from light meet the requirements under *Light Transmission*.

Water-Vapor Permeation— Fit the containers with impervious seals obtained by heat-sealing the bottles with an aluminum foil-polyethylene laminate or other suitable seal.[5] Test the containers as described under *Containers—Permeation* ⟨671⟩: the high-density polyethylene containers so tested meet the requirements if the moisture permeability exceeds 10 mg per day per L in not more than 1 of the 10 test containers and exceeds 25 mg per day per L in none of them. The low-density polyethylene containers so tested meet the requirements if the moisture permeability exceeds 20 mg per day per L in not more than 1 of the 10 test containers and exceeds 30 mg per day per L in none of them.

Heavy Metals and Nonvolatile Residue— Prepare extracts of specimens for these tests as directed for *Preparation of Sample* in the *Procedure* under *Physicochemical Tests—Plastics*, except that for each 20.0 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS— Containers meet the requirements for *Heavy Metals* under *Physicochemical Tests—Plastics*.

NONVOLATILE RESIDUE— Proceed as directed for *Nonvolatile Residue* under *Physicochemical Tests—Plastics*, except that the blank shall be the same solvent used in each of the tests set forth below. The difference between the amounts obtained from the specimen and the blank does not exceed 12.0 mg when water maintained at a temperature of 70° is used as the extracting medium; does not exceed 75.0 mg when alcohol maintained at a temperature of 70° is used as the extracting medium; and does not exceed 100.0 mg for high-density polyethylene and does not exceed 350.0 mg for low-density polyethylene when hexanes maintained at a temperature of 50° are used as the extracting medium. Containers meet these requirements for *Nonvolatile Residue* for all of the above extracting media. [NOTE— When evaporating these solvents, use a current of air with the water bath; when drying the residue, use an explosion-proof oven.]

POLYETHYLENE TEREPHTHALATE BOTTLES AND POLYETHYLENE TEREPHTHALATE-G BOTTLES

The standards and tests provided in this section characterize polyethylene terephthalate (PET) and polyethylene terephthalate-G (PETG) bottles that are interchangeably suitable for packaging liquid oral dosage forms.

[4] The multiple internal reflectance accessory and KRS-5 plate are available from several sources, including Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, CA 92634, and from Perkin-Elmer Corp., Main Ave., Norwalk, CT 06856.

[5] A suitable laminate for sealing has as the container contact layer polyethylene of not less than 0.025 mm (0.001 inch) and a second layer of aluminum foil of not less than 0.018 mm (0.0007 inch), with additional layers of suitable backing materials. A suitable seal can be obtained also by using glass plates and a sealing wax consisting of 60% of refined amorphous wax and 40% of refined crystalline paraffin wax.

Where stability studies have been performed to establish the expiration date of a particular liquid oral dosage form in a bottle meeting the requirements set forth herein for either PET or PETG bottles, any other PET or PETG bottle meeting these requirements may be similarly used to package such dosage form, provided that the appropriate stability programs are expanded to include the alternative bottle in order to assure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

The suitability of a specific PET or PETG bottle for use in the dispensing of a particular pharmaceutical liquid oral dosage form must be established by appropriate testing.

PET resins are long-chain crystalline polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid. PET copolymer resins are prepared in a similar way, except that they may also contain a small amount of either isophthalic acid (not more than 3 mole percent) or 1,4-cyclohexanedimethanol (not more than 5 mole percent). Polymerization is conducted under controlled conditions of heat and vacuum, with the aid of catalysts and stabilizers.

PET copolymer resins have physical and spectral properties similar to PET and for practical purposes are treated as PET. The tests and specifications provided in this section to characterize PET resins and bottles apply also to PET copolymer resins and to bottles fabricated from them.

PET and PET copolymer resins generally exhibit a large degree of order in their molecular structure. As a result, they exhibit characteristic composition-dependent thermal behavior, including a glass transition temperature of about 76° and a melting temperature of about 250°. These resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials (e.g., polycarbonate, polystyrene, polyethylene, and PETG resins). PET and PET copolymer resins have a density between 1.3 and 1.4 g per cm^3 and a minimum intrinsic viscosity of 0.7 dL per g, which corresponds to a number average molecular weight of about 23,000 daltons.

PETG resins are high molecular weight polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid and 15 to 34 mole percent of 1,4-cyclohexanedimethanol. PETG resins are clear, amorphous polymers, having a glass transition temperature of about 81° and no crystalline melting point, as determined by differential scanning calorimetry. PETG resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials, including PET. PETG resins have a density of approximately 1.27 g per cm^3 and a minimum intrinsic viscosity of 0.65 dL per g, which corresponds to a number average molecular weight of about 16,000 daltons.

PET and PETG resins, and other ingredients used in the fabrication of these bottles, conform to the requirements in the applicable sections of the Code of Federal Regulations, Title 21, regarding use in contact with food and alcoholic beverages. PET and PETG resins do not contain any plasticizers, processing aids, or antioxidants. Colorants, if used in the manufacture of PET and PETG bottles, do not migrate into the contained liquid.

Multiple Internal Reflectance—

APPARATUS—Use an IR spectrophotometer capable of correcting for the blank spectrum and equipped with a multiple internal reflectance accessory and a KRS-5 internal reflection plate.[6] A KRS-5 crystal having a thickness of 2 mm and an angle of incidence of 45° provides a sufficient number of reflections.

PREPARATION OF SPECIMEN—Cut 2 flat sections representative of the average wall thickness of the bottle, and trim them as necessary to obtain segments that are convenient for mounting in the multiple internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimens with dry paper or, if necessary, clean them with a soft cloth dampened with methanol, and permit them to dry. Securely mount the specimens on both sides of the KRS-5 internal reflection plate, ensuring adequate surface contact.

PROCEDURE—Place the mounted specimen sections within the multiple internal reflectance accessory, and place the assembly in the specimen beam of the IR spectrophotometer. Adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated beams. (For a double-beam instrument, upon completing the adjustments in the accessory, attenuate the reference beam to permit full-scale deflection during the scanning of the specimen.) Determine the IR spectrum from 4000 to 400 cm^{-1}. The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of the USP Polyethylene Terephthalate RS, or the USP Polyethylene Terephthalate G RS, similarly determined.

Thermal Analysis—Cut a section weighing about 12 mg from the bottle, and place it in the test specimen pan. Determine the thermogram under nitrogen, using the heating and cooling conditions as specified for the resin type and using equipment capable of performing the determinations as described under *Thermal Analysis* ⟨891⟩.

Polyethylene Terephthalate—Heat the specimen from room temperature to 280° at a heating rate of about 20° per minute. Hold the specimen at 280° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 280° at a heating rate of about 5° per minute. The thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate RS, similarly determined: the melting point (T_m) of the specimen does not differ from that of the Standard by more than 9.0°, and the glass transition temperature (T_g) of the specimen does not differ from that of the Standard by more than 4.0°.

Polyethylene Terephthalate G—Heat the specimen from room temperature to 120° at a heating rate of about 20° per minute. Hold the specimen at 120° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 120° at a heating rate of about 10° per minute. The thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate G RS, similarly determined: the glass transition temperature (T_g) of the specimen does not differ from that of the Standard by more than 6.0°.

Light Transmission—PET and PETG bottles intended to provide protection from light meet the requirements under *Light Transmission*.

Water Vapor Permeation—[NOTE—Throughout the following procedure, determine the weights of bottles and closures, both as tare weights and weights of filled bottles, to the nearest 0.1 mg if the bottle volume is less than 200 mL; to the nearest mg if the bottle volume is 200 mL or more but less than 1000 mL; or to the nearest centigram (10 mg) if the bottle volume is 1000 mL or more.] Select 10 bottles of a uniform size and type, clean the sealing surfaces with a lint-free cloth, and close and open each bottle 30 times. Apply the closure firmly and uniformly each time the bottle is closed. Close screw-capped bottles with a torque that is within the range of tightness specified in the table provided under *Containers—Permeation* ⟨671⟩. Weigh each empty bottle and its closure. Fill ten bottles with water at 25 ± 2° until the meniscus is tangent to the top of the bottle opening. Record the weight of each bottle and its closure, and determine the average bottle volume, in L, taken by the following formula:

$$\sum_{i=1}^{10} (W_{ci} - W_{ti})/9970,$$

where W_{ci} is the total weight, in g, of bottle I and its closure, W_{ti} is the tare weight, in g, of bottle I and its closure, and 9970 is the density of water at 25° times 10,000 (the number of bottles tested times the conversion factor for converting milliliters to liters).

Using a pipet, adjust the water level in the bottles to the fill point. Apply the closures using a torque that is within the range specified in the table provided under *Containers—Permeation* ⟨671⟩, and store the bottles at a temperature of 25 ± 2° and a relative humidity of 50 ± 2%. After 168 ± 1 hours (7 days), record the weight of the individual bottles. Return the bottles to storage for another 168 ± 1 hours. After the second 168 ± 1 hours, remove the bottles, record

[6] The multiple-internal-reflectance accessory and KRS-5 plate are available from several sources, including Beckman Instruments, Inc., 2500 Harbor Boulevard, Fullerton, CA 92634, and from Perkin-Elmer Corporation, 761 Main Ave., Norwalk, CT 06859-01560.

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the weights of the individual bottles, and calculate the water vapor permeation rate, in mg per day per L, for each bottle taken by the formula:

$$(W_{Ii} - W_{Ji})/TV_a,$$

in which W_{Ii} is the weight, in mg, of bottle I at 14 days, W_{Ji} is the weight, in mg, of bottle J at 7 days, T is the test time, in days, after the 7-day equilibration period, and V_a is the average bottle volume, in L.

The bottles so tested meet the requirements and are *tight containers* if the water vapor permeation rate exceeds 100 mg per day per L in not more than 1 of the 10 test bottles and exceeds 200 mg per day per L in none of them.

Colorant Extraction— Select 3 test bottles. Cut a relatively flat portion from the side wall of one bottle, and trim it as necessary to fit the sample holder of the spectrophotometer. Obtain the visible spectrum of the side wall by scanning the portion of the visible spectrum from 350 to 700 nm. Determine, to the nearest 2 nm, the wavelength of maximum absorbance. Fill the remaining two test bottles, using 50% alcohol for PET bottles and 25% alcohol for PETG bottles. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Fill a glass bottle having the same capacity as that of the test bottles with the corresponding solvent, fit the bottle with an impervious seal, such as aluminum foil, and apply a closure. Incubate the test bottles and the glass bottle in a constant temperature room or in an oven at 49° for ten days. Remove the bottles, and allow them to equilibrate to room temperature. Concomitantly determine the absorbances of the test solutions in 5-cm cells at the wavelength of maximum absorbance (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the corresponding solvent from the glass bottle as the blank. The absorbance values so obtained are less than 0.01 for both test solutions.

Heavy Metals, Total Terephthaloyl Moieties, and Ethylene Glycol—

EXTRACTING MEDIA—

Purified Water— (see monograph).

50 Percent Alcohol— Dilute 125 mL of alcohol with water to 238 mL, and mix.

25 Percent Alcohol— Dilute 125 mL of *50 Percent Alcohol* with water to 250 mL, and mix.

n-Heptane

PROCEDURE— [NOTE—Use the *50 Percent Alcohol Extracting Medium* with PET bottles. Use the *25 Percent Alcohol Extracting Medium* with PETG bottles.]For each *Extracting Medium*, fill a sufficient number of test bottles to 90% of their nominal capacity to obtain not less than 30 mL of extract. Fill a corresponding number of glass bottles with *Purified Water Extracting Medium*, a corresponding number of glass bottles with *50 Percent Alcohol Extracting Medium* or *25 Percent Alcohol Extracting Medium*, and a corresponding number of glass bottles with *n-Heptane Extracting Medium* for use as *Extracting Media* blanks. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Incubate the test bottles and the glass bottles in a constant temperature room or in an oven at 49° for ten days. Remove the test bottles with the *Extracting Media* samples and the glass bottles with the *Extracting Media* blanks, and store them at room temperature. Do not transfer the *Extracting Media* samples to alternative storage vessels.

HEAVY METALS— Pipet 20 mL of the *Purified Water* extract of the test bottles, filtered if necessary, into one of two matched 50-mL color comparison tubes, and retain the remaining *Purified Water* extract in the test bottles for use in the test for *Ethylene Glycol*. Adjust the extract with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

Into the second color comparison tube, pipet 2 mL of freshly prepared (on day of use) *Standard Lead Solution* (see *Heavy Metals* ⟨231⟩), and add 20 mL of *Purified Water*. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

To each tube add 1.2 mL of thioacetamide-glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer* (see *Heavy Metals* ⟨231⟩), dilute with water to 50 mL, and mix: any color produced within 10 minutes in the tube containing the *Purified Water* extract of the test bottles does not exceed that in the tube containing the *Standard Lead Solution*, both tubes being viewed downward over a white surface (1 ppm in extract).

Total Terephthaloyl Moieties— Determine the absorbance of the *50 Percent Alcohol* or *25 Percent Alcohol* extract in a 1-cm cell at the wavelength of maximum absorbance at about 244 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the corresponding *Extracting Medium* blank as the blank: the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

Determine the absorbance of the *n-Heptane* extract in a 1-cm cell at the wavelength of maximum absorbance at about 240 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the *n-Heptane Extracting Medium* blank as the blank: the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

ETHYLENE GLYCOL—

Periodic Acid Solution— Dissolve 125 mg of periodic acid in 10 mL of water.

Dilute Sulfuric Acid— To 50 mL of water add slowly and with constant stirring 50 mL of sulfuric acid, and allow to cool to room temperature.

Sodium Bisulfite Solution— Dissolve 0.1 g of sodium bisulfite in 10 mL of water. Use this solution within seven days.

Disodium Chromotropate Solution— Dissolve 100 mg of disodium chromotropate in 100 mL of sulfuric acid. Protect this solution from light, and use within seven days.

Standard Solution— Dissolve an accurately weighed quantity of ethylene glycol in water, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1 µg per mL.

Test Solution— Use the *Purified Water* extract.

Blank— Use the *Purified Water Extracting Medium* blank.

Procedure— Transfer 1.0 mL of *Standard Solution* to a 10-mL volumetric flask. Transfer 1.0 mL of *Test Solution* to a second 10-mL volumetric flask. Transfer 1.0 mL of *Purified Water Extracting Medium* blank to a third 10-mL volumetric flask. To each of the three flasks, add 100 µL of *Periodic Acid Solution*, swirl to mix, and allow to stand for 60 minutes. Add 1.0 mL of *Sodium Bisulfite Solution* to each flask, and mix. Add 100 µL of *Disodium Chromotropate Solution* to each flask, and mix. [NOTE—All solutions should be analyzed within one hour after addition of the *Disodium Chromotropate Solution*.] Cautiously add 6 mL of sulfuric acid to each flask, mix, and allow the solutions to cool to room temperature. Dilute each solution with *Dilute sulfuric acid* to volume, and mix. Concomitantly determine the absorbances of the solutions from the *Standard Solution* and the *Test Solution* in 1-cm cells at the wavelength of maximum absorbance at about 575 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the solution from the *Purified Water Extracting Medium* blank as the blank: the absorbance of the solution from the *Test solution* does not exceed that of the solution from the *Standard solution*, corresponding to not more than 1 ppm of ethylene glycol.

POLYPROPYLENE CONTAINERS

The standards and tests provided in this section characterize polypropylene containers, produced from either homopolymers or copolymers, that are interchangeably suitable for packaging dry solid and liquid oral dosage forms.

Where suitable stability studies have been performed to establish the expiration date of a particular dosage form in the appropriate polypropylene container, then any other polypropylene container meeting these requirements may be similarly used to package such dosage form, provided that the appropriate stability programs are ex-

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panded to include the alternative container, in order to assure that the potency, identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Propylene polymers are long-chain polymers synthesized from propylene or propylene and other olefins under controlled conditions of heat and pressure, with the aid of catalysts. Examples of other olefins most commonly used include ethylene and butene. The propylene polymers, the ingredients used to manufacture the propylene polymers, and the ingredients used in the fabrication of the containers conform to the applicable sections of the *Code of Federal Regulations*, Title 21.

Factors such as plastics composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. The suitability of a specific polypropylene must be established by appropriate testing.

Polypropylene has a distinctive IR spectrum and possesses characteristic thermal properties. It has a density between 0.880 and 0.913 g per cm^3. The permeation properties of molded polypropylene containers may be altered when reground polymer is incorporated, depending on the proportion of reground material in the final product. Other properties that may affect the suitability of polypropylene used in containers for packaging drugs are the following: oxygen and moisture permeability, modulus of elasticity, melt flow index, environmental stress crack resistance, and degree of crystallinity after molding. The requirements in this section are to be met when dry solid and liquid oral dosage forms are to be packaged in a container defined by this section.

Multiple Internal Reflectance—

APPARATUS—Use an IR spectrophotometer capable of correcting for the blank spectrum and equipped with a multiple internal reflectance accessory and a KRS-5 internal reflection plate. A KRS-5 crystal 2 mm thick having an angle of incidence of 45° provides a sufficient number of reflections.

PREPARATION OF SPECIMEN—Cut 2 flat sections, representative of the average wall thickness of the container, and trim them as necessary to obtain segments that are convenient for mounting in the internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimens with dry paper, or if necessary with a soft cloth dampened with methanol, and permit them to dry. Securely mount the specimens on both sides of the KRS-5 internal reflection plate, ensuring adequate surface contact. Prior to mounting the specimens on the plate, they may be compressed to flat uniform films by exposure to temperatures between 220° and 240°. The specimen's time/temperature history during this operation should be limited to that necessary to mold the films.

PROCEDURE—Place the mounted specimen sections within the multiple internal reflectance accessory, and place the assembly in the specimen beam of the IR spectrophotometer. Adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, upon completing the adjustment in the accessory, attenuate the reference beam to permit full-scale deflection during the scanning of the specimen.) Determine the IR spectrum from 3500 to 600 cm^{-1}. The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of the USP Reference Standard for either a polypropylene homopolymer or copolymer, similarly determined.

Thermal Analysis—Cut a section weighing about 12 mg, and place it in the test specimen pan. Intimate contact between the pan and the thermocouple is essential for reproducible results. Determine the thermogram under nitrogen at temperatures ranging from ambient to 30° above the melting point. Maintain the temperature for 10 minutes, then cool to 50° below the peak crystallization temperature at a rate of 10° to 20° per minute, using equipment capable of performing the determinations as described under *Thermal Analysis* ⟨891⟩. The thermogram of the specimen is similar to the thermogram of the appropriate USP Reference Standard for polypropylene. The temperatures of the endotherms and exotherms in the thermogram do not differ from those of the USP Reference Standard for homopolymers by more than 12.0° or from those of the USP Reference Standard for copolymers by more than 6.0°.

Light Transmission—Polypropylene containers intended to provide protection from light meet the requirements under *Light Transmission*.

Water-Vapor Permeation—Fit the containers with impervious seals obtained by heat sealing the bottles with an aluminum foil–polyethylene laminate or other suitable seal. Test the containers as described under *Containers—Permeation* ⟨671⟩. The containers meet the requirements if the moisture permeability exceeds 15 mg per day per L in not more than one of the 10 test containers and exceeds 25 mg per day per L in none of them.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Procedure* under *Physicochemical Tests—Plastics*, except that for each 20 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Heavy Metals* under *Physicochemical Tests—Plastics*.

NONVOLATILE RESIDUE—Proceed as directed for *Nonvolatile Residue* under *Physicochemical Tests—Plastics*, except that the blank shall be the same solvent used in each of the tests set forth below. The difference between the amounts obtained from the specimen and the blank does not exceed 10.0 mg when water maintained at a temperature of 70° is used as the extracting medium, does not exceed 60.0 mg when alcohol maintained at a temperature of 70° is used as the extracting medium, and does not exceed 225.0 mg when hexanes maintained at a temperature of 50° is used as the extracting medium. Containers meet these requirements for *Nonvolatile Residue* for all of the above extracting media. [NOTE—Hexanes and alcohol are flammable. When evaporating these solvents, use a current of air with the water bath; when drying the residue, use an explosion-proof oven.]

Buffering Capacity—Prepare extracts of the specimen as described for *Procedure* under *Physicochemical Tests—Plastics*. Containers meet the requirements for *Buffering Capacity* under *Physicochemical Tests—Plastics*.

REPACKAGING INTO SINGLE-UNIT CONTAINERS AND UNIT-DOSE CONTAINERS FOR NONSTERILE SOLID AND LIQUID DOSAGE FORMS

An official dosage form is required to bear on its label an expiration date assigned for the particular formulation and package of the article. This date limits the time during which the product may be dispensed or used. Because the expiration date stated on the manufacturer's or distributor's package has been determined for the drug in that particular package and is not intended to be applicable to the product where it has been repackaged in a different container, repackaged drugs dispensed pursuant to a prescription are exempt from this expiration date labeling requirement. It is necessary, therefore, that other precautions be taken by the dispenser to preserve the strength, quality, and purity of drugs that are repackaged for ultimate distribution or sale to patients.

The following guidelines and requirements are applicable where official dosage forms are repackaged into single-unit or unit-dose containers or mnemonic packs for dispensing pursuant to prescription.

Labeling—It is the responsibility of the dispenser, taking into account the nature of the drug repackaged, any packaging and beyond-use dating information in the manufacturer's product labeling, the characteristics of the containers, and the storage conditions to which the article may be subjected, to place a suitable beyond-use date on the label. Repackaged dosage forms must bear on their labels beyond-use dates as determined from information in the product labeling. Each single-unit or unit-dose container bears a separate label, unless the device holding the unit-dose form does not allow for the removal or separation of the intact single-unit or unit-dose container therefrom.

Storage—Store the repackaged article in a humidity-controlled environment and at the temperature specified in the individual monograph or in the product labeling. Where no temperature or humidity is specified in the monograph or in the labeling of the product, controlled room temperature and a relative humidity corresponding to 75% at 23° are not to be exceeded during repackaging or storage.

A refrigerator or freezer shall not be considered to be a humidity-controlled environment, and drugs that are to be stored at a cold temperature in a refrigerator or freezer shall be placed within an outer container that meets the monograph requirements for the drug contained therein.

Reprocessing— Reprocessing of repackaged unit-dose containers (i.e., removing dosage unit from one unit-dose container and placing dosage unit into another unit-dose container) shall not be done. However, reprocessing of the secondary package (e.g., removing the blister card from the cardboard carrier and placing the blister card into another cardboard carrier) is allowed provided that the original beyond-use date is maintained.

CUSTOMIZED PATIENT MEDICATION PACKAGES

In lieu of dispensing two or more prescribed drug products in separate containers, a pharmacist may, with the consent of the patient, the patient's caregiver, or a prescriber, provide a customized patient medication package (patient med pak).[2]

A patient med pak is a package prepared by a pharmacist for a specific patient comprising a series of containers and containing two or more prescribed solid oral dosage forms. The patient med pak is so designed or each container is so labeled as to indicate the day and time, or period of time, that the contents within each container are to be taken.

It is the responsibility of the dispenser to instruct the patient or caregiver on the use of the patient med pak.

Label— The patient med pak shall bear a label stating:

(1) the name of the patient;
(2) a serial number for the patient med pak itself and a separate identifying serial number for each of the prescription orders for each of the drug products contained therein;
(3) the name, strength, physical description or identification, and total quantity of each drug product contained therein;
(4) the directions for use and cautionary statements, if any, contained in the prescription order for each drug product therein;
(5) any storage instructions or cautionary statements required by the official compendia;
(6) the name of the prescriber of each drug product;
(7) the date of preparation of the patient med pak and the beyond-use date or period of time assigned to the patient med pak (such beyond-use date or period of time shall be not longer than the shortest recommended beyond-use date for any dosage form included therein or not longer than 60 days from the date of preparation of the patient med pak and shall not exceed the shortest expiration date on the original manufacturer's bulk containers for the dosage forms included therein); alternatively, the package label shall state the date of the prescription(s) or the date of preparation of the patient med pak, provided the package is accompanied by a record indicating the start date and the beyond-use date;
(8) the name, address, and telephone number of the dispenser (and the dispenser's registration number where necessary); and
(9) any other information, statements, or warnings required for any of the drug products contained therein.

If the patient med pak allows for the removal or separation of the intact containers therefrom, each individual container shall bear a label identifying each of the drug products contained therein.

Labeling— The patient med pak shall be accompanied by a patient package insert, in the event that any medication therein is required to be dispensed with such insert as accompanying labeling. Alternatively, such required information may be incorporated into a single, overall educational insert provided by the pharmacist for the total patient med pak.

Packaging— In the absence of more stringent packaging requirements for any of the drug products contained therein, each container of the patient med pak shall comply with the moisture permeation requirements for a Class B single-unit or unit-dose container (see *Containers—Permeation* ⟨671⟩). Each container shall be either not reclosable or so designed as to show evidence of having been opened.

Guidelines— It is the responsibility of the dispenser, when preparing a patient med pak, to take into account any applicable compendial requirements or guidelines and the physical and chemical compatibility of the dosage forms placed within each container, as well as any therapeutic incompatibilities that may attend the simultaneous administration of the medications. In this regard, pharmacists are encouraged to report to USP headquarters any observed or reported incompatibilities. Once a medication has been placed in a patient med pak with another solid dosage form, it may not be returned to stock, redistributed, or resold if unused.

Recordkeeping— In addition to any individual prescription filing requirements, a record of each patient med pak shall be made and filed. Each record shall contain, as a minimum:

(1) the name and address of the patient;
(2) the serial number of the prescription order for each drug product contained therein;
(3) the name of the manufacturer or labeler and lot number for each drug product contained therein;
(4) information identifying or describing the design, characteristics, or specifications of the patient med pak sufficient to allow subsequent preparation of an identical patient med pak for the patient;
(5) the date of preparation of the patient med pak and the beyond-use date that was assigned;
(6) any special labeling instructions; and
(7) the name or initials of the pharmacist who prepared the patient med pak.

[2] It should be noted that there is no special exemption for patient med paks from the requirements of the Poison Prevention Packaging Act. Thus the patient med pak, if it does not meet child-resistant standards, shall be placed in an outer package that does comply, or the necessary consent of the purchaser or physician, to dispense in a container not intended to be child-resistant, shall be obtained.

■INTRODUCTION

It is the purpose of this chapter to provide standards for plastic materials and components used to package medical articles (pharmaceuticals, biologics, dietary supplements, and devices). Definitions that apply to this chapter are provided in the *Preservation, Packaging, Storage, and Labeling* section of the *General Notices and Requirements*. Standards and tests for the functional properties of containers and their components are provided in general chapter *Containers—Performance Testing* ⟨671⟩.

In addition to the standards provided herein, the ingredients added to the polymers, and those used in the fabrication of the containers, must conform to the requirements in the applicable sections of the *Code of Federal Regulations,* Title 21, *Indirect Food Additives,* or have been evaluated by the FDA and determined to be acceptable substances for the listed use.

Plastic articles are identified and characterized by IR spectroscopy and differential scanning calorimetry. Standards are provided in this chapter for the identification and characterization of the different types of plastic, and the test procedures are

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provided at the end of the chapter. The degree of testing is based on drug contact, and the risk is based on the end use of the component.

Plastics are composed of a mixture of homologous polymers, having a range of molecular weights. Plastics may contain other substances such as residues from the polymerization process, plasticizers, stabilizers, antioxidants, pigments, and lubricants. These materials meet the requirements for food contact as provided in the *Code of Federal Regulations,* Title 21. Factors such as plastic composition, processing and cleaning procedures, surface treatment, contacting media, inks, adhesives, absorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. Extraction tests are designed to characterize the extracted components and identify possible migrants. The degree or extent of testing for extractables of the component is dependent upon the intended use and the degree of risk to adversely impact the efficacy of the compendial article (drug, biologic, dietary supplement, or device). Resin-specific extraction tests are provided in this chapter for polyethylene, polypropylene, polypropylene terephthalate, and polypropylene terephthalate G. Test all other plastics as directed under *Physicochemical Tests* in the section *Test Methods.* Conduct the *Buffering Capacity* test only when the containers are intended to hold a liquid product.

Plastic components used for products of high risk, such as those intended for inhalation, parenteral preparation, and ophthalmics are tested using the *Biological Tests* in the section *Test Methods.*

Plastic containers intended for packaging products prepared for parenteral use meet the requirements under *Biological Tests* and *Physicochemical Tests* in the section *Test Methods.* Standards are also provided for polyethylene containers used to package dry oral dosage forms that are not meant for constitution into solution.

POLYETHYLENE CONTAINERS

Scope

The standards and tests provided in this section characterize containers and components produced from either low density polyethylene or high density polyethylene of either homopolymer or copolymer resin. All polyethylene components are subject to testing by IR spectroscopy and differential scanning calorimetry. Where stability studies have been performed to establish the expiration date of a particular dosage form in the appropriate polyethylene container, then any other polyethylene container meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative container, in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Background

High and low density polyethylene are long-chain polymers synthesized under controlled conditions of heat and pressure, with the aid of catalysts from not less than 85.0% ethylene and not less than 95.0% total olefins. Other olefin ingredients that are most frequently used are butene, hexene, and propylene. High density polyethylene and low density polyethylene both have an IR absorption spectrum that is distinctive for polyethylene, and each possesses characteristic thermal properties. High density polyethylene has a density between 0.941 and 0.965 g per cm^3. Low density polyethylene has a density between 0.850 and 0.940 g per cm^3. Other properties that may affect the suitability of polyethylene include modulus of elasticity, melt index, environmental stress crack resistance, and degree of crystallinity after molding.

High Density Polyethylene

Infrared Spectroscopy—Proceed as directed under *Multiple Internal Reflectance* in the section *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP High Density Polyethylene RS.

Differential Scanning Calorimetry—Proceed as directed under *Thermal Analysis* in the section *Test Methods.* The thermogram of the specimen is similar to the thermogram of USP High Density Polyethylene RS, similarly determined, and the temperatures of the endotherms and exotherms in the thermogram of the specimen do not differ from those of the USP Reference Standard by more than 6.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Sample Preparation* under *Physicochemical Tests* in the section *Test Methods,* except that for each 20.0 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Heavy Metals* under *Physicochemical Tests* in the section *Test Methods.*

NONVOLATILE RESIDUE—Proceed as directed for *Nonvolatile Residue* under *Physicochemical Tests,* except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 12.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium;* does not exceed 75.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium;* and does not exceed 100.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium*.

Components Used in Contact with Oral Liquids—Proceed as directed under *Buffering Capacity* under *Physicochemical Tests* in the section *Test Methods.*

Low Density Polyethylene

Infrared Spectroscopy—Proceed as directed under *Multiple Internal Reflectance* in the section *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP Low Density Polyethylene RS.

Differential Scanning Calorimetry—Proceed as directed under *Thermal Analysis* in the section *Test Methods.* The thermogram of the specimen is similar to the thermogram of USP Low Density Polyethylene RS, similarly determined, and the temperatures of the endotherms and exotherms in the thermogram of the specimen do not differ from those of the USP Reference Standard by more than 8.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Sample Preparation* under *Physicochemical Tests* in the section *Test Methods,* except that for each 20.0 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Heavy Metals* under *Physicochemical Tests* in the section *Test Methods*.

NONVOLATILE RESIDUE—Proceed as directed for *Nonvolatile Residue* under *Physicochemical Tests* in the section *Test Methods,* except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 12.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium;* does not exceed 75.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium;* and does not exceed 350.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium*.

Components Used in Contact with Oral Liquids—Proceed as directed under *Buffering Capacity* under *Physicochemical Tests* in the section *Test Methods*.

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POLYPROPYLENE CONTAINERS

Scope

The standards and tests provided in this section characterize polypropylene containers, produced from either homopolymers or copolymers, that are interchangeably suitable for packaging dry solid and liquid oral dosage forms. Where suitable stability studies have been performed to establish the expiration date of a particular dosage form in the appropriate polypropylene container, then any other polypropylene container meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative container, in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period.

Background

Propylene polymers are long-chain polymers synthesized from propylene or propylene and other olefins under controlled conditions of heat and pressure, with the aid of catalysts. Examples of other olefins most commonly used include ethylene and butene. The propylene polymers, the ingredients used to manufacture the propylene polymers, and the ingredients used in the fabrication of the containers conform to the applicable sections of the *Code of Federal Regulations,* Title 21.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives, and conditions of storage may also affect the suitability of a plastic for a specific use. The suitability of a specific polypropylene must be established by appropriate testing.

Polypropylene has a distinctive IR spectrum and possesses characteristic thermal properties. It has a density between 0.880 and 0.913 g per cm^3. The permeation properties of molded polypropylene containers may be altered when reground polymer is incorporated, depending on the proportion of reground material in the final product. Other properties that may affect the suitability of polypropylene used in containers for packaging drugs are the following: oxygen and moisture permeability, modulus of elasticity, melt flow index, environmental stress crack resistance, and degree of crystallinity after molding. The requirements in this section are to be met when dry solid and liquid oral dosage forms are to be packaged in a container defined by this section.

Infrared Spectroscopy—Proceed as directed under *Multiple Internal Reflectance* in the section *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of the respective USP Homopolymer Polypropylene RS or USP Copolymer Polypropylene RS, similarly determined.

Differential Scanning Calorimetry—Proceed as directed under *Thermal Analysis* in the section *Test Methods.* The temperatures of the endotherms and exotherms in the thermogram do not differ from those of the USP Homopolymer Polypropylene RS by more than 12.0° or from those of the USP Copolymer Polypropylene RS by more than 6.0°.

Heavy Metals and Nonvolatile Residue—Prepare extracts of specimens for these tests as directed for *Sample Preparation* under *Physicochemical Tests* in the section *Test Methods,* except that for each 20 mL of *Extracting Medium* the portion shall be 60 cm^2, regardless of thickness.

HEAVY METALS—Containers meet the requirements for *Heavy Metals* under *Physicochemical Tests* in the section *Test Methods.*

NONVOLATILE RESIDUE—Proceed as directed for *Nonvolatile Residue* under *Physicochemical Tests* in the section *Test Methods,* except that the *Blank* shall be the same solvent used in each of the following test conditions: the difference between the amounts obtained from the *Sample Preparation* and the *Blank* does not exceed 10.0 mg when water maintained at a temperature of 70° is used as the *Extracting Medium;* does not exceed 60.0 mg when alcohol maintained at a temperature of 70° is used as the *Extracting Medium;* and does not exceed

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225.0 mg when hexanes maintained at a temperature of 50° is used as the *Extracting Medium*. Containers meet these requirements for *Nonvolatile Residue* for all of the above extracting media. [NOTE—Hexanes and alcohol are flammable. When evaporating these solvents, use a current of air with the water bath; when drying the residue, use an explosion-proof oven.]

Components Used in Contact with Oral Liquids—Proceed as directed in *Buffering Capacity* under *Physicochemical Tests* in the section *Test Methods.*

POLYETHYLENE TEREPHTHALATE BOTTLES AND POLYETHYLENE TEREPHTHALATE G CONTAINERS

Scope

The standards and tests provided in this section characterize polyethylene terephthalate (PET) and polyethylene terephthalate G (PETG) bottles that are interchangeably suitable for packaging liquid oral dosage forms. Where stability studies have been performed to establish the expiration date of a particular liquid oral dosage form in a bottle meeting the requirements set forth herein for either PET or PETG bottles, any other PET or PETG bottle meeting these requirements may be similarly used to package such a dosage form, provided that the appropriate stability programs are expanded to include the alternative bottle in order to ensure that the identity, strength, quality, and purity of the dosage form are maintained throughout the expiration period. The suitability of a specific PET or PETG bottle for use in the dispensing of a particular pharmaceutical liquid oral dosage form must be established by appropriate testing.

Background

PET resins are long-chain crystalline polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid. PET copolymer resins are prepared in a similar way, except that they may also contain a small amount of either isophthalic acid (not more than 3 mole percent) or 1,4-cyclohexanedimethanol (not more than 5 mole percent). Polymerization is conducted under controlled conditions of heat and vacuum, with the aid of catalysts and stabilizers.

PET copolymer resins have physical and spectral properties similar to PET and for practical purposes are treated as PET. The tests and specifications provided in this section to characterize PET resins and bottles apply also to PET copolymer resins and to bottles fabricated from them.

PET and PET copolymer resins generally exhibit a large degree of order in their molecular structure. As a result, they exhibit characteristic composition-dependent thermal behavior, including a glass transition temperature of about 76° and a melting temperature of about 250°. These resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials (e.g., polycarbonate, polystyrene, polyethylene, and PETG resins). PET and PET copolymer resins have a density between 1.3 and 1.4 g per cm^3 and a minimum intrinsic viscosity of 0.7 dL per g, which corresponds to a number average molecular weight of about 23,000 Da.

PETG resins are high molecular weight polymers prepared by the condensation of ethylene glycol with dimethyl terephthalate or terephthalic acid and 15 to 34 mole percent of 1,4-cyclohexanedimethanol. PETG resins are clear, amorphous polymers, having a glass transition temperature of about 81° and no crystalline melting point, as determined by differential scanning calorimetry. PETG resins have a distinctive IR absorption spectrum that allows them to be distinguished from other plastic materials, including PET. PETG resins have a density of approximately 1.27 g per cm^3 and a minimum intrinsic viscosity of 0.65 dL per g, which corresponds to a number average molecular weight of about 16,000 Da.

PET and PETG resins, and other ingredients used in the fabrication of these bottles, conform to the requirements in the applicable sections of the *Code of Federal Regulations,* Title 21, regarding use in contact with food and alcoholic bever-

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ages. PET and PETG resins do not contain any plasticizers, processing aids, or antioxidants. Colorants, if used in the manufacture of PET and PETG bottles, do not migrate into the contained liquid.

Infrared Spectroscopy—Proceed as directed under *Multiple Internal Reflectance* in the section *Test Methods.* The corrected spectrum of the specimen exhibits major absorption bands only at the same wavelengths as the spectrum of USP Polyethylene Terephthalate RS, or USP Polyethylene Terephthalate G RS, similarly determined.

Differential Scanning Calorimetry—Proceed as directed under *Thermal Analysis* in the section *Test Methods.* For polyethylene terephthalate, the thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate RS, similarly determined: the melting point (T_m) of the specimen does not differ from that of the USP Reference Standard by more than 9.0°, and the glass transition temperature (T_g) of the specimen does not differ from that of the USP Reference Standard by more than 4.0°. For polyethylene terephthalate G, the thermogram of the specimen is similar to the thermogram of USP Polyethylene Terephthalate G RS, similarly determined: the glass transition temperature (T_g) of the specimen does not differ from that of the USP Reference Standard by more than 6.0°.

Colorant Extraction—Select three test bottles. Cut a relatively flat portion from the side wall of one bottle, and trim it as necessary to fit the sample holder of the spectrophotometer. Obtain the visible spectrum of the side wall by scanning the portion of the visible spectrum from 350 to 700 nm. Determine, to the nearest 2 nm, the wavelength of maximum absorbance. Fill the remaining two test bottles, using 50% alcohol for PET bottles and 25% alcohol for PETG bottles. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Fill a glass bottle having the same capacity as that of the test bottles with the corresponding solvent, fit the bottle with an impervious seal, such as aluminum foil, and apply a closure. Incubate the test bottles and the glass bottle at 49° for 10 days. Remove the bottles, and allow them to equilibrate to room temperature. Concomitantly determine the absorbances of the test solutions in 5-cm cells at the wavelength of maximum absorbance (see *Spectrophotometry and Light–Scattering* ⟨851⟩), using the corresponding solvent from the glass bottle as the blank. The absorbance values so obtained are less than 0.01 for both test solutions.

Heavy Metals, Total Terephthaloyl Moieties, and Ethylene Glycol—

EXTRACTING MEDIA—

Purified Water—(see monograph).

50 Percent Alcohol—Dilute 125 mL of alcohol with water to 238 mL, and mix.

25 Percent Alcohol—Dilute 125 mL of *50 Percent Alcohol* with water to 250 mL, and mix.

n-Heptane.

GENERAL PROCEDURE—[NOTE—Use an *Extracting Medium* of *50 Percent Alcohol* for PET bottles and *25 Percent Alcohol* for PETG bottles.] For each *Extracting Medium,* fill a sufficient number of test bottles to 90% of their nominal capacity to obtain not less than 30 mL. Fill a corresponding number of glass bottles with *Purified Water,* a corresponding number of glass bottles with *50 Percent Alcohol* or *25 Percent Alcohol,* and a corresponding number of glass bottles with *n-Heptane* for use as *Extracting Media* blanks. Fit the bottles with impervious seals, such as aluminum foil, and apply closures. Incubate the test bottles and the glass bottles at 49° for 10 days. Remove the test bottles with the *Extracting Media* samples and the glass bottles with the *Extracting Media* blanks, and store them at room temperature. Do not transfer the *Extracting Media* samples to alternative storage vessels.

HEAVY METALS—Pipet 20 mL of the *Purified Water* extract of the test bottles, filtered if necessary, into one of two matched 50-mL color-comparison tubes, and retain the remaining *Purified Water* extract in the test bottles for use in the test for *Ethylene Glycol*. Adjust the extract with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

Into the second color-comparison tube, pipet 2 mL of freshly prepared (on day of use) *Standard Lead Solution* (see *Heavy Metals* ⟨231⟩), and add 20 mL of *Purified Water*. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator. Dilute with water to about 35 mL, and mix.

To each tube add 1.2 mL of thioacetamide–glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer* (see *Heavy Metals* ⟨231⟩), dilute with water to 50 mL, and mix: any color produced within 10 minutes in the tube containing the *Purified Water* extract of the test bottles does not exceed that in the tube containing the *Standard Lead Solution,* both tubes being viewed downward over a white surface (1 ppm in extract).

TOTAL TEREPHTHALOYL MOIETIES—Determine the absorbance of the *50 Percent Alcohol* or *25 Percent Alcohol* extract in a 1-cm cell at the wavelength of maximum absorbance at about 244 nm (see *Spectrophotometry and Light–Scattering* ⟨851⟩), using as the blank the corresponding *Extracting Medium* blank: the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

Determine the absorbance of the *n-Heptane* extract in a 1-cm cell at the wavelength of maximum absorbance at about 240 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using as the blank the *n-Heptane Extracting Medium:* the absorbance of the extract does not exceed 0.150, corresponding to not more than 1 ppm of total terephthaloyl moieties.

ETHYLENE GLYCOL—

Periodic Acid Solution—Dissolve 125 mg of periodic acid in 10 mL of water.

Dilute Sulfuric Acid—To 50 mL of water add slowly and with constant stirring 50 mL of sulfuric acid, and allow to cool to room temperature.

Sodium Bisulfite Solution—Dissolve 0.1 g of sodium bisulfite in 10 mL of water. Use this solution within 7 days.

Disodium Chromotropate Solution—Dissolve 100 mg of disodium chromotropate in 100 mL of sulfuric acid. Protect this solution from light, and use within 7 days.

Standard Solution—Dissolve an accurately weighed quantity of ethylene glycol in water, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 1 µg per mL.

Test Solution—Use the *Purified Water* extract.

Procedure—Transfer 1.0 mL of the *Standard Solution* to a 10-mL volumetric flask. Transfer 1.0 mL of the *Test Solution* to a second 10-mL volumetric flask. Transfer 1.0 mL of the *Purified Water Extracting Medium* to a third 10-mL volumetric flask. To each of the three flasks, add 100 µL of *Periodic Acid Solution,* swirl to mix, and allow to stand for 60 minutes. Add 1.0 mL of *Sodium Bisulfite Solution* to each flask, and mix. Add 100 µL of *Disodium Chromotropate Solution* to each flask, and mix. [NOTE—All solutions should be analyzed within 1 hour after addition of the *Disodium Chromotropate Solution*.] Cautiously add 6 mL of sulfuric acid to each flask, mix, and allow the solutions to cool to room temperature. *[Caution–Dilution of sulfuric acid produces substantial heat and can cause the solution to boil. Perform this addition carefully. Sulfur dioxide gas will be evolved. Use of a fume hood is recommended.]* Dilute each solution with *Dilute Sulfuric Acid* to volume, and mix. Concomitantly determine the absorbances of the solutions from the *Standard Solution* and the *Test Solution* in 1-cm cells at the wavelength of maximum absorbance at about 575 nm (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using as the blank the solution from the *Purified Water Extracting Medium:* the absorbance of the solution from the *Test Solution* does not exceed that of the solution from the *Standard Solution,* corresponding to not more than 1 ppm of ethylene glycol.

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TEST METHODS

Multiple Internal Reflectance

Apparatus—Use an IR spectrophotometer capable of correcting for the blank spectrum and equipped with a multiple internal reflectance accessory and a KRS-5 internal reflection plate.[4] A KRS-5 crystal 2-mm thick having an angle of incidence of 45° provides a sufficient number of reflections.

Specimen Preparation—Cut two flat sections representative of the average wall thickness of the container, and trim them as necessary to obtain segments that are convenient for mounting in the multiple internal reflectance accessory. Taking care to avoid scratching the surfaces, wipe the specimens with dry paper or, if necessary, clean them with a soft cloth dampened with methanol, and permit them to dry. Securely mount the specimens on both sides of the KRS-5 internal reflection plate, ensuring adequate surface contact. Prior to mounting the specimens on the plate, they may be compressed to thin uniform films by exposing them to temperatures of about 177° under high pressures (15,000 psi or more).

General Procedure—Place the mounted specimen sections within the multiple internal reflectance accessory, and place the assembly in the specimen beam of the IR spectrophotometer. Adjust the specimen position and mirrors within the accessory to permit maximum light transmission of the unattenuated reference beam. (For a double-beam instrument, upon completing the adjustments in the accessory, attenuate the reference beam to permit full-scale deflection during the scanning of the specimen.) Determine the IR spectrum from 3500 to 600 cm^{-1} for polyethylene and polypropylene and from 4000 to 400 cm^{-1} for PET and PETG.

[4] The multiple internal reflectance accessory and KRS-5 plate are available from several sources, including Beckman Instruments, Inc., 2500 Harbor Blvd., Fullerton, CA 92634, and from Perkin Elmer Corp., Main Ave., Norwalk, CT 06856.

Thermal Analysis

General Procedure—Cut a section weighing about 12 mg, and place it in the test specimen pan. [NOTE—Intimate contact between the pan and the thermocouple is essential for reproducible results.] Determine the thermogram under nitrogen, using the heating and cooling conditions as specified for the resin type and using equipment capable of performing the determinations as specified under *Thermal Analysis* ⟨891⟩.

For Polyethylene—Determine the thermogram under nitrogen at temperatures between 40° and 200° at a heating rate between 2° and 10° per minute followed by cooling at a rate between 2° and 10° per minute to 40°.

For Polypropylene—Determine the thermogram under nitrogen at temperatures ranging from ambient to 30° above the melting point. Maintain the temperature for 10 minutes, then cool to 50° below the peak crystallization temperature at a rate of 10° to 20° per minute.

For Polyethylene Terephthalate—Heat the specimen from room temperature to 280° at a heating rate of about 20° per minute. Hold the specimen at 280° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 280° at a heating rate of about 5° per minute.

For Polyethylene Terephthalate G—Heat the specimen from room temperature to 120° at a heating rate of about 20° per minute. Hold the specimen at 120° for 1 minute. Quickly cool the specimen to room temperature, and reheat it to 120° at a heating rate of about 10° per minute.

Biological Tests

The in vitro biological tests are performed according to the procedures set forth under *Biological Reactivity Test, In Vitro* ⟨87⟩. Components that meet the requirements of the in vitro tests are not required to undergo further testing. No plastic class designation is assigned to these materials. Materials that do not meet the requirements of the in vitro tests are not suitable for containers for drug products.

If a plastic class designation is needed for plastics and other polymers that meet the requirements under *Biological Reactivity Test, In Vitro* ⟨87⟩, perform the appropriate in vivo test specified for *Classification of Plastics* under *Biological Reactivity Test, In Vivo* ⟨88⟩.

Physicochemical Tests

The following tests, designed to determine physical and chemical properties of plastics and their extracts, are based on the extraction of the plastic material, and it is essential that the designated amount of the plastic be used. Also, the specified surface area must be available for extraction at the designated temperature.

Testing Parameters—

Extracting Medium—Unless otherwise directed in a specific test below, use *Purified Water* (see monograph) as the *Extracting Medium,* maintained at a temperature of 70° during the extraction of the *Sample Preparation.*

Blank—Use *Purified Water* where a blank is specified in the tests that follow.

Apparatus—Use a water bath and the *Extraction Containers* as described under *Biological Reactivity Tests, In Vivo* ⟨88⟩. Proceed as directed in the first paragraph of *Preparation of Apparatus* under *Biological Reactivity Tests, In Vivo* ⟨88⟩. [NOTE—The containers and equipment need not be sterile.]

Sample Preparation—From a homogeneous plastic specimen, use a portion, for each 20.0 mL of *Extracting Medium,* equivalent to 120 cm^2 total surface area (both sides combined), and subdivide into strips approximately 3 mm in width and as near to 5 cm in length as is practical. Transfer the subdivided sample to a glass-stoppered, 250-mL graduated cylinder of Type I glass, and add about 150 mL of *Purified Water.* Agitate for about 30 seconds, drain off and discard the liquid, and repeat with a second washing.

Sample Preparation Extract—Transfer the prepared *Sample Preparation* to a suitable extraction flask, and add the required amount of *Extracting Medium.* Extract by heating in a water bath at the temperature specified for the *Extracting Medium* for 24 hours. Cool, but not below 20°. Pipet 20 mL of the prepared extract into a suitable container. [NOTE—Use this portion in the test for *Buffering Capacity.*] Immediately decant the remaining extract into a suitably cleansed container, and seal.

Nonvolatile Residue—Transfer, in suitable portions, 50.0 mL of the *Sample Preparation Extract* to a suitable, tared crucible (preferably a fused-silica crucible that has been acid-cleaned), and evaporate the volatile matter on a steam bath. Similarly evaporate 50.0 mL of the *Blank* in a second crucible. [NOTE—If an oily residue is expected, inspect the crucible repeatedly during the evaporation and drying period, and reduce the amount of heat if the oil tends to creep along the walls of the crucible.] Dry at 105° for 1 hour: the difference between the amounts obtained from the *Sample Preparation Extract* and the *Blank* does not exceed 15 mg.

Residue on Ignition ⟨281⟩—[NOTE—It is not necessary to perform this test when the *Nonvolatile Residue* test result does not exceed 5 mg.] Proceed with the residues obtained from the *Sample Preparation Extract* and from the *Blank* in the test for *Nonvolatile Residue* above, using, if necessary, additional sulfuric acid but adding the same amount of sulfuric acid to each crucible: the difference between the amounts of residue on ignition obtained from the *Sample Preparation Extract* and the *Blank* does not exceed 5 mg.

Heavy Metals—Pipet 20 mL of the *Sample Preparation Extract,* filtered if necessary, into one of two matched 50-mL color-comparison tubes. Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator, dilute with water to about 35 mL, and mix.

Into the second color-comparison tube pipet 2 mL of *Standard Lead Solution* (see *Heavy Metals* ⟨231⟩), and add 20 mL of the *Blank.* Adjust with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, using short-range pH paper as an external indicator, dilute with water to about 35 mL, and mix. To each tube add 1.2 mL of thioacetamide–glycerin base TS and 2 mL of *pH 3.5 Acetate Buffer*

(see *Heavy Metals* ⟨231⟩), dilute with water to 50 mL, and mix: any brown color produced within 10 minutes in the tube containing the *Sample Preparation Extract* does not exceed that in the tube containing the *Standard Lead Solution,* both tubes being viewed downward over a white surface (1 ppm in extract).

Buffering Capacity—Titrate the previously collected 20-mL portion of the *Sample Preparation Extract* potentiometrically to a pH of 7.0, using either 0.010 N hydrochloric acid or 0.010 N sodium hydroxide, as required. Treat a 20.0-mL portion of the *Blank* similarly: if the same titrant was required for both the *Sample Preparation Extract* and the *Blank*, the difference between the two volumes is not greater than 10.0 mL; and if acid was required for either the *Sample Preparation Extract* or the *Blank* and alkali for the other, the total of the two volumes required is not greater than 10.0 mL.■2S (*USP30*)

BRIEFING

⟨**671**⟩ **Containers—Permeation,** *USP 29* page 2663. It has been proposed to revise the current chapter to include all standards and tests used to determine the functional properties of plastic containers. To accurately represent the new intent of this chapter, it will be renamed *Containers—Performance Testing* ⟨671⟩. The permeation test for polyethylene and polypropylene containers without closures and the light transmission test in *Containers* ⟨661⟩ will be added to the current chapter. As part of the ongoing re-evaluation of USP plastic container standards, the Packaging and Storage Expert Committee (PSEC) requested information and support from industry on the establishment of specifications and functional test procedures for plastic containers for liquids. Currently, a large number of liquid products are packaged in high density polyethylene, low density polyethylene, polypropylene terephthalate and polyethylene terephthalate (PET/PETG); however, only a permeation (liquid weight loss) test exists for PET/PETG containers. PSEC, using the performance standard used to evaluate PET/PETG containers for liquids, has developed a permeation (liquid weight loss) test intended to be used on all containers used to package liquids.

(P&S: D. Hunt) RTS—C45774

Change to read:

⟨671⟩ CONTAINERS—~~PERMEATION~~

■PERFORMANCE TESTING■2S (*USP30*)

~~The tests that follow are provided to determine the moisture permeability of containers utilized for drugs being dispensed on prescription. The section *Multiple Unit Containers for Capsules and Tablets* applies to multiple unit containers (see *Preservation, Packaging, Storage, and Labeling* under *General Notices and Requirements*). The section *Single Unit Containers and Unit Dose Containers for Capsules and Tablets* applies to single unit and unit dose containers (see *Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms* under *Containers* ⟨661⟩). As used herein, the term "container" refers to the entire system comprising, usually, the container itself, the liner (if used), the closure in the case of multiple-unit containers, and the lidding and blister in the case of single-unit and unit-dose containers.~~

~~Where the manufacturer's unopened multiple unit, single unit, or unit dose packages are used for dispensing the drug, such containers are exempt from the requirements of this test.~~

■It is the purpose of this chapter to provide standards for the functional properties of plastic containers and their components used to package regulated articles (pharmaceuticals, biologics, dietary supplements, and devices). Definitions that apply to this chapter are provided in the *Preservation, Packaging, Storage, and Labeling* section of the *General Notices and Requirements*. The tests that follow are provided to determine the moisture permeability and light transmission of plastic containers utilized for regulated articles. The section *Multiple-Unit Containers for Capsules and Tablets* applies to multiple-unit containers. The section *Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets* applies to single-unit and unit-dose containers. The section *Multiple-Unit Containers for Capsules and Tablets (Without Closure)* applies to polyethylene and polypropylene containers that have no closures. The section *Multiple-Unit and Single-Unit Containers for Liquids* applies to multiple-unit and single-unit containers.

A container intended to provide protection from light or offered as a *light-resistant* container meets the requirements for *Light Transmission*, where such protection or resistance is by virtue of the specific properties of the material of which the

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container is composed, including any coating applied thereto. A clear and colorless or a translucent container that is made *light-resistant* by means of an opaque enclosure (see *General Notices and Requirements*) is exempt from the requirements for *Light Transmission*. As used herein, the term "container" refers to the entire system comprising, usually, the container itself, the liner (if used), the closure in the case of multiple-unit containers, and the lidding and blister in the case of unit-dose containers.■2S (*USP30*)

Change to read:

MULTIPLE-UNIT CONTAINERS FOR CAPSULES AND TABLETS

Desiccant—Place a quantity of 4- to 8-mesh, anhydrous calcium chloride[1] in a shallow container, taking care to exclude any fine powder, then dry at 110° for 1 hour, and cool in a desiccator.

Procedure—Select 12 containers of a uniform size and type, clean the sealing surfaces with a lint-free cloth, and close and open each container 30 times. Apply the closure firmly and uniformly each time the container is closed. Close screw-capped containers with a torque that is within the range of tightness specified in the accompanying table. Add *Desiccant* to 10 of the containers, designated *test containers,* filling each to within 13 mm of the closure if the container volume is 20 mL or more, or filling each to two-thirds of capacity if the container volume is less than 20 mL. If the interior of the container is more than 63 mm in depth, an inert filler or spacer may be placed in the bottom to minimize the total weight of the container and *Desiccant*; the layer of *Desiccant* in such a container shall be not less than 5 cm in depth. Close each immediately after adding *Desiccant*, applying the torque designated in the accompanying table when closing screw-capped containers. To each of the remaining 2 containers, designated *controls*, add a sufficient number of glass beads to attain a weight approximately equal to that of each of the *test containers*, and close, applying the torque designated in the accompanying table when closing screw-capped containers. Record the weight of the individual containers so prepared to the nearest 0.1 mg if the container volume is less than 20 mL; to the nearest mg if the container volume is 20 mL or more but less than 200 mL; or to the nearest centigram (10 mg) if the container volume is 200 mL or more; and store at 75 ± 3% relative humidity and a temperature of 23 ± 2°. [NOTE—A saturated system of 35 g of sodium chloride with each 100 mL of water placed in the bottom of a desiccator maintains the specified humidity. Other methods may be employed to maintain these conditions.] After 336 ± 1 hours (14 days), record the weight of the individual containers in the same manner. Completely fill 5 empty containers of the same size and type as the containers under test with water or a noncompressible, free-flowing solid such as well-tamped fine glass beads, to the level indicated by the closure surface when in place. Transfer the contents of each to a graduated cylinder, and determine the average container volume, in mL. Calculate the rate of moisture permeability, in mg per day per L, by the formula:

$$(1000 / 14V)[(T_F - T_I) - (C_F - C_I)]$$

in which V is the volume, in mL, of the container; $(T_F - T_I)$ is the difference, in mg, between the final and initial weights of each *test container;* and $(C_F - C_I)$ is the difference, in mg, between the average final and average initial weights of the 2 *controls.* For containers used for drugs being dispensed on prescription, the containers so tested are *tight containers* if not more than 1 of the 10 *test containers* exceeds 100 mg per day per L in moisture permeability, and none exceeds 200 mg per day per L.

For containers used for drugs being dispensed on prescription, the containers are *well-closed containers* if not more than 1 of the 10 *test containers* exceeds 2000 mg per day per L in moisture permeability, and none exceeds 3000 mg per day per L.

Table 1. Torque Applicable to Screw-Type Container

Closure Diameter[a] (mm)	Suggested Tightness Range with Manually Applied Torque;[b] (inch-pounds)
8	5
10	6
13	8
15	5–9
18	7–10
20	8–12
22	9–14
24	10–18
28	12–21
30	13–23
33	15–25
38	17–26
43	17–27
48	19–30
53	21–36
58	23–40
63	25–43
66	26–45
70	28–50
83	32–65
86	40–65
89	40–70
100	45–70
110	45–70
120	55–95
132	60–95

[a] The torque designated for the next larger closure diameter is to be applied in testing containers having a closure diameter intermediate to the diameters listed.

[b] A suitable apparatus is available from Owens-Illinois, Toledo, OH 43666. (Model 25 torque tester is used for testing between 0 and 25; Model 50 for testing between 0 and 50; and Model 100 for testing between 0 and 100 inch-pounds of torque.) The torque values refer to application, not removal, of the closure. For further detail regarding instructions, reference may be made to "Standard Test Method for Application and Removal Torque of Threaded or Lug-Style Closures" ASTM Method D3198-~~97,~~

■02,■2S (*USP30*)
published by the American Society for Testing and Materials, ~~1916 Race St., Philadelphia, PA 19103.~~

■100 Barr Harbor Drive, P. O. Box C700, West Conshohocken, PA 19428-2959.■2S (*USP30*)

[1] Suitable 4- to 8-mesh, anhydrous calcium chloride is available commercially as Item JT1313-1 from VWR Scientific. Consult the VWR Scientific catalog for ordering information or call 1-800-234-9300.

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Add the following:

▪MULTIPLE-UNIT CONTAINERS FOR CAPSULES AND TABLETS (WITHOUT CLOSURE)

Polyethylene Container—Fit the containers with impervious seals obtained by heat-sealing the bottles with an aluminum foil–polyethylene laminate or other suitable seal.[2] Test the containers as specified under *Multiple-Unit Containers for Capsules and Tablets:* the high–density polyethylene containers so tested meet the requirements if the moisture permeability exceeds 10 mg per day per L in not more than 1 of the 10 test containers and exceeds 25 mg per day per L in none of them. The low–density polyethylene containers so tested meet the requirements if the moisture permeability exceeds 20 mg per day per L in not more than 1 of the 10 test containers and exceeds 30 mg per day per L in none of them.

Polypropylene Containers—Fit the containers with impervious seals obtained by heat-sealing the bottles with an aluminum foil–polyethylene laminate or other suitable seal. Test the containers as described under *Multiple-Unit Containers for Capsules and Tablets*. The containers meet the requirements if the moisture permeability exceeds 15 mg per day per L in not more than 1 of the 10 test containers and exceeds 25 mg per day per L in none of them.▪2S (*USP30*)

Add the following:

▪MULTIPLE-UNIT CONTAINERS AND UNIT-DOSE CONTAINERS FOR LIQUIDS

The standards and tests provided in this section measure the functional and performance characteristics of plastic containers used to package aqueous products by measuring the liquid water weight loss as a percent of the contents. This test can also be used to demonstrate performance or functional comparability. [NOTE—Throughout the following procedure, determine the weights of individual container–closure systems (bottle, innerseal if used, and closure) both as tare weights and fill weights, to the nearest 0.1 mg if the bottle overflow capacity is less than 200 mL; to the nearest mg if the bottle overflow capacity is 200 mL or more but less than 1000 mL; or to the nearest centigram (10 mg) if the bottle overflow capacity is 1000 mL or more.]

Procedure for Testing Unopened Market Containers (cap liner [if applicable], innerseal, and cap)—Select 10 bottles of a uniform size and type, and clean the sealing surfaces with a lint-free cloth. Fit each bottle with a closure liner (if applicable) and closure. Number each container closure system, and record the tare weight.

Remove the closures and, using a pipette, fill the bottles with water to the overflow capacity. Fit the bottles with seals and apply the closures. If using screw closures, apply a torque that is within the range specified in *Table 1,* and store the sealed containers at a temperature of 25 $\pm$ 2° and a relative humidity of 50 $\pm$ 2%. After 168 $\pm$ 1 hours (7 days), record the weight of the individual containers. Return the containers to storage for another 168 $\pm$ 1 hours. After the second 168 $\pm$ 1 hours, remove the containers, record the weights of each of the individual container systems, and calculate the water vapor permeation rate, in percent water weight loss, for each bottle taken by the formula:

$$(W_7 - W_{14})365 \times 100/(W_7 - W_T)7 = \text{Percent per year}$$

in which W_7 is the weight, in mg, of the container at 7 days; W_{14} is the weight, in mg, of the container at 14 days; W_T is the tare weight in g; and 7 is the test time, in days, after the 7-day equilibration period. The containers so tested meet the requirements and are tight containers if the percentage of water weight loss exceeds 2.5% per year in not more than 1 of the 10 test containers and exceeds 5.0% per year in none of them.

Unit-dose containers for liquids meet the requirement of a tight container if the average water weight loss is less than or equal to 2.5% (w/w) loss per year (5% at the end of 2 years).

[2] A suitable laminate for sealing has as the container layer polyethylene of not less than 0.025 mm (0.001 inch) and a second layer of aluminum foil of not less than 0.018 mm (0.0007 inch), with additional layers of suitable backing materials. A suitable seal can be obtained also by using glass plates and a sealing wax consisting of 60% of refined amorphous wax and 40% of refined crystalline paraffin wax.

Procedure for Testing Multiple-Unit Containers Under Conditions of Use—Select 10 bottles of a uniform size and type. If an innerseal is used, carefully open the individual containers and remove the innerseal from each container. Fit each bottle with a closure liner (if applicable) and closure. Number each container–closure system, and record the tare weight. Open and close the containers 30 times being careful not to lose liquid in the process. Close screw-capped bottles with a torque that is within the range of tightness provided in *Table 1,* and store the sealed containers at a temperature of 25 ± 2° and a relative humidity of 50 ± 2%. After 168 ± 1 hours (7 days), record the weight of the individual containers. Return the containers to storage for another 168 ± 1 hours. After the second 168 ± 1 hours, remove the containers, record the weights of each of the individual container systems, and calculate the water vapor permeation rate, in percent water weight loss, for each bottle taken by the formula:

$$(W_7 - W_{14})365 \times 100/(W_7 - W_T)7 = \text{Percent per year}$$

in which W_7 is the weight, in mg, of the container at 7 days; W_{14} is the weight, in mg, of the container at 14 days; W_T is the tare weight, in g; and 7 is the test time, in days, after the 7-day equilibration period. The containers so tested meet the requirements and are tight containers if the percentage of water weight loss exceeds 2.5% per year in not more than 1 of the 10 test containers and exceeds 5.0% per year in none of them.■2S (*USP30*)

Add the following:

■LIGHT TRANSMISSION TEST

Apparatus[5]—Use a spectrophotometer of suitable sensitivity and accuracy, adapted for measuring the amount of light transmitted by either transparent or translucent glass or plastic materials used for pharmaceutical containers. In addition, the spectrophotometer is capable of measuring and recording light transmitted in diffused as well as parallel rays.

Procedure—Select sections to represent the average wall thickness. Cut circular sections from two or more areas of the container and trim them as necessary to give segments of a size convenient for mounting in the spectrophotometer. After cutting, wash and dry each specimen, taking care to avoid scratching the surfaces. If the specimen is too small to cover the opening in the specimen holder, mask the uncovered portion of the opening with opaque paper or masking tape, provided that the length of the specimen is greater than that of the slit in the spectrophotometer. Immediately before mounting in the specimen holder, wipe the specimen with lens tissue. Mount the specimen with the aid of a tacky wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks on the surfaces through which light must pass. Place the section in the spectrophotometer with its cylindrical axis parallel to the plane of the slit and approximately centered with respect to the slit. When properly placed, the light beam is normal to the surface of the section and reflection losses are at a minimum.

Continuously measure the transmittance of the section with reference to air in the spectral region of interest with a recording instrument or at intervals of about 20 nm with a manual instrument, in the region of 290 to 450 nm.

Limits—The observed light transmission does not exceed the limits given in *Table 2* for containers intended for parenteral use. [NOTE—Any container of a size intermediate to those

[5] For further detail regarding apparatus and procedures, reference may be made to the following publications of the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19428-2959: "Standard Method of Test for Haze and Luminous Transmittance of Transparent Plastics," ASTM Designation D-1003-61; "Tentative Method of Test for Luminous Reflectance, Transmittance, and Color of Materials," ASTM E 308-66.

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listed above exhibits a transmission not greater than that of the next larger size container listed in the table. For containers larger than 50 mL, the limits for 50 mL apply.]

Table 2. Limits for Plastic Classes I–VI

Nominal Size (in mL)	Maximum Percentage of Light Transmission at Any Wavelength Between 290 and 450 nm: Closure-Sealed Containers
1	25
2	20
5	15
10	13
20	12
50	10

The observed light transmission for plastic containers for products intended for oral or topical administration does not exceed 10% at any wavelength in the range from 290 to 450 nm.■2S (*USP30*)

BRIEFING

⟨681⟩ Repackaging into Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms. It is proposed to remove the sections relating to repackaging in ⟨661⟩ *Containers* and place them in this proposed new chapter. The intent of this proposed change is to make the content of ⟨661⟩ consistent with that chapter's testing requirements and thus clarify the intent of that chapter. The content removed from ⟨661⟩ was practitioner based and this is now reflected in this proposed new chapter.

(P&S: D. Hunt) RTS—C44241

Add the following:

■⟨681⟩ REPACKAGING INTO SINGLE-UNIT CONTAINERS AND UNIT-DOSE CONTAINERS FOR NONSTERILE SOLID AND LIQUID DOSAGE FORMS

An official dosage form is required to bear on its label an expiration date assigned for the particular formulation and package of the article. This date limits the time during which the product may be dispensed or used. Because the expiration date stated on the manufacturer's or distributor's package has been determined for the drug in that particular package and is not intended to be applicable to the product where it has been repackaged in a different container, repackaged drugs dispensed pursuant to a prescription are exempt from this expiration date labeling requirement. It is necessary, therefore, that other precautions be taken by the dispenser to preserve the strength, quality, and purity of drugs that are repackaged for ultimate distribution or sale to patients.

The following guidelines and requirements are applicable where official dosage forms are repackaged into single-unit or unit-dose containers or mnemonic packs for dispensing pursuant to prescription.

Labeling—It is the responsibility of the dispenser, taking into account the nature of the drug repackaged, any packaging and expiration dating information in the manufacturer's product labeling, the characteristics of the containers, and the storage conditions to which the article may be subjected, to place a suitable expiration date on the label. Repackaged dosage forms must bear on their labels expiration dates as determined from information in the product labeling. Each single-

unit or unit-dose container bears a separate label, unless the device holding the unit-dose form does not allow for the removal or separation of the intact single-unit or unit-dose container therefrom.

Storage—Store the repackaged article in a humidity-controlled environment and at the temperature specified in the individual monograph or in the product labeling. Where no temperature or humidity is specified in the monograph or in the labeling of the product, controlled room temperature and a relative humidity corresponding to 75% at 23° are not to be exceeded during repackaging or storage.

A refrigerator or freezer shall not be considered to be a humidity-controlled environment, and drugs that are to be stored at a cold temperature in a refrigerator or freezer shall be placed within an outer container that meets the monograph requirements for the drug contained therein.

Reprocessing—Reprocessing of repackaged unit-dose containers (i.e., removing dosage unit from one unit-dose container and placing dosage unit into another unit-dose container) shall not be done. However, reprocessing of the secondary package (e.g., removing the blister card from the cardboard carrier and placing the blister card into another cardboard carrier) is allowed provided that the original expiration date is maintained.

CUSTOMIZED PATIENT MEDICATION PACKAGES

In lieu of dispensing two or more prescribed drug products in separate containers, a pharmacist may, with the consent of the patient, the patient's caregiver, or a prescriber, provide a customized patient medication package (patient med pak).[1]

A patient med pak is a package prepared by a pharmacist for a specific patient comprising a series of containers and containing two or more prescribed solid oral dosage forms. The patient med pak is so designed or each container is so labeled as to indicate the day and time, or period of time, that the contents within each container are to be taken.

It is the responsibility of the dispenser to instruct the patient or caregiver on the use of the patient med pak.

Label—The patient med pak shall bear a label stating:

(1) the name of the patient;

(2) a serial number for the patient med pak itself and a separate identifying serial number for each of the prescription orders for each of the drug products contained therein;

(3) the name, strength, physical description or identification, and total quantity of each drug product contained therein;

(4) the directions for use and cautionary statements, if any, contained in the prescription order for each drug product therein;

(5) any storage instructions or cautionary statements required by the official compendia;

(6) the name of the prescriber of each drug product;

(7) the date of preparation of the patient med pak and the beyond-use date or period of time assigned to the patient med pak (such beyond-use date or period of time shall be not longer than the shortest recommended beyond-use date for any dosage form included therein or not longer than 60 days from the date of preparation of the patient med pak and shall not exceed the shortest expiration date on the original manufacturer's bulk containers for the

[1] It should be noted that there is no special exemption for patient med paks from the requirements of the Poison Prevention Packaging Act. Thus the patient med pak, if it does not meet child-resistant standards, shall be placed in an outer package that does comply, or the necessary consent of the purchaser or physician, to dispense in a container not intended to be child-resistant, shall be obtained.

dosage forms included therein); alternatively, the package label shall state the date of the prescription(s) or the date of preparation of the patient med pak, provided the package is accompanied by a record indicating the start date and the beyond-use date;

(8) the name, address, and telephone number of the dispenser (and the dispenser's registration number where necessary); and

(9) any other information, statements, or warnings required for any of the drug products contained therein.

If the patient med pak allows for the removal or separation of the intact containers therefrom, each individual container shall bear a label identifying each of the drug products contained therein.

Labeling—The patient med pak shall be accompanied by a patient package insert, in the event that any medication therein is required to be dispensed with such insert as accompanying labeling. Alternatively, such required information may be incorporated into a single, overall educational insert provided by the pharmacist for the total patient med pak.

Packaging—In the absence of more stringent packaging requirements for any of the drug products contained therein, each container of the patient med pak shall comply with the moisture permeation requirements for a Class B single-unit or unit-dose container (see *Containers—Permeation* ⟨671⟩). Each container shall be either not reclosable or so designed as to show evidence of having been opened.

Guidelines—It is the responsibility of the dispenser, when preparing a patient med pak, to take into account any applicable compendial requirements or guidelines and the physical and chemical compatibility of the dosage forms placed within each container, as well as any therapeutic incompatibilities that may attend the simultaneous administration of the medications. In this regard, pharmacists are encouraged to report to USP headquarters any observed or reported incompatibilities. Once a medication has been placed in a patient med pak with another solid dosage form, it may not be returned to stock, redistributed, or resold if unused.

Recordkeeping—In addition to any individual prescription filing requirements, a record of each patient med pak shall be made and filed. Each record shall contain, as a minimum:

(1) the name and address of the patient;

(2) the serial number of the prescription order for each drug product contained therein;

(3) the name of the manufacturer or labeler and lot number for each drug product contained therein;

(4) information identifying or describing the design, characteristics, or specifications of the patient med pak sufficient to allow subsequent preparation of an identical patient med pak for the patient;

(5) the date of preparation of the patient med pak and the beyond-use date that was assigned;

(6) any special labeling instructions; and

(7) the name or initials of the pharmacist who prepared the patient med pak.■2S (*USP30*)

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BRIEFING

⟨**721**⟩ **Distilling Range,** *USP 29* page 2682. In response to comments received, the General Chapters Expert Committee proposes a conversion equation in the *Procedure* under *Method II* to correct temperature readings due to deviations from normal barometric pressure instead of the current fixed factors. Justification for this calculation is presented in a *Stimuli* article appearing elsewhere in this issue of *PF.*

(GC: A. Hernández-Cardoso) RTS—C44230

Change to read:

METHOD II

Apparatus—Use an apparatus consisting of the following parts:

Distilling Flask—A round-bottom distilling flask, of heat-resistant glass, of 200-mL capacity, and having a total length of 17 to 19 cm, and an inside neck diameter of 20 to 22 mm. Attached about midway on the neck, approximately 12 cm from the bottom of the flask, is a side-arm 10 to 12 cm long and 5 mm in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Condenser—A straight glass condenser 55 to 60 cm in length with a water jacket about 40 cm in length, or a condenser of other design having equivalent condensing capacity. The lower end of the condenser may be bent to provide a delivery tube, or it may be connected to a bent adapter that serves as a delivery tube.

Insulating Boards—Two pieces of insulating board, 5 to 7 mm thick and 14 to 16 cm square, suitable for confining the heat to the lower part of the flask. Each board has a hole in its center, and the two boards differ only with respect to the diameter of the hole, i.e., the diameters are 4 cm and 10 cm, respectively. In use, the boards are placed one upon the other, and rest on a tripod or other suitable support, with the board having the larger hole on top.

Receiver—A 100-mL cylinder graduated in 1-mL subdivisions.

Thermometer—In order to avoid the necessity for an emergent stem correction, an accurately standardized, partial-immersion thermometer having the smallest practical subdivisions (not greater than 0.2°) is recommended. Suitable thermometers are available as the ASTM E-1 series ~~37C through 41C, and 102C through 107C~~ ■37° through 41°, and 102° through 107°■2S (*USP30*) (see *Thermometers* ⟨21⟩). When placed in position, the stem is located in the center of the neck, and the top of the contraction chamber (or bulb, if ~~37C or 38C~~ ■37° or 38°■2S (*USP30*) is used) is level with the bottom of the outlet to the side-arm.

Heat Source—A small Bunsen burner or an electric heater or mantle capable of adjustment comparable to that possible with a Bunsen burner.

Procedure—Assemble the apparatus, and place in the flask 100 mL of the liquid to be tested, taking care not to allow any of the liquid to enter the side-arm. Insert the thermometer, shield the entire burner and flask assembly from external air currents, and apply heat, regulating it so that between 5 and 10 minutes elapse before the first drop of distillate falls from the condenser. Continue the distillation at a rate of 4 to 5 mL of distillate per minute, collecting the distillate in the receiver. Note the temperature when the first drop of distillate falls from the condenser, and again when the last drop of liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. ~~Correct the observed temperature readings for any variation in the observed ambient barometric pressure from the normal (760 mm), adding if the pressure is lower or subtracting if the pressure is higher than 760 mm, and apply the emergent stem correction where necessary. Unless otherwise specified in the individual monograph, allow 0.1° for each 2.7 mm (0.037° per mm) of variation.~~

■Unless otherwise specified in the individual monograph, report the temperatures, making corrections for barometric pressure, using the following formula:

$$t = t_0 + [(t_0 10^{-4} + 0.033)(760 - p)]$$

in which t is the corrected boiling temperature, in Celsius scale; t_0 is the measured boiling temperature, in Celsius scale; and p is the barometric pressure at the time of measurement, in mm Hg.■2S (*USP30*)

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BRIEFING

〈**905**〉 **Uniformity of Dosage Units,** *USP 29* page 2780 and page 3599 of the *First Supplement*. The United States Pharmacopeia is the coordinating pharmacopeia in the efforts toward international harmonization of the specifications provided in this general test chapter. The Stage 5B text for this chapter has been signed-off by the Pharmacopeial Discussion Group members. However, subsequent revisions to the Stage 5B text are under PDG review. The national text presented herein represents a merger of the revised Stage 5B text and national USP text. It is proposed to implement this combined text via the *Sixth Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of January 1, 2007.

Major differences between this current text and the text that was published on pages 3599–3604 of the *First Supplement* are listed below.

(1) New text at the end of the opening paragraph has been added to emphasize that these uniformity of dosage units requirements are not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for topical administration.

(2) The proposed replacement of the text ''external, cutaneous'' with the text ''topical'' in item C3 under the list of dosage forms for which the *Content Uniformity* test is required is intended to clarify that not only products intended for application to skin but also products intended for application to hair, nails, etc., are included in this category.

(3) Comments were received regarding that portion of the unofficial, harmonized general chapter text that provides for the use of the *Weight Variation* test in place of the *Content Uniformity* test in cases where ''the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data.'' The comments indicated that dosage unit uniformity should be independent of process validation data and product development data because these data may not always be available to regulatory agencies. The comments indicated further that the proposed wording would therefore require regulatory agencies and others that conduct dosage unit uniformity testing to obtain data from the sponsoring firm to determine whether to use a *Weight Variation* test or a *Content Uniformity* test in certain cases. Therefore, the proposed wording creates a private standard because an analyst would need information outside that provided in the *USP–NF* to conduct the compendial test. The proposed standard would allow for different standards based on proprietary data held only by the drug sponsor. USP feels that these comments merit further discussion among the PDG members. At the same time, USP is proposing revised wording in the national text published herein to address the above concerns. This proposed wording provides the option of applying the *Weight Variation* test under the 2% drug substance concentration RSD condition as an alternative test method in place of the *Content Uniformity* test. As stated in the proposed new text, where the *Weight Variation* test is used as an alternative test, the product must nevertheless comply with the official compendial test for *Content Uniformity.*

(4) Revisions proposed for the *T* value definition in *Table 2* are intended for clarity. The definition proposed herein is consistent with the approach in the current *USP* chapter where the headings (A) and (B) under the section *Criteria* refer to ''the average of the limits specified in the potency definition in the individual monograph.''

(5) Revisions proposed to the definitions of the *w* and $\overline{W}$ terms in the *Calculation of Acceptance Value* section under *Weight Variation* are intended to clarify these terms by indicating that the *w* term applies to the weights of the dosage forms obtained in the *Weight Variation* test itself, while the $\overline{W}$ term applies to the weights of the dosage forms used in the *Assay.*

Comments regarding these proposals are invited and should be submitted to William E. Brown by September 30, 2006.

(PDF: W. Brown) RTS—C45151

Change to read:

[NOTE—In this chapter, *unit* and *dosage unit* are synonymous.]

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit.

•The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for topical administration.•6

The term ''uniformity of dosage unit'' is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified in the individual monograph.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or *Weight Variation* (see *Table 1*). The test for *Content Uniformity* is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases. The test for *Content Uniformity* is required for those dosage forms described in *(C1)–(C6)* below:

(C1) coated tablets, other than film-coated tablets containing 25 mg or more of a drug substance that comprises 25% or more (by weight) of one tablet;

(C2) transdermal systems;

(C3) suspensions or emulsions or gels in ~~unit-dose~~ •single-unit•6 containers or in soft capsules that are intended for systemic administration only (not for those drug products that are intended for ~~external, cutaneous~~ •topical•6 administration);

(C4) inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units. For inhalers and premetered dosage units labeled for use with a named inhalation device, also see *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* 〈601〉;

(C5) solids (including sterile solids) that are packaged in single-unit containers and that contain active or inactive added substances, except that the test for *Weight Variation* may be applied in the special ~~situations~~ •cases•6 stated in ~~*(W2)* and~~ ••6 *(W3)* below; and

(C6) suppositories.

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The test for *Weight Variation* is applicable for the following dosage forms:

(W1) solutions for inhalation that are packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules;

(W2) solids (including sterile solids) that are packaged in single-unit containers and contain no added substances, whether active or inactive;

(W3) solids (including sterile solids) that are packaged in single-unit containers, with or without added substances, whether active or inactive, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and

(W4) hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting *Content Uniformity* requirements.

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the *Weight Variation* test. ~~Alternatively, products listed in item (W4) above that do not meet the 25 mg/25% threshold limit may be tested for uniformity of dosage units by *Weight Variation* instead of the *Content Uniformity* test if the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%, based on process validation data and development data.~~

•Where compliance with the *Content Uniformity* test is required, then, by application of the provision for use of alternative methods provided in the *General Notices* section of this Pharmacopeia, it is possible for manufacturers to ensure this compliance by application of the *Weight Variation* test where the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%. This RSD determination may be based on the manufacturer's process validation and product development data.•6 The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in *Table 2*.

•Where the *Weight Variation* test is used in this way, the product must, if tested, nevertheless comply with the official compendial test for *Content Uniformity.*•6

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance: ≥25 mg & ≥25%	Dose & Ratio of Drug Substance: <25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Suspension, emulsion, or gel for systemic use only, packaged in single-unit containers			CU	CU
Solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules			WV	WV
Inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers packaged in premetered dosage units			CU	CU
Transdermal systems			CU	CU
Suppositories			CU	CU
Others			CU	CU

In-Process Revision

Change to read:

CONTENT UNIFORMITY

Select not fewer than 30 units, and proceed as follows for the dosage form designated. Where the amount of drug substance in a single dosage unit differs from that required in the *Assay,* adjust the degree of dilution of the solutions and/or the volume of aliquots so that the concentration of the drug substances in the final solution is of the same order as that obtained in the *Assay* procedure; or, in the case of a titrimetric assay, use a titrant of a different concentration, if necessary, so that an adequate volume of titrant is required (see *Titrimetry* ⟨541⟩); see also *Procedures* under *Tests and Assays* in the *General Notices and Requirements*. If any such modifications are made in the *Assay* procedure set forth in the individual monograph, make the appropriate corresponding changes in the calculation formula and titration factor.

Where a special *Procedure for content uniformity* is specified in the test for *Uniformity of dosage units* in the individual monograph, make any necessary correction of the results obtained as follows.

(1) Prepare a composite specimen of a sufficient number of dosage units to provide the amount of specimen called for in the *Assay* in the individual monograph plus the amount required for the special *Procedure for content uniformity* in the monograph by finely powdering tablets or mixing the contents of capsules or oral solutions, suspensions, emulsions, gels, or solids in single-unit containers to obtain a homogeneous mixture. If a homogeneous mixture cannot be obtained in this manner, use suitable solvents or other procedures to prepare a solution containing all of the drug substance, and use appropriate aliquot portions of this solution for the specified procedures.

(2) Assay separate, accurately measured portions of the composite specimen of capsules or tablets or suspensions or inhalations or solids in single-unit containers, both (a) as directed in the *Assay,* and (b) using the special *Procedure for content uniformity* in the monograph.

(3) Calculate the weight of drug substance equivalent to 1 average dosage unit, by (a) using the results obtained by the *Assay* procedure, and by (b) using the results obtained by the special procedure.

(4) Calculate the correction factor, *F,* by the formula:

$$F = W/P$$

in which W is the weight of drug substance equivalent to 1 average dosage unit obtained by the *Assay* procedure, and P is the weight of drug substance equivalent to 1 average dosage unit obtained by the special procedure. If

$$\frac{100|W - P|}{W}$$

is greater than 10, the use of a correction factor is not valid.

(5) The correction factor is to be applied only if F is not less than 1.030 nor greater than 1.100, or not less than 0.900 nor greater than 0.970. If F is between 0.970 and 1.030, no correction is required.

(6) If F lies between 1.030 and 1.100, or between 0.900 and 0.970, calculate the weight of drug substance in each dosage unit by multiplying each of the weights found using the special procedure by F.

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in ~~Single-Unit Containers, Oral Suspensions or Oral Emulsions or Oral Gels in Single-Unit Containers~~

•Unit-Dose Containers, Suspensions or Emulsions or Gels in Single-Unit Containers (that are intended for systemic administration only),•[6]
and Solids (including Sterile Solids) in Single-Unit Containers—Assay 10 units individually as directed in the *Assay* in the individual monograph, unless otherwise specified in the *Procedure for content uniformity* in the individual monograph. Calculate the acceptance value as directed below.

For oral solutions ~~, oral suspensions, oral emulsions, or oral gels in single-unit containers~~

•in unit-dose containers, and for suspensions, emulsions, or gels in single-unit containers that are intended for systemic administration only,•[6]
conduct the *Assay* on the amount of well-mixed material that drains from an individual container in not more than 5 seconds, or for highly viscous products, conduct the *Assay* on the amount of well-mixed material that is obtained by quantitatively removing the contents from an individual container, and express the results as the delivered dose.

Calculation of Acceptance Value—Calculate the acceptance value by the formula:

$$\left|M - \overline{X}\right| + ks$$

in which the terms are as defined in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents (χ_1, χ_2, … , χ_n), expressed as a percentage of the label claim		
χ_1, χ_2, … , χ_n	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If $n = 10$, then $k =$	2.4
		If $n = 30$, then $k =$	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}\left(\chi_i - \overline{X}\right)^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$\frac{100s}{\overline{X}}$
M (case 1) to be applied when $T \leq 101.5$	Reference value	If $98.5\% \leq \overline{X} \leq 101.5\%$, then	$M = \overline{X}$ $(AV = ks)$
		If $\overline{X} < 98.5\%$, then	$M = 98.5\%$ $(AV = 98.5 - \overline{X} + ks)$
		If $\overline{X} > 101.5\%$, then	$M = 101.5\%$ $(AV = \overline{X} - 101.5 + ks)$
M (case 2) to be applied when $T > 101.5$	Reference value	If $98.5 \leq \overline{X} \leq T$, then	$M = \overline{X}$ $(AV = ks)$
		If $\overline{X} < 98.5\%$, then	$M = 98.5\%$ $(AV = 98.5 - \overline{X} + ks)$
		If $\overline{X} > T$, then	$M = T\%$ $(AV = \overline{X} - T + ks)$

Table 2 *(Continued)*

Variable	Definition	Conditions	Value
Acceptance value *(AV)*			general formula: $\left\|M - \overline{X}\right\| + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		*L1* = 15.0 unless otherwise specified in the individual monograph
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of *M*	On the low side, no dosage unit result can be less than ~~(1 – *L2**0.01)*M*.~~ •$[1 – (0.01)(L2)]M$,• while on the high side no dosage unit result can be greater than ~~(1 + *L2**0.01)*M*.~~ •$[1 + (0.01)(L2)]M$• (This is based on an *L2* value of 25.0.)	*L2* = 25.0 unless otherwise specified in the individual monograph
T	Target ~~test sample amount at time of manufacture.~~ •content per dosage unit at the time of manufacture, expressed as a percentage of the label claim.• For purposes of this Pharmacopeia, unless otherwise specified in the individual monograph, *T* is ~~100.0%, and for manufacturing purposes, *T* is the manufacturer's approved target test amount value at the time of manufacture.~~ •the average of the limits specified in the potency definition in the individual monograph.•		

Suppositories, Transdermal Systems, and Inhalations Packaged in Premetered Dosage Units—[NOTE—Acceptance value calculations are not required for these dosage forms.] Assay 10 units individually as directed in the *Assay* in the individual monograph, unless otherwise specified in the *Procedure for content uniformity.*

Change to read:

WEIGHT VARIATION

Select not fewer than 30 dosage units, and proceed as follows for the dosage form designated. The result of the *Assay,* obtained as directed in the individual monograph, is designated as result *A,* expressed as % of label claim (see *Calculation of the Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. [NOTE—Specimens other than these test units may be drawn from the same batch for assay determinations.]

Uncoated or Film-Coated Tablets—Accurately weigh 10 tablets individually. Calculate the drug substance content, expressed as % of label claim, of each tablet from the weight of the individual tablet and the result of the *Assay.* Calculate the acceptance value.

Hard Capsules—Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Calculate the drug substance content, expressed as % of label claim, of each capsule from the net weight of the individual capsule content and the result of the *Assay.* Calculate the acceptance value.

Soft Capsules—Accurately weigh 10 intact capsules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content, expressed as % of label claim, in each capsule from the net weight of product removed from the individual capsules and the result of the *Assay.* Calculate the acceptance value.

Solids (Including Sterile Solids) in Single-Unit Containers—Proceed as directed for *Hard Capsules,* treating each unit as described therein. Calculate the acceptance value.

Oral Solutions Packaged in ~~Single Unit~~

•Unit-Dose•6 Containers—Accurately weigh the amount of liquid that drains in not more than 5 seconds from each of 10 individual containers. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content, expressed as % of label claim, in the liquid drained from each unit from the net weight of the individual container content and the result of the *Assay.* Calculate the acceptance value.

Calculation of Acceptance Value—Calculate the acceptance value as shown in *Content Uniformity,* except that the individual contents of the units are replaced with the individual estimated contents defined below.

$\chi_1, \chi_2, \ldots, \chi_n$ = individual estimated contents of the units tested, where $\chi_i = w_i \times A / \overline{W}$,

$w_1, w_2, \ldots, w_n$ = individual weights of the units tested

•for weight variation,•6

A = content of drug substance (% of label claim) determined as described in the *Assay,* and

$\overline{W}$ = mean of individual weights $(w_1, w_2, \ldots, w_n)$

•of the units used in the *Assay.*•6

Solutions for Inhalation Packaged in Glass or Plastic Ampuls and Intended for Use in Nebulizers—[NOTE—Acceptance value calculations are not required for these dosage forms.] Accurately weigh 10 containers individually, taking care to preserve the identity of each container. Remove the contents of each container by a suitable means. Accurately weigh the emptied containers individually, and calculate for each container the net weight of its contents by subtracting the weight of the container from the respective gross weight. From the results of the *Assay,* obtained as directed in the individual monograph, calculate the drug substance content, expressed as % of label claim, in each of the containers.

Change to read:

CRITERIA

Apply the following criteria, unless otherwise specified in the individual monograph.

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in ~~Single-Unit Containers, Oral Suspensions or Oral Emulsions or Oral Gels in Single-Unit Containers~~

•Unit-Dose Containers, Suspensions or Emulsions or Gels in Single-Unit Containers (that are intended for systemic administration only),•6 and Solids (Including Sterile Solids) in Single-Unit Containers—The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to *L1*%. If the acceptance value is greater than *L1*%, test the next 20 units, and

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calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to *L1*%, and no individual content of any dosage unit is less than ~~(1 – *L2**0.01)*M*~~

•[1 – (0.01)(*L2*)] $M_{•6}$
nor more than ~~(1 + *L2**0.01)*M*~~

•[1 + (0.01)(*L2*)] $M_{•6}$
as specified in the *Calculation of Acceptance Value* under *Content Uniformity* or under *Weight Variation.* Unless otherwise specified in the individual monograph, *L1* is 15.0 and *L2* is 25.0.

Suppositories—

Limit A (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)—Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in each of the 10 dosage units as determined from the *Content Uniformity* method lies within the range of 85.0% to 115.0% of the label claim, and the RSD is less than or equal to 6.0%.

If 1 unit is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim and the RSD of the 30 dosage units does not exceed 7.8%.

Limit B (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

(1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A.*
(2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A,* except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100".
(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A,* except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".

Transdermal Systems and Inhalations Packaged in Premetered Dosage Units—

Limit A (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)—Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in not fewer than 9 of the 10 dosage units as determined from the *Content Uniformity* method (or, in the case of solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, from either the *Content Uniformity* or the *Weight Variation* method) lies within the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 10 dosage units is less than or equal to 6.0%.

If 2 or 3 dosage units are outside the range of 85.0% to 115.0% of label claim, but not outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0% or if both conditions prevail, test 20 additional units. The requirements are met if not more than 3 units of the 30 are outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 30 dosage units does not exceed 7.8%.

Limit B (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

(1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A.*
(2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100".
(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words "label claim" are replaced by the words "label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100".

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1079**⟩ **Good Storage and Shipping Practices,** *USP 29* page 2915. It is proposed to revise this general chapter to include *Controlled Cold Temperature,* which was proposed to be added in the *General Notices and Requirements* on page 721 of *PF* 31(3) [May–June 2005] under *Preservation, Packaging, Storage, and Labeling* (see *Storage Temperature and Humidity*) and will become official in the *Second Supplement,* with an official date of August 1, 2006.

(P&S: D. Hunt) RTS—C45420

Change to read:

STORAGE IN WAREHOUSES, PHARMACIES, TRUCKS, SHIPPING DOCKS, AND OTHER LOCATIONS

Pharmacopeial articles are to be stored in locations that adhere to conditions established by the manufacturer. Where the desired conditions are not established, use storage conditions described in the *General Notices and Requirements* or in the applicable monograph.

Warehouses

Observation of the temperature variations in a warehouse should be made over a period of time to establish a meaningful temperature profile, including the temperature variations and conditions in the different parts of the warehouse. Such observations provide data and information as to where various products should and should not be stored.

ESTABLISHING TEMPERATURE PROFILES

Temperature profiles can be compiled by using a suitable number of thermometers or other temperature recording instruments. They should be placed throughout the warehouse in divided sections and should record the maximum and minimum temperatures during a 24-hour period for a total of three consecutive 24-hour periods. The following factors, some of which may give rise to extreme temperatures, should be considered during the process of temperature profiling: the size of the space, location of space heaters, sun-facing walls, low ceilings or roofs, and geographic location of the warehouse. Temperature profiling for warehouses already in use should be done at known times of external temperature extremes, e.g., for a period of not less than 3 hours when air temperatures are higher than 25° or less than 15°. Profiling should be conducted in both summer and winter. A mean kinetic temperature (MKT) should be obtained for any separate areas within the warehouse (see *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩ for samples of MKT calculations). The temperature profile report should provide recommendations for the use of each area and identification of any areas that are found unsuitable for storage of Pharmacopeial articles.

CONTROLLED ROOM TEMPERATURE

■AND CONTROLLED COLD TEMPERATURE■2S (*USP30*)

The *General Notices* provide a definition for *Controlled Room Temperature*

■and *Controlled Cold Temperature.*■2S (*USP30*)
A temperature profiling study should demonstrate suitability for storing Pharmacopeial articles in areas determined to be ~~at room or controlled room temperature.~~

■at room temperature, controlled room temperature, or controlled cold temperature.■2S (*USP30*)
A suitable number of temperature and humidity recording instruments should be installed to record temperatures and to provide temperature and humidity profiles. Temperature recording should be conducted to meet the recommendations for establishing mean kinetic temperature and to comply with the warehouse's written procedures. These written procedures should have a reporting mechanism in place whereby a management tree is informed in the event that predefined high or low temperatures or humidity limits have been exceeded. Records can be reviewed as determined by the management system in accordance with established guidelines. Suitable training should be provided to persons who record temperatures, and proper quality accountability and tracking systems should be maintained.

STORAGE AT "COOL," "COLD," "REFRIGERATOR," AND "FREEZING" CONDITIONS

The *General Notices* provide definitions for cool, cold, refrigerator, and freezer temperatures. A temperature profiling study can be used to establish suitable areas for storing Pharmacopeial articles designated to be stored under these conditions. Equipment used for storing Pharmacopeial articles at these low temperatures should be qualified according to written procedures provided by the management system. Recording devices can be installed within the equipment and used to enable both air and product temperatures to be recorded at regular intervals. The number and location of monitoring devices should be determined based on the result of the temperature profile. Temperature records should be examined at least once every 24 hours or as provided in the equipment protocol. Cool or cold conditions are moisture-condensing conditions. Humidity-monitoring devices should be used in cases where the repackaged Pharmacopeial article is humidity-sensitive or labeled to avoid moisture. Additionally, there can be installed temperature-monitoring, and where necessary, humidity-monitoring alarm devices that have the capability of alerting personnel in the event that control is compromised. There should be protocols in place to address procedures for responding to failed temperature and humidity ranges both for normal working hours and outside normal working hours. Temperature and humidity should be reviewed at the times designated by the established protocol. The calibration and functioning of all temperature and humidity monitoring devices, including alarms and other associated equipment, should be checked on an annual or semiannual basis. Regular maintenance protocols should be in place for refrigeration equipment. There should be written agreements in place for all maintenance and evaluation procedures, and this may include an emergency situation protocol.

PERSONNEL TRAINING

Suitable training should be provided for personnel who handle Pharmacopeial articles with special storage temperature requirements. Personnel should know how to monitor temperatures and how to react to situations where adverse temperatures are identified. There should be written procedures in place such that the adverse temperatures are recorded and a report provided to the parties designated in the protocol.

QUALIFICATION OF "COLD" EQUIPMENT OR STORES

Only climate control equipment for which a contractor has provided documentation to assure its suitability for temperature and humidity requirements should be considered for use in cold storage. Qualification procedures on a regular basis should be independently conducted on equipment in cold stores to guarantee suitability and proper functioning. The procedure should demonstrate the temperature profile for both air and product temperatures when empty as well as when loaded. The procedure should also demonstrate the time taken for temperatures to exceed the maximum temperature in the event of a power failure. Qualification should consider thermal fluctuations that occur during stock replenishment and order removal. The results of the qualification should demonstrate the ability of the equipment to maintain the required temperature range in all areas, defining any zones which should not be used for storage such as those areas in close proximity to cooling coils, cold air streams from equipment ventilation, or doors. The variability of the system can be characterized by using the relative standard deviation. Thermal monitoring should establish that the system is rugged in that its temperature profile is consistent and reliable.

Change to read:

SPECIAL HANDLING

Certain classes of Pharmacopeial articles may require special handling. Such articles include products classified as dangerous goods under the Department of Transportation (DOT), state, local, or carrier rules; or products classified as controlled substances by the Drug Enforcement Administration (DEA) or by individual states.

Receipt of Pharmacopeial Articles

Upon arrival of Pharmacopeial articles to warehouse loading docks, premises, and other arrival areas, the Pharmacopeial articles are to be transferred to their manufacturer-designated storage environment within 2 hours of receipt. Limitation of the time spent in the uncontrolled environments of the loading dock is important to ensure that the integrity of the preparation is maintained. This is particularly important for temperature-sensitive items. The delivery document should be reviewed at receiving sites to ensure that the Pharmacopeial articles have not been subjected to any delays during shipment that could result in exposure of the article to extremes of temperature, or to any other extreme or undesirable conditions. In addition, to the extent possible, the receiving personnel should ensure that the ruggedness requirements in shipment have been met. For Pharmacopeial articles requiring extreme caution, special handling, or refrigerator temperature storage conditions, those who supply the articles (e.g., wholesalers and manufacturers) and delivery contractors should provide documented evidence to show that the required temperature range has been maintained during transportation. In the event that a deviation from the required temperature range has been observed during shipment of an article requiring such a shipping condition, the supplier or delivery contractors should document the temperature and the length of time the compendial article was not within the designated storage temperature. The pharmaceutical manufacturer may be contacted to determine the significance of unusual variances.

Distribution or Shipping Vehicles

Vehicles used for shipping or distribution of Pharmacopeial articles designated for storage at controlled room temperature

■or controlled cold temperature■2S (*USP30*)
should be suitably equipped to ensure that the temperature excursions encountered are within those allowed under the definition. ~~of controlled room temperature.~~

■■2S (*USP30*)
Steps should be taken so that extremes of temperature, whether above or below the specified temperatures, should not be encountered during delivery procedures.

Vehicle Qualification

Where practical, suitable monitoring devices, as determined by the manufacturer and vehicle supplier, should be placed in different areas of the truck to establish a temperature profile of the truck over a 24-hour period during a hot summer day, average high, and a cold winter day, average low, and during a normal or typical day. The derived temperature of the different parts of the truck may be used to determine the location on the truck where Pharmacopeial articles can be stored appropriately during shipping (see *Monitoring Devices—Time, Temperature, and Humidity* ⟨1118⟩).

Pharmaceutical Delivery Staff

As part of the contractual agreement between the delivery contractors and the manufacturers, the delivery staff should receive appropriate training to ensure that they are aware of the correct procedures to follow in maintaining products at the correct temperature. There may be written procedures that should be documented. In addition, the transportation personnel should have proper knowledge of the temperature profile of the vehicle to ensure proper placement of the Pharmacopeial articles in the vehicle. Pharmacopeial articles requiring special handling (e.g., refrigeration) or environmentally sensitive preparations should be transported in a suitably equipped vehicle to ensure that the articles are maintained at the correct temperature during distribution, shipping, and delivery and up to the point of receipt. Special arrangements should be made to inform receiving personnel, pharmacists, or other appropriate customers that the package includes articles with special storage and handling specifications and are to be transferred immediately to the appropriate storage location. The manufacturer, shipper, or delivery agency should provide appropriate evidence to show that the required temperature has been maintained throughout shipment and distribution.

Change to read:

SHIPMENT FROM MANUFACTURER TO WHOLESALER

Wholesaler

The wholesaler receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment without delay, as directed by the manufacturer, ideally within 2 hours of receipt. The wholesaler should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution that could result in products being exposed to extreme temperatures (see also the previous section, *Pharmaceutical Delivery Staff,* for staff expectations). The vehicles used for shipping of Pharmacopeial articles to the wholesaler, especially products requiring storage at low temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt. The receiving wholesaler staff should be informed

that the articles are transferred to appropriate storage locations without delays. The vehicles used for shipping of Pharmacopeial articles requiring storage ~~at room or controlled room temperatures~~

■at room temperature, controlled room temperature, or controlled cold temperature■2S (*USP30*)
should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures. Warehouse staff may receive appropriate training to ensure that the correct procedures are followed to maintain required temperature conditions (see *Pharmaceutical Delivery Staff*). Where necessary, a monitoring device for temperature and/or humidity should be used during shipping and distribution.

Compromised Temperature Conditions

A procedure should be in place in the warehouse to define the action that should be taken in the event of deviation from required storage conditions. Suitable records should be maintained to explain the reason for deviation and the resulting action that is taken. The product in question should then be placed in a quarantine status. Advice on the suitability of the product for use should be sought from the manufacturer or supplier of the product. The manufacturer's response should be documented prior to issuing the product to the customer, if that product is to be issued to the customer.

Change to read:

SHIPMENT FROM MANUFACTURER OR WHOLESALER TO PHARMACY

Pharmacy

The pharmacy receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment without delay, as directed by the manufacturer, ideally within 2 hours of receipt. The pharmacy personnel should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution, which could result in the products being exposed to extreme temperatures (see also the section, *Pharmaceutical Delivery Staff,* for staff expectations). The vehicles used for shipping of Pharmacopeial articles to the pharmacy, especially products requiring storage at low temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt. Receiving pharmacy staff should be informed that the articles are to be transferred to appropriate storage without delays. The vehicles used for shipping of Pharmacopeial articles requiring storage ~~at room or controlled room temperatures~~

■at room temperature, controlled room temperature, or controlled cold temperature■2S (*USP30*)
should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures. Pharmacy staff may receive appropriate training to ensure that the correct procedures are followed to maintain required temperature conditions (see *Pharmaceutical Delivery Staff*). Where necessary, a monitoring device for temperature and/or humidity may be used during shipping and distribution.

Compromised Temperature Conditions

The pharmacy should maintain appropriate procedures to define action that should be taken in the event of deviation from the required storage conditions. Suitable records should be maintained to explain the reason for deviation and the resulting action taken (including whether the product is issued to the patient or customer). Advice on the suitability of the product for use as an acceptable drug article should be sought from the manufacturer or supplier of the product.

Change to read:

SHIPMENT FROM PHARMACY TO PATIENT OR CUSTOMER

The pharmacy should provide an appropriate label on the package sent through air or surface routes so that the deliverer does not place the package in a mailbox exposed to extremes in temperature. In the event that no one is available to receive the package, the deliverer should return the package to the post office or service office, and store it in a cool or air-conditioned area until the patient can receive the medication. In the event that the package has not been delivered for more than 2 days, the package may be returned to the pharmacy. For temperature-sensitive articles, it is important that proper arrangements be made to protect the drug from exposure to high temperatures, or in some cases, from freezing conditions. Such arrangements may include the following: insulating the packaging, or packaging with coolant included; overnight shipping; and pre-arranged pick-up. In such cases, the pharmacy should provide on the external package a statement of an acceptable period of delay for delivery. The patient or customer should examine the delivery documentation to ensure that the package has not been subjected to any unacceptable delays during shipping and distribution. The patient or customer receiving the pharmaceutical articles, either by mail, delivery vehicle from the pharmacy, or directly from the physician or pharmacy, should be advised that upon receipt the articles are to be transferred to appropriate storage conditions without delay, as directed by the pharmacy, ideally within 2 hours of receipt. The vehicle used for air or surface shipping and distribution of pharmaceutical packages to the patient or customer, especially those requiring low temperatures, should contain the article suitably packaged in containers that maintain the desired storage conditions until the article reaches the patient or customer. The vehicles used for shipping and distribution of pharmaceutical articles to a patient or customer, especially those requiring storage ~~at room or controlled room temperatures~~

■at room temperature, controlled room temperature, or controlled cold temperature■2S (*USP30*)
should be suitably equipped during extreme temperature conditions such that the packages are not exposed to extremes of temperature either in winter or summer months. In the event that the vehicle is not adequately equipped with air conditioning or heating to protect the product, the time that the article is exposed to ambient conditions should be strictly limited, ideally not more than 2 hours. Where appropriate, a monitoring device may be used to ensure that required temperatures are maintained until the package reaches the patient or customer. If stability studies for the Pharmacopeial preparation indicate that it is particularly sensitive to environmental insults or if appropriate shipping safeguards described in this section are not feasible, then the preparation should be shipped by a different method whereby environmental control can be maintained.

Compromised Temperature Conditions

There should be appropriate procedures in the pharmacy that ships the article to the patient or customer defining the action that should be taken in the event that a patient reports that there has been a deviation from required storage conditions for an article, including any environmentally sensitive preparations, prior to the point of receipt. Advice on the suitability of the product for use should be provided to the patient or customer after the manufacturer or supplier's advice has been sought by the pharmacy. If the patient is advised to use the article, such advice should be documented and noted appropriately by the pharmacy. Otherwise, appropriate arrangements should be made to promptly replace the suspect article. For mail order items, replacement from local pharmacies may be an option to ensure an uninterrupted supply of medication.

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Change to read:

STORAGE OF PHYSICIAN SAMPLES HANDLED BY SALES REPRESENTATIVES IN AUTOMOBILES

Storage of physician samples by sales representatives is regulated under 21CFR 203.34(b)(4); each manufacturer or distributor is to have appropriate policies in place to ensure that proper storage is maintained. The following suggestions may be considered in response to this need and are of interest to practitioners who may observe actual practices. Automobile trunks or passenger cabins used for the storage and distribution of physician samples should be monitored to determine the temperature profile of the trunk or passenger cabin. Suitable monitoring devices as determined by the sales representative may be placed in different areas of the trunk or passenger cabin on a hot summer and a cold winter day. Measurements should also be made during typical 24-hour periods, and the derived temperature should be used for calculation of the mean kinetic temperature at which the sample is stored (see *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩ for examples of MKT calculations). If the Pharmacopeial article designated for storage requires storage at controlled room temperature

■or controlled cold temperature,■2S (*USP30*)
then suitable measures should be taken to maintain the sample within the allowable limits of the storage parameters. Environmentally-sensitive preparations should not be stored in automobile trunks or passenger cabins. Medications stored in automobile trunks or passenger cabins should be removed at the end of 3 days. Sales representatives should consider parking automobiles in shaded areas to avoid extreme heat during the summer and in garages to avoid freezing temperatures during the winter. The use of vouchers from the manufacturer that patients could use to obtain medication samples from participating pharmacies is an alternative way of providing drug samples.

Change to read:

STATEMENTS/LABELING OF THE IMMEDIATE CONTAINERS OR PACKAGE INSERT

Storage statements should be based on the stability evaluations of the Pharmacopeial drug substances and in accordance with national and international requirements.

Room Temperature Storage Statements—For products with a storage statement reading, ''Store at controlled room temperature,'' the labeling should read as follows on the package insert: ''Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted between 15 °C and 30 °C (between 59 °F and 86 °F). Brief exposure to temperatures up to 40 °C (104 °F) may be tolerated provided the mean kinetic temperature does not exceed 25 °C (77 °F); however, such exposure should be minimized.''

On the immediate container label, the following may read for controlled room temperature (CRT): ''Store at 20 °C to 25 °C (68 °F to 77 °F), excursions permitted between 15 °C and 30 °C (between 59 °F and 86 °F).''

Cool Storage Statement—The storage statement for labeling may be as follows: ''Store in a cool place, 8 °C to 15 °C (46 °F to 59 °F).''

Refrigerator Storage Statement—The storage statement for labeling may be as follows: ''Store in a refrigerator, 2 °C to 8 °C (36 °F to 46 °F).''

■For products with a storage statement reading ''Store at controlled cold temperaure'' the labeling should read as follows on the package insert: ''Store at between 2 °C and 8 °C (36 °F and 46 °F), excursions permitted between 0 °C and 15 °C (32 °F and 59 °F). Brief exposure to temperatures up to 25 °C (77 °F) may be tolerated provided the mean kinetic temperature does not exceed 8 °C (46 °F); however, such exposure should be minimized.'' On the immediate container label, the following may read for controlled cold temperature (CCT): ''Store at between 2 °C and 8 °C (36 °F and 46 °F), excursions permitted between 0 °C and 15 °C (32 °F and 59 °F).''■2S (*USP30*)

Freezer Storage Statement—The storage statement for labeling may be as follows: ''Store in a freezer, –25 °C to –10 °C (–13 °F to 14 °F).''

See the *General Notices* for all other applicable storage conditions, such as *Storage Under Nonspecific Conditions* and store in a *Dry Place.* Additional cautionary statements to protect the Pharmacopeial drug product from extreme temperature and humidity conditions may be included on the container label and package insert, as the manufacturer desires.

BRIEFING

⟨**1120**⟩ Raman Spectrophotometry, *USP 29* page 2983. On the basis of comments received by Subcommittee G of the General Chapters Expert Committee, it is proposed to revise this general information chapter. The subcommittee asked that in addition to their revisions the chapter sponsor, as well as the National Institute of Standards and Technology (NIST) experts on Raman, also critically review and suggest revisions to the chapter. Extensive editorial revisions have also been made.

(GC: G. Ritchie) RTS—C42437

Change to read:

⟨1120⟩ RAMAN ~~SPECTROPHOTOMETRY~~

■SPECTROMETRY■2S (*USP30*)

~~INTRODUCTION~~

~~Raman spectroscopy shares many of the principles that apply to other spectroscopic measurements discussed in *Spectrophotometry and Light-Scattering* ⟨851⟩. Raman is a vibrational spectroscopic technique and is therefore related to IR (IR) and near-IR (NIR) spectroscopy. The Raman effect itself arises as a result of a change in the polarizability of a molecular bond and is measured as inelastically scattered radiation.~~

~~A Raman spectrum is generated by exciting the sample of interest to a virtual state with a monochromatic source, typically a laser. Light elastically scattered (no change in wavelength) is known as Rayleigh scatter and is not of analytical interest. However, if the sample relaxes to a vibrational energy level differing from the initial state, the scattered radiation is shifted in energy. The shift is commensurate with~~

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the energy difference between the initial and final vibrational states. This "inelastically scattered" light is referred to as Raman scatter. Only about one in 10^8 photons incident to the sample undergoes Raman scattering. If the Raman scattered photon is of lower energy, it is referred to as Stokes scattering. If it is of higher energy, it is referred to as anti-Stokes scattering. In practice, nearly all analytically useful Raman measurements make use of Stokes-shifted Raman scatter.

The appearance of a Raman spectrum is much like an absorption Fourier transform–IR (FT–IR) spectrum. The intensities, or the number of Raman photons counted, are plotted against the shifted energies. The *x*-axis is generally labeled "Raman Shift/cm^{-1}" or "Wavenumber/cm^{-1}". The shift position is usually expressed in frequency and represents the frequency of the peak *relative* to the laser frequency. The spectrum is interpreted in the same manner as the commensurate absorption FT–IR spectrum. The positions of the shift frequencies for a given bond in an analyte are similar to their respective absorption frequencies in an IR spectrum. However, the peaks emphasized in a Raman spectrum are often de-emphasized in an IR spectrum and vice versa. This is why the two spectroscopic techniques are often said to be complementary.

Raman spectroscopy is advantageous because quick and accurate measurements can often be made without destroying the sample (solid, semi-solid, liquid, or gas) and with minimal or no sample preparation. The signal is typically in the visible or NIR range, allowing efficient coupling to fiber optics. This also means that a signal can be obtained from any medium transparent to the laser, such as glass, plastics, or samples in aqueous media. From an instrumental point of view, modern systems are easy to use, provide fast analysis times (seconds to several minutes), and are reliable. The Raman spectrum contains information on fundamental vibrational modes of the sample that can yield both sample and process understanding. Finally, the analysis modeling may be simpler than that associated with other spectroscopic techniques. (Both univariate and multivariate methods and calibrations can be used.)

In addition to normal Raman spectroscopy, there are a number of more specialized Raman techniques. These include resonance Raman (RR), surface-enhanced Raman spectroscopy (SERS), Raman optical activity (ROA), coherent anti-Stokes Raman spectroscopy (CARS), Raman gain or loss spectroscopy, and hyper-Raman spectroscopy. These techniques are not widely implemented currently, and are not addressed in this general information chapter.

QUALITATIVE AND QUANTITATIVE RAMAN MEASUREMENTS

There are two general classes of commonly performed Raman measurements: qualitative and quantitative.

Qualitative Raman Measurements

Qualitative Raman measurements yield accurate spectral information about the vibrational bands present in the sample. Because the Raman spectrum is specific for a given compound, qualitative Raman measurements may be used as a compendial ID test, as well as for structural elucidation.

Quantitative Raman Measurements

Quantitative Raman measurements follow a relationship comparable to Beer's law:

$$I_s = KLCI_o,$$

in which I_s is the peak intensity at a given wavelength, K represents instrument and sample constants, L is the path length, C is the molar concentration of a particular component in the sample, and I_o is the laser intensity. In practice, path length is more accurately described as sampling volume, which is an instrumental variable described by the focus of the laser and the collection optics. From the equation, it is apparent that peak intensity is directly correlated to concentration. It is this relationship that is the basis for the majority of quantitative Raman applications.

FACTORS AFFECTING QUANTITATION

Sample-Based Factors

The most important sample-based factors are fluorescence, sample heating, and matrix absorption. Fluorescence is typically observed as a broad sloping background underlying the Raman spectrum. The effect on quantitation is therefore that of an unstable baseline and decreased signal-to-noise ratio. The exact wavelength and intensity are dependent on the identity and concentration of the fluorescing material. Because fluorescence is generally a much more efficient process, even very minor amounts of fluorescent impurities can lead to significant Raman signal degradation. Fluorescence can be minimized by using longer wavelength excitation sources such as 785 nm or 1064 nm. However, the intensity of the Raman signal is proportional to ν^{-4}, where ν is the excitation wavelength. The optimum signal-to-noise ratio will be obtained by balancing fluorescence rejection, signal strength, and detector response.

Fluorescence in solids can also be mitigated by exposing the sample to the laser source for a period of time before measurement. This process is called photobleaching, and operates by degrading the highly absorbing species. Photobleaching is less effective in liquids, where the sample is mobile, or if the amount of fluorescent material is more than a trace.

Sample heating can cause a variety of issues, such as physical form change (melting), polymorph conversion, or sample burning. This is usually an issue for colored, highly absorbing species, or very small particles that have low heat transfer. The effects of sample heating are usually observable either as changes in the Raman spectrum over time or by visual inspection of the sample. Besides decreasing the laser flux, a variety of methods can be employed to diminish heating, such as moving the sample or laser during the measurement or improving the heat transfer of the sample with thermal contact or liquid immersion.

Absorption of the Raman signal by the matrix can also occur. This problem is more prevalent with long-wavelength FT–Raman systems where the Raman signal can overlap with a NIR overtone absorption. This effect will be dependent on the optics of the system as well as on the sample presentation. Associated with this effect is variability from scattering in solids as a result of packing and particle size differences. The magnitude of all of these effects, however, is typically less severe than in NIR because of the limited depth of penetration and the relatively narrower wavelength region sampled in Raman spectroscopy.

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Sampling Factors

Quantitative Raman spectroscopy differs from many other spectroscopic techniques in that it is a single-beam measurement with no background. Careful instrument design and sampling can minimize this variation but not entirely remove it. Thus the absolute Raman signal intensity is very difficult to use for direct quantitation of an analyte. Among the potential sources of variation are changes in sample opacity, sample heterogeneity, changes in laser power at the sample, and changes in optical collection geometry or sample position. These effects can be minimized by sampling in a reproducible, representative manner.

Use of an internal reference is the most common and robust method of eliminating variations due to absolute intensity fluctuations. There are several choices for this approach. An internal standard can be deliberately added, and isolated peaks from this standard can be employed. In a solution, an isolated solvent band can be employed because the solvent will remain relatively unchanged from sample to sample. Also, in a formulation, an excipient peak can be used if it is in substantial excess compared to the analyte. The entire spectrum can also be used as a reference, with the assumption that laser and sample orientation changes will affect the entire spectrum equally.

A second important sampling-based factor to consider is spectral contamination. Raman is a weak effect that can be masked by a number of external sources. Common contamination sources include sample holder artifacts (container or substrate) and ambient light. Typically, these issues can be identified and resolved by careful experimentation.

APPARATUS

Components

All modern Raman measurements involve irradiating a sample with a laser, collecting the scattered radiation, rejecting the Rayleigh scattered light, differentiating the Raman photons by wavelength, and detecting the resulting Raman spectrum. All commercial Raman instruments therefore share the following common features to perform these functions:

1. Excitation source (laser)
2. Sampling device
3. Device to filter/reject light scattered at the laser wavelength
4. Wavelength processing unit
5. Detector and electronics

EXCITATION SOURCE (LASER)

Table 1 identifies several common lasers used for pharmaceutical applications. UV lasers have also been used for specialized applications but have various drawbacks that severely limit their utility for general analytical measurements.

Table 1. Typical Lasers Used in Pharmaceutical Applications

Laser λ, nm (nearest whole number)	Type	Typical Power at Laser	Wavelength Range, nm (Stokes Region, 100 cm^{-1} to 3000 cm^{-1} shift)	Comments
NIR Lasers				
1064	Solid state (Nd:YAG)	Up to 3W	1075–1563	Commonly used in Fourier transform instruments
785	Diode	Up to 500 mW	791–1027	Most ubiquitous dispersive Raman laser
Visible Lasers				
488–632.8	Ion gas and solid state frequency doubled lasers	Up to 1W	488–781	Fluorescence risks

~~SAMPLING DEVICE~~

~~A wide variety of sampling arrangements are possible, including direct optical interfaces, microscopes, fiber optic–based probes (either noncontact or immersion optics), and sample chambers (including specialty sample holders and automated sample changers). The sampling optics may also be designed to obtain the polarization-dependent Raman spectrum, which often contains additional information. Selection of the sampling device will often be dictated by the analyte. However, considerations such as sampling volume, speed of the measurement, laser safety, and reproducibility of sample presentation should be evaluated to optimize the sampling device for any given application.~~

~~FILTERING DEVICE~~

~~Scattered light at the laser wavelength (Rayleigh) is many orders of magnitude greater than the Raman signal and must be rejected prior to the detector. Notch filters are almost universally used for this purpose and provide excellent rejection and stability combined with small size. The traditional use of multistage monochromators for this purpose, although still viable, is now rare. In addition, various filters or physical barriers to shield the sample from external radiation sources (e.g., room lights, laser plasma lines) may be required depending on the collection geometry of the instrument.~~

~~WAVELENGTH PROCESSING UNIT~~

~~The wavelength may be processed by either dispersion or interferometry (Fourier transform). The specific benefits and drawbacks of each of the dispersive designs compared to the FT instrument are beyond the scope of this chapter. Any properly qualified instruments should be suitable for qualitative measurements. However, care must be taken when selecting an instrument for quantitative measurements, as dispersion and response linearity may not be uniform across the full spectral range (for example, when using an echelle spectrograph).~~

~~DETECTOR~~

~~The silicon-based charge-coupled device (CCD) is the most common detector for dispersive instruments. The cooled-array detector allows fast, full-spectrum measurements with low noise. It also has peak wavelength responsivity when matched to the commonly used 785-nm diode laser. Fourier transform instruments typically use single-channel germanium or indium–gallium–arsenide (InGaAs) detectors responsive in the NIR to match neodymium:yttrium–aluminum–garnet (Nd:YAG) 1064-nm excitation.~~

~~Calibration~~

~~Raman instrument calibration consists of three components: primary wavelength (*x*-axis), laser wavelength, and intensity (*y*-axis).~~

~~PRIMARY WAVELENGTH (*X*-AXIS)~~

~~In the case of FT-Raman instruments, primary wavelength-axis calibration is maintained with an internal He–Ne laser. Most dispersive instruments utilize atomic emission lamps for primary wavelength-axis calibration. In all Raman systems suitable for analytical Raman measurements, the vendor will offer a procedure of *x*-axis calibration that can be performed by the user. For dispersive-Raman instruments, a calibration based on multiple atomic emission lines is preferred. The validity of this calibration approach can be verified subsequent to laser wavelength calibration using a suitable Raman shift standard. For scanning dispersive instruments, calibration may need to be performed more frequently, and precision in both a scanning and static operation mode may need to be verified.[1]~~

~~[1] ASTM E1840-96(2002) Standard Guide for Raman Shift Standards for Spectrometer Calibration, ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA, USA 19428-2959.~~

~~LASER WAVELENGTH~~

~~Laser wavelength variation can impact both the wavelength precision and the photometric (intensity) precision of a given instrument. Even the most stable current lasers can vary slightly in their measured wavelength output. The laser wavelength must therefore be confirmed to ensure that the Raman shift positions are accurate for both FT-Raman or dispersive Raman instruments. A reference Raman shift standard material such as those outlined in ASTM E1840-96(2002)[1] or other suitably verified materials can be utilized for this purpose. [NOTE—Reliable Raman shift standard values for frequently used liquid and solid reagents, required for wavenumber calibration of Raman spectrometers, are provided in the ASTM Standard Guide cited. These values can be used in addition to the highly accurate and precise low-pressure arc-lamp emission lines that are also available for use in Raman instrument calibration.] Spectrophotometric-grade material can be purchased from appropriate suppliers for this use. Certain instruments may use an internal Raman standard separate from the primary optical path. External calibration devices exactly reproduce the optical path taken by the scattered radiation. [NOTE—When chemical standards are used, care must be taken to avoid standard contamination and to confirm standard stability.]~~

~~Unless the instrument is of a continuous calibration type, the primary wavelength-axis calibration should be performed, as per vendor procedures, just prior to measuring the laser wavelength. For external calibration, the Raman shift standard should be placed at the sample location and measured using appropriate acquisition parameters. The peak center of a strong, well-resolved band in the spectral region of interest should be evaluated. The position can be assessed manually or with a suitable, valid peak-picking algorithm. The software provided by the vendor may measure the laser wavelength and adjust the laser wavelength appropriately so that this peak is at the proper position. If the vendor does not provide this functionality, the laser wavelength should be adjusted manually.~~

~~INTENSITY (*Y*-AXIS)~~

~~Calibration of the photometric axis can be critical for successful quantitation using certain analytical methods (chemometrics) and method transfer between instruments. Both FT-Raman units and dispersive Raman units should undergo similar calibration procedures. The tolerance of photometric precision acceptable for a given measurement should be assessed during the method development stage.~~

~~To calibrate the photometric response of a Raman instrument, a broad-band emission source should be used. There are two accepted methods: *Method A*, which utilizes an NIST-traceable tungsten white light source[2] (and is applicable to all common laser excitation wavelengths listed in *Table 1*) and *Method B*, which utilizes NIST SRM 2241,[3] a doped glass fluorescence source that is currently available only for systems with 785-nm nominal excitation.~~

~~**Method A**—The NIST-traceable source should be placed at the sample location with the laser off and the response of the detector measured (using parameters appropriate for the instrument). The output for the source used for calibration should be known. The ratio of the measured response to the true response should be determined and a correction file generated. This correction should be applied to all spectra acquired with the instrument. Most manufacturers will provide both appropriate calibration sources and software for this approach. If the manufacturer does not provide a procedure or method, the user may accomplish the task using a source obtained from NIST and appropriate software. If using a manufacturer's method, attention must be paid to the calibration procedure and source validity. The user should obtain appropriate documentation from the manufacturer to ensure a qualified approach.~~

~~[2] NIST-traceable tungsten white light source statement: While the calibration of the Raman frequency (or Raman shift, cm^{-1}) axis using pure materials and an existing ASTM standard is well accepted, techniques for calibration of the Raman intensity axis are not. Intensity calibrations of Raman spectra can be accomplished with certified white light sources.~~

~~[3] NIST SRM 2241: Ray, K. G.; McCreery, R. L. Raman intensity correction standard for systems operating with 785-nm excitation. Appl. Spectrosc. 1997, 51, 108–116.~~

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Method B—The NIST SRM 2241 should be placed at the sample location. With the laser on, a spectrum of the SRM should be obtained (using parameters appropriate for the instrument). The output for the source used for calibration should be known. The ratio of the measured response to the true response should be determined and a correction file generated. This correction should be applied to all spectra acquired with the instrument. Most manufacturers will provide both appropriate calibration sources and software for this approach. If the manufacturer does not provide a procedure or method, the user may accomplish the task using a source obtained from NIST and appropriate software. If using a manufacturer's method, attention must be paid to the calibration procedure and source validity. The user should obtain appropriate documentation from the manufacturer to ensure a qualified approach. [NOTE—*Method B* is currently appropriate only for a system with 785-nm laser excitation. NIST is currently producing other SRM materials that will be wavelength-specific for 1064-, 632.8-, 532-, and 514-nm excitation (and available in the 2004–2006 timeframe).]

EXTERNAL CALIBRATION

Detailed functional validation employing external reference standards is recommended to demonstrate instrumental suitability for laboratory instruments, even for instruments possessing an internal calibration approach. The use of external reference standards does not negate the need for internal quality control procedures; rather, it provides independent documentation of the fitness of the instrument to perform the specific analysis/purpose. For instruments installed in a process location or in a reactor where positioning of an external standard routinely is not possible, including those instruments possessing an internal calibration approach, periodic checking of the relative performance of an internal vs. external calibration approach should be made. The purpose of this test is to check for change in components that may not be included in the internal calibration method (process lens, fiber optic probe, etc.), e.g., photometric calibration of the optical system.

QUALIFICATION AND VERIFICATION OF RAMAN INSTRUMENTS

The suitability of a specific instrument for use in a given method is ensured by a thorough technology suitability evaluation for the application; a routine, periodic instrument operational qualification; and the more frequent performance verification (see *Definition of Terms and Symbols*). The purpose of the technology suitability evaluation is to ensure that the technology proposed is suitable for the intended application. The purpose of the instrument qualification is to ensure that the instrument to be used is suitable for its intended application and, when requalified periodically, continues to function properly over extended time periods. When the device is used for a specific qualitative or quantitative analysis, regular performance verifications are made. Because there are many different approaches to measuring Raman spectra, instrument operational qualification and performance verification often employ external standards that can be used on any instrument. As with any spectrophotometric device, a Raman instrument needs to be qualified for both wavelength (*x* axis and shift from the excitation source) and photometric (intensity axis) precision.

In performance verification, a quality of fit to an initial scan or group of scans (often referred to in nonscanning instruments as an accumulation) included in the instrumental qualification can be employed. In such analysis, it is assumed that reference standard spectra collected on a new or a newly repaired, properly operating instrument represent the best available spectra. Comparison of spectra taken over time on identical reference standards [either the original standard or identical new standards (if stability of the reference standards is a concern)] form the basis for evaluating the long-term stability of a Raman measurement system.

Frequency of Testing

Instrumental qualification is performed at designated intervals or following a repair or significant optical reconfiguration, such as a laser replacement or changing excitation wavelengths. Full instrument requalification may not be necessary when changing between sampling accessories such as a microprobe, a sample compartment, or a fixed fiber optic probe. Performance verification tests may be sufficient in these cases; instrument-specific guidance from the vendor on qualification requirements should be followed. Tests include wavelength (*x* axis and shift from the excitation source) and photometric (intensity axis) precision. Instrument qualification tests require that specific application dependent tolerances be met.

Performance verification is carried out on the instrument configured for the analytical measurements and is done more frequently than instrument qualification. Performance verification includes wavelength uncertainty and intensity scale precision. Wavelength precision and intensity scale precision tests may be needed prior to any data collection on a given day. Performance is verified by matching the current spectra to those collected during the previous instrument qualification.

Instrument Operational Qualification

It is important to note that the acceptance specifications given in both the *Instrument Operational Qualification* and *Performance Qualification* sections are applicable for general use; specifications for particular instruments and applications may vary depending on the analysis method used and the desired accuracy of the final result. ASTM standard reference materials are also specified, with the understanding that under some circumstances (specifically remote on-line applications) calibration using one of these materials may be impractical, and other suitably verified materials may be employed. At this juncture it is important to note that specific parameters such as spectrometer noise, limits of detection (LOD), limits of quantification (LOQ), and acceptable spectral bandwidth for any given application should be developed as part of the analytical method development. Specific values for tests such as spectrometer noise and bandwidth will be dependent on the instrument chosen and the purpose required. In view of this, specific instrument tests for these parameters are not dictated in this information chapter.

WAVELENGTH (*X* AXIS) PRECISION

It is important to ensure the precision of the wavelength axis via calibration to maintain the integrity of Raman peak positions. Wavelength calibration of a Raman spectrometer consists of two parts: primary wavelength axis and laser wavelength calibration. After calibrating both the primary wavelength axis and the laser wavelength, instrument wavelength uncertainty can be determined. This can be accomplished using a Raman shift standard such as the ASTM shift standards or other suitably verified material. Selection of a standard with bands present across the full Raman spectral range is recommended so that instrument wavelength uncertainty can be evaluated at multiple locations within the spectrum. The tolerance of wavelength precision that is required for a given measurement should be assessed during the method development stage. [NOTE—For scanning dispersive instruments, calibration may need to be performed more frequently, and precision in both a scanning and static operation mode may need to be verified.]

PHOTOMETRIC PRECISION

Laser variation in terms of the total emitted photons occurring between two measurements can give rise to changes in the photometric precision of the instrument. Unfortunately, it is very difficult to deconvolute changes in the photometric response associated with variations in the total emitted laser photons from the sample and sampling-induced perturbations. This is one of the reasons why absolute Raman measurements are strongly discouraged and why the photometric precision specification is set relatively loosely. The tolerance of photometric precision required for a given measurement should be assessed during the method development stage.

Performance Qualification

The objective of performance qualification is to ensure that the instrument is performing within specified limits with respect to wavelength precision, intensity axis precision, and sensitivity. In certain cases when the instrument has been set up for a specific measurement (for example, installed in a process reactor), it may no longer be possible or desirable to measure the wavelength and photometric (intensity) qualification reference standards identified above. Provided instrument operational qualification has shown that the equipment is fit for use, a single external performance verification standard can be used to reverify function on a continuing basis (for example, a routinely used process solvent signal, for both wavelength and photometric precision, following reactor cleaning). The performance verification standard should match the format of the samples in the current analysis as closely as possible and use similar spectral acquisition parameters. Quantitative measurements of an external performance verification standard spectrum checks both the wavelength (*x*-axis and laser wavelength) and the photometric (intensity) precision. Favorable comparison of a series of performance verification spectra demonstrates proper continued operation of the instrument.

WAVELENGTH PRECISION

The wavelength precision should be measured by collecting data for a single spectrum of the selected Raman shift standard for a period equal to that used in the photometric consistency test. Peak positions across the spectral range of interest are used to calculate precision. Performance is verified by matching the current peak position to those collected during the previous instrument qualification and should not vary by more than ± 0.3 cm^{-1}, although this specification may be adjusted according to the required accuracy of the measurement.

PHOTOMETRIC CONSISTENCY

The photometric consistency should be measured by collecting data for a single spectrum of a suitably verified reference standard material for a specified time. The areas of a number of bands across the spectral range of interest should be calculated using an appropriate algorithm. The most intense band area is set to an intensity of 1, and all other envelopes are normalized to this band. Performance is verified by matching the current band areas to their respective areas collected during the previous instrument qualification. The areas should vary by no more than 10%, although this specification may be adjusted according to the required accuracy of the measurement.

LASER POWER OUPUT PRECISION AND ACCURACY

This test is applicable only to Raman instruments with automatic, internal laser power meters. Instruments without laser power measurement should utilize a calibrated laser power meter from a reputable supplier. The laser output should be set on a representative output, dictated by the requirements of the analytical measurement and the laser power measured. The output should be measured and checked against the output measured at instrument qualification. The power (in milliwatts or watts) should vary by no more than 25% compared to the qualified level. If the power varies by more than this amount, the instrument should be serviced (as this variation may indicate, among other things, a gross misalignment of the system or the onset of failure of the laser).

For instruments with an automatic, internal laser power meter, the accuracy of the values generated from the internal power meter should be compared to a calibrated external laser power meter at an interval of not more than 12 months. The internally calculated value should be compared to that generated by the external power meter. Performance is verified by matching the current value to that generated during the previous instrument qualification. The manufacturer may provide software to facilitate this analysis. If the instrument design prevents the use of an external power meter, then the supplier should produce documentation to ensure the quality of the instrument and provide a recommended procedure for the above analysis to be accomplished during a scheduled service visit.

METHOD VALIDATION

Validation of Raman methods will follow the same protocols described in *Validation of Compendial Methods* ⟨1225⟩ in terms of accuracy, precision, etc. However, several of these criteria are affected by variables specific to Raman.

Fluorescence is the primary variable that can affect the suitability of a method. The presence of fluorescent impurities in samples can be quite variable and have little effect on the acceptability of a material. The method must be flexible enough to accommodate different sampling regimes that may be necessary to minimize the effects of these impurities.

Detector linearity must be confirmed over the range of possible signal levels. Fluorescence may drive the signal baseline higher than that used in the validation, in which case the fluorescence must be decreased, or the method validated to accommodate the higher fluorescence levels. This is also true for the precision, LOD, and LOQ of the method, as increased baseline noise will negatively impact all of these values. Because fluorescence may also affect quantitation due to baseline shifts, confirmation of acceptable quantitation at different levels of photobleaching, when used, should also be obtained.

The impact of the laser on the sample must be determined. Visual inspection of the sample and qualitative inspection of the Raman spectrum for measurements with differing laser powers and exposure times will confirm that the sample is not being altered (other than by photobleaching). Specific variables to confirm in the spectrum are shifts in peak position, changes in peak intensity and band width, and unexpected changes in background intensity.

Method precision must also encompass sample position. The sample presentation is a critical factor for both solids and liquids, and must be either tightly controlled or accounted for in the calibration model. Sample position sensitivity can often be minimized by appropriate sample preparation or sample holder geometry, but will vary from instrument to instrument based on excitation and collection optical configuration.

DEFINITION OF TERMS AND SYMBOLS

Calibration model is a mathematical expression that relates the response from an analytical instrument to the properties of samples.

Instrument bandwidth is a measure of the ability of a spectrometer to separate radiation of similar wavelengths.

Multiple linear regression is a calibration algorithm used to relate the response from an analytical instrument to the properties of samples. The distinguishing feature of this algorithm is the use of a limited number of independent variables. Linear least squares calculations are performed to establish a relationship between these independent variables and the properties of the samples.

Multivariate curve resolution (MCR) is a curve deconvolution technique that separates spectral components on the basis of their linear contributions to the overall spectrum.

Operational qualification is the process by which it is demonstrated and documented that the instrument performs according to specifications, and that it can perform the intended task. This process is required following any significant change such as instrument installation, relocation, major repair, etc.

Partial least squares (PLS) is a calibration algorithm used to relate instrument responses to the properties of samples. The distinguishing feature of this algorithm is that, although similar to PCR, this algorithm includes data concerning the properties of the samples used for calibration in the calculation of the factors used to describe the instrument responses.

Performance qualification is the process of using one or more well characterized and stable reference materials to verify consistent instrument performance. Qualification may employ the same or different standards for different performance characteristics.

In-Process Revision

Principal component analysis and regression (PCA and PCR) is a calibration algorithm used to relate the response from an analytical instrument to the properties of samples. This algorithm, which expresses a set of independent variables as a linear combination of factors, is a method of relating those factors to the properties of the samples for which the independent variables were obtained.

Raman spectrum[4] is a graph of the radiant energy, or number of photons, scattered by the sample through the indirect interaction between the molecular vibrations in the sample and monochromatic radiation of frequency much higher than that of the vibrations. The abscissa is usually the difference in wavenumber between the incident and scattered radiation.

(Normal) Raman scattering[4] is Raman scattering that occurs through the polarizability, not the hyper-polarizabilities, and is excited by radiation that is not in resonance with electronic transitions in the sample. The scattering, in fact, occurs through the derived polarizability tensors, i.e., through changes in the polarizability during the vibrations.

Raman wavenumber shift[4],

$$\Delta\tilde{\nu}$$

is the wavenumber of the exciting line minus the wavenumber of the scattered radiation. SI unit: m^{-1}. Common unit: cm^{-1}. = 100 m^{-1}.

$$\Delta\tilde{\nu}$$

is positive for Stokes scattering and negative for anti-Stokes scattering.

APPENDIX: CHEMOMETRIC APPLICATIONS AND MODEL BUILDING

Chemometrics can legitimately be used with Raman data to create models that can be used for qualitative and/or quantitative analysis.

Data Pretreatments

Pretreatments are mathematical manipulations of the spectra performed prior to the primary modeling step. The goal of pretreatments is to reduce the amount of irrelevant information, eliminating it from the model prior to the application of the primary technique. There are several data pretreatments that are typically used for removal of baseline anomalies. These include multiplicative scatter correction (MSC), standard normal variate (SNV), and derivatives. Pearson's method, an iterative approach to baseline decurvature, works well for the correction of some sets of data.

Library Construction and Use

Raman libraries are often used for compound identification. The test material can be tentatively known to the user or not. Libraries used for the purpose of raw material, intermediate, or formulation identity confirmation are best constructed from real production materials. This is particularly prudent in light of the fact that materials differing in crystallinity or polymorphic constitution will yield varying Raman spectra. Raman libraries purchased from a third party should be used judiciously.

Qualitative algorithms vary, and the appropriate choice is application dependent. For simple identifications, correlation algorithms often work well. These algorithms can be based on a variety of mathematical manipulations. Principal component based methods such as discriminant analysis can also be used for qualitative analysis.

Quantitative Calibration Approach

Raman spectroscopy can be used for quantitative analysis both for in-line and off-line work. There are some unique aspects concerning the use of quantitative Raman spectra that should be noted.

ALGORITHMS FOR QUANTITATION

As in the case of NIR spectroscopy (see *Near-Infrared Spectrophotometry* ⟨1119⟩), multivariate methods may be used to model Raman data. However, univariate analyses are often appropriate because of the resolution of information that Raman affords.

Both peak areas and peak heights can appropriately be used for Raman quantitation when univariate models are employed. Peaks should be reasonably well resolved when this approach is employed. As described above, peak ratios, as a rule, should be employed to account for peak intensity changes not related to the analyte. The judicious choice for a reference band is critical in such cases. Multivariate methods are also viable for Raman quantitation.

Multivariate curve resolution (MCR), which attempts to deconvolute the spectral data as a linear sum of its contributions, is a particularly effective means of dealing with Raman data that exhibit substantial change. This algorithm can potentially isolate the contribution from the analyte of interest and quantify the level of this contribution from sample to sample. The method is often employed in a non-negative mode, making the resulting factors potentially interpretable.

Principal components analysis (PCA) can be used similarly to MCR. The contribution of each component generated can be used to semiquantitatively estimate the level of the analyte. Related to PCA, principal component regression (PCR) can also be used. This provides an opportunity for reference data to be employed and is thus truly quantitative.

In many circumstances, multiple linear regression (MLR) can be very effective for Raman quantitation. MLR gives the user the capability of using denominator data points, which can be very useful for Raman data. As with other types of data, the ability to choose multiple numerators can also work synergistically in a quantitative analysis.

Partial least squares (PLS) regression remains one of the more popular choices for Raman quantitation. PLS uses the reference data to orient the factor generation. This can be very effective, especially for the quantitation of low-level analytes.

The choice of appropriate quantitation tools varies from project to project. Both pretreatment methods and quantitative algorithms should be chosen wisely according to the goals. If isolated analyte and reference bands are available, univariate models are often a good choice. If quantitative estimates are all that are necessary or the sample set is a closed set (no future predictions will be made), then MCR or PCA is a good choice. For reasonably extensive data sets with available reference data, MLR, PCR, or PLS can be used.

■INTRODUCTION

Raman spectroscopy shares many of the principles that apply to other spectroscopic measurements discussed in *Spectrophotometry and Light-Scattering* ⟨851⟩. Raman is a vibrational spectroscopic technique and is therefore related to infrared (IR) and near-infrared (NIR) spectroscopy. The Raman effect itself arises as a result of a change in the polarizability of molecular bonds during a given vibrational mode and is measured as inelastically scattered radiation.

[4] Chalmers, J., Griffiths, P., Eds. Handbook of Vibrational Spectroscopy; John Wiley & Sons, Ltd: New York, 2002.

In-Process Revision

A Raman spectrum is generated by exciting the sample of interest to a virtual state with a monochromatic source, typically a laser. Light elastically scattered (no change in wavelength) is known as Rayleigh scatter and is not of interest in Raman spectrometry, except for marking the laser wavelength. However, if the sample relaxes to a vibrational energy level that differs from the initial state, the scattered radiation is shifted in energy. This shift is commensurate with the energy difference between the initial and final vibrational states. This ''inelastically scattered'' light is referred to as Raman scatter. Only about one in 10^6–10^8 photons incident on the sample undergoes Raman scattering. Thus lasers are employed in Raman spectrometers. If the Raman-scattered photon is of lower energy, it is referred to as Stokes scattering. If it is of higher energy, it is referred to as anti-Stokes scattering. In practice, nearly all analytically useful Raman measurements make use of Stokes-shifted Raman scatter.

The appearance of a Raman spectrum is much like an infrared spectrum plotted linearly in absorbance. The intensities, or the number of Raman photons counted, are plotted against the shifted energies. The *x*-axis is generally labeled ''Raman Shift/cm^{-1}'' or ''Wavenumber/cm^{-1}''. The Raman shift is usually expressed in wavenumber and represents the difference in the absolute wavenumber of the peak and the laser wavenumber. The spectrum is interpreted in the same manner as the corresponding mid-infrared spectrum. The positions of the (Raman shifted) wavenumbers for a given vibrational mode are identical to the wavenumbers of the corresponding bands in an IR absorption spectrum. However, the stronger peaks in a Raman spectrum are often weak in an IR spectrum, and vice versa. Thus the two spectroscopic techniques are often said to be complementary.

Raman spectroscopy is advantageous because quick and accurate measurements can often be made without destroying the sample (solid, semisolid, liquid or, less frequently, gas) and with minimal or no sample preparation. The Raman spectrum contains information on fundamental vibrational modes of the sample that can yield both sample and process understanding. The signal is typically in the visible or NIR range, allowing efficient coupling to fiber optics. This also means that a signal can be obtained from any medium transparent to the laser light; examples are glass, plastics, or samples in aqueous media. In addition, because Raman spectra are ordinarily excited with visible or NIR radiation, standard glass/quartz optics may be used. From an instrumental point of view, modern systems are easy to use, provide fast analysis times (seconds to several minutes), and are reliable. However, the danger of using high-powered lasers must be recognized, especially when their wavelengths are in the NIR and, therefore, not visible to the eye. Fiber-optic probes should be used with caution and with reference to appropriate government regulations regarding lasers and laser classes.

In addition to ''normal'' Raman spectroscopy, there are several more specialized Raman techniques. These include resonance Raman (RR), surface-enhanced Raman spectroscopy (SERS), Raman optical activity (ROA), coherent anti-Stokes Raman spectroscopy (CARS), Raman gain or loss spectroscopy, and hyper-Raman spectroscopy. These techniques are not widely employed in pharmaceutical laboratories, and are not addressed in this general information chapter.

QUALITATIVE AND QUANTITATIVE RAMAN MEASUREMENTS

There are two general classes of measurements that are commonly performed by Raman spectrometry: qualitative and quantitative.

Qualitative Raman Measurements

Qualitative Raman measurements yield spectral information about the functional groups that are present in a sample. Because the Raman spectrum is specific for a given compound, qualitative Raman measurements can be used as a compendial ID test, as well as for structural elucidation.

Quantitative Raman Measurements

For instruments equipped with a detector that measures optical power (such as Fourier transform [FT]-Raman spectrometers), quantitative Raman measurements utilize the following relationship between signal, S_ν, at a given wavenumber, ν, and the concentration of an analyte, C:

$$S_\nu = K\sigma_\nu (\nu_L - \nu_\beta)^4 P_0 C$$

in which K is a constant that depends on laser beam diameter, collection optics, sample volume, and temperature; σ_ν is the Raman cross section of the particular vibrational mode; ν_L is the laser wavenumber; ν_β is the wavenumber of the vibrational mode; and P_0 is the laser power. The Raman cross section, σ_ν, is characteristic of the nature of the particular vibrational mode. The sample volume is defined by size of the focus of the laser beam at the sample, the optic being used for focusing, and the optical properties of the sample itself. Spot sizes at the sample can range from less than 1 µm for a microprobe to 6 mm for a large area sample system. For Raman spectrometers that measure the number of photons per second (such as change-coupled device [CCD]-Raman spectrometers) the corresponding equation is:

$$Si_\nu = KP\, s\nu_0(\nu_0 - \nu_i)^3$$

From the above equations, it is apparent that peak signal is directly proportional to concentration. It is this relationship that is the basis for the majority of quantitative Raman applications.

FACTORS AFFECTING QUANTIFICATION

Sample-Based Factors

The most important sample-based factors that deleteriously affect quantitative Raman spectrometry are fluorescence, sample heating, absorption by the matrix or the sample itself, and the effect of polarization. If the sample matrix includes fluorescent compounds, the measured signal will usually contain a contribution from fluorescence. Fluorescence will be observed only if the laser excitation wavelength overlaps with an absorption band of a fluorescent compound. Fluorescence is typically observed as a broad sloping background underlying the Raman spectrum. Fluorescence can cause both a baseline offset and reduced signal-to-noise ratio. The wavelength range and intensity of the fluorescence is dependent on the chemical composition of the fluorescent material. Because fluorescence is generally a much more efficient process than Raman scattering, even very minor amounts of fluorescent impurities can lead to significant degradation of the Raman signal. Fluorescence can be reduced by using longer wavelength excitation sources such as 785 nm or 1064 nm. However, it should be remembered that the strength of the Raman signal is proportional to $(\nu_L - \nu_\beta)^4$, so the advantage of using a long-wavelength excitation laser to minimize fluorescence is at least partially offset by the reduced strength of the Raman signal. The greatest signal-to-noise ratio will be obtained by balancing fluorescence rejection, signal strength, and detector response.

Fluorescence in solids can sometimes be mitigated by exposing the sample to the laser radiation for a period of time before measurement. This process is called photobleaching, and operates by degrading the highly absorbing species. Photobleaching is less effective in liquids, where the sample is mobile, or if the amount of fluorescent material is more than a trace.

Sample heating by the laser source can cause a variety of effects, such as physical form change (melting), polymorph conversion, or sample burning. The chance for sample heating is greatest when the spot size at the sample is the smallest, i.e., when a microprobe is being used. This is usually an issue for colored, highly absorbing species, or very small particles that have low heat transfer. The effects of sample heating are usually observable either as changes in the Raman spectrum over time or by visual inspection of the sample. Besides decreasing the laser flux, a variety of methods can be employed to dimin-

ish laser-induced heating, such as moving the sample or laser during the measurement or improving the heat transfer from the sample with thermal contact or liquid immersion.

Absorption of the Raman signal by the matrix or the sample itself can also occur. This problem is more prevalent with long-wavelength FT-Raman systems where the Raman signal can overlap with an NIR overtone absorption. This effect will be dependent on the optics of the system as well as on the sample presentation. Associated with this effect is variability from scattering in solids as a result of packing and particle-size differences. The magnitude of all of these effects, however, is typically less severe than in NIR because of the limited depth of penetration and the relatively narrower wavelength region sampled in Raman spectroscopy.

Finally, it should be recognized that laser radiation is polarized and the Raman spectra of crystalline materials and other oriented samples can differ significantly depending on the way that the sample is mounted. If the Raman spectrometer is capable of producing linearly polarized radiation at the sample then a polarization scrambler is recommended for routine sample analysis.

Sampling Factors

Raman spectroscopy is a zero-background technique, in that the signal at the detector is expected to be zero in the absence of a sample. This situation can be contrasted with absorption spectrometry, where the signal at the detector is at a maximum in the absence of a sample. Zero-background techniques are inherently sensitive because small changes in sample concentration lead to proportionate changes in the signal level. The instrument will also be sensitive to other sources of light that can cause sample-to-sample variations in the measured signal level. In addition, a large background signal caused by fluorescence will lead to an increased noise level (photon shot noise). Thus it may be very difficult to use the absolute Raman signal for direct determination of an analyte. Other potential sources of variation are changes in the sample opacity and heterogeneity, changes in the laser power at the sample, and changes in optical collection geometry or sample position. These effects can be minimized by sampling in a reproducible, representative manner. Careful design of the instrumentation can reduce these effects but they cannot be eliminated entirely.

Use of an internal reference standard is the most common and robust method of eliminating variations caused by absolute intensity fluctuations. There are several choices for this approach. An internal standard can be deliberately added, and isolated peaks from this standard can be employed or a band due to a moiety such as an aromatic ring, the Raman cross-section of which does not change with the way the sample is prepared, can also be used. For solution spectra, an isolated solvent band can be employed because the solvent will remain relatively unchanged from sample to sample. Also, in a formulation, an excipient peak can be used if it is in substantial excess compared to the analyte. The entire spectrum can also be used as a reference, with the assumption that laser and sample-orientation changes will affect the entire spectrum equally.

A second important sampling-based factor to consider is spectral contamination. Raman scattering is a weak effect that can be masked by a number of external sources. Common contamination sources include sample-holder artifacts (container or substrate) and ambient light. Typically, these issues can be identified and resolved by careful experimentation.

APPARATUS

Components

All modern Raman measurements involve irradiating a sample with a laser, collecting the scattered radiation, rejecting the Rayleigh-scattered light, differentiating the Raman photons by wavelength, and detecting the resulting Raman spectrum. All commercial Raman instruments therefore share the following common features to perform these functions:

1. Excitation source (laser)
2. Sampling device
3. Device to filter/reject light scattered at the laser wavelength
4. Wavelength processing unit
5. Detector and electronics

EXCITATION SOURCE (LASER)

Table 1 identifies several common lasers used for pharmaceutical applications or Raman spectrometry. UV lasers have also been used for specialized applications but have various drawbacks that limit their utility for general analytical measurements. As more applications for UV lasers are described, it is likely that they may become more common for Raman spectrometry.

Table 1. Lasers Used in Pharmaceutical Applications

Laser λ, nm (nearest whole number)	Type	Typical Power at Laser	Wavelength Range, nm (Stokes Region, 100 cm^{-1} to 3000 cm^{-1} shift)	Comments
NIR Lasers				
1064	Solid state (Nd:YAG)	Up to 3W	1075–1563	Commonly used in Fourier transform instruments
830	Diode	Up to 300 mW	827–980	Typically limited to 2000 cm^{-1}; Ramon shift because of CCD spectral response; less common than the other lasers
785	Diode	Up to 500 mW	791–1027	Most widely used dispersive Raman laser
Visible Lasers				
632.8	He–Ne	Up to 500 mW	637–781	Relatively small fluorescence risk
532	Doubled (Nd:YAG)	Up to 1W	535–632.8	High fluorescence risk
514.5	Ar+	Up to 1W	517–608	High fluorescence risk
488–632.8	Ar+	Up to 1W	490–572	High fluorescence risk

SAMPLING DEVICE

Several sampling arrangements are possible, including direct optical interfaces, microscopes, fiber optic-based probes (either noncontact or immersion optics), and sample chambers (including specialty sample holders and automated sample changers). The sampling optics can also be designed to obtain the polarization-dependent Raman spectrum, which often contains additional information. Selection of the sampling device will often be dictated by the analyte and sample. However, considerations such as sampling volume, speed of the measurement, laser safety, and reproducibility of sample presentation should be evaluated to optimize the sampling device for any given application.

FILTERING DEVICE

The intensity of scattered light at the laser wavelength (Rayleigh) is many orders of magnitude greater than the Raman signal and must be rejected prior to the detector. Notch filters are almost universally used for this purpose and provide excellent rejection and stability combined with small size. The traditional use of multistage monochromators for this purpose, although still viable, is now rare. In addition, various filters or physical barriers to shield the sample from external radiation sources (e.g., room lights, laser plasma lines) may be required depending on the collection geometry of the instrument.

WAVELENGTH PROCESSING UNIT

The wavelength scale may be encoded by either a scanning monochromator, a grating polychromator (in CCD-Raman spectrometers) or a two-beam interferometer (in FT-Raman spectrometers). A discussion of the specific benefits and drawbacks of each of the dispersive designs compared to the FT instrument is beyond the scope of this chapter. Any properly qualified instruments should be suitable for qualitative measurements. However, care must be taken when selecting an instrument for quantitative measurements, as dispersion and response linearity might not be uniform across the full spectral range.

DETECTOR

The silicon-based CCD array is the most common detector for dispersive instruments. The cooled array detector allows measurements over the spectral range from 3100 to 100 cm^{-1} Raman shift with low noise even with excitation wavelengths as long as 785 nm. It also has peak wavelength responsivity when matched to the commonly used 632.8-nm He–Ne gas laser or 785-nm diode laser. FT instruments typically use single-channel germanium or indium–gallium–arsenide (InGaAs) detectors responsive in the NIR to match neodymium-doped yttrium–aluminum–garnet (Nd:YAG) 1064-nm excitation.

Calibration

Raman instrument calibration involves three components: primary wavelength (*x*-axis), laser wavelength, and intensity (*y*-axis).

PRIMARY WAVELENGTH (*X*-AXIS)

In the case of FT-Raman instruments, primary wavelength-axis calibration is maintained, at least to a first approximation, with an internal He–Ne laser. Most dispersive instruments utilize atomic emission lamps for primary wavelength-axis calibration. In all instruments suitable for analytical Raman measurements, the vendor will offer a procedure of *x*-axis calibration that can be performed by the user. For dispersive Raman instruments, a calibration based on multiple atomic emission lines is preferred. The validity of this calibration approach can be verified subsequent to laser wavelength calibration by using a suitable Raman shift standard. For scanning

dispersive instruments, calibration might need to be performed more frequently, and precision in both a scanning and static operation mode may need to be verified.[1]

LASER WAVELENGTH

Laser wavelength variation can impact both the wavelength precision and the photometric (signal) precision of a given instrument. Even the most stable current lasers can vary slightly in their measured wavelength output. The laser wavelength must therefore be confirmed to ensure that the Raman shift positions are accurate for both FT-Raman or dispersive Raman instruments. A reference Raman shift standard material such as those outlined in ASTM E1840-96 (2002)[1] or other suitably verified materials can be utilized for this purpose. [NOTE—Reliable Raman shift standard values for frequently used liquid and solid reagents, required for wavenumber calibration of Raman spectrometers, are provided in the ASTM Standard Guide cited. These values can be used in addition to the highly accurate and precise low-pressure arc lamp emission lines that are also available for use in Raman instrument calibration.] Spectrometric grade material can be purchased from appropriate suppliers for this use. Certain instruments may use an internal Raman standard separate from the primary optical path. External calibration devices exactly reproduce the optical path taken by the scattered radiation. [NOTE—When chemical standards are used, care must be taken to avoid contamination and to confirm standard stability.]

Unless the instrument is of a continuous calibration type, the primary wavelength axis calibration should be performed, as per vendor procedures, just prior to measuring the laser wavelength. For external calibration, the Raman shift standard should be placed at the sample location and measured using appropriate acquisition parameters. The peak center of a strong, well-resolved band in the spectral region of interest should be evaluated. The position can be assessed manually or with a suitable, valid peak-picking algorithm. The software provided by the vendor might measure the laser wavelength and adjust the laser wavelength appropriately so that this peak is at the proper position. If the vendor does not provide this functionality, the laser wavelength should be adjusted manually. Depending on the type of laser, the laser wavelength can vary with temperature, current, and voltage. Wavelength tolerances can vary depending on the specific application.

SIGNAL LEVEL (*Y*-AXIS)

Calibration of the photometric axis can be critical for successful quantification by using certain analytical methods (chemometrics) and method transfer between instruments. Both FT-Raman and dispersive Raman spectrometers should undergo similar calibration procedures. The tolerance of photometric precision acceptable for a given measurement should be assessed during the method development stage.

To calibrate the photometric response of a Raman instrument, a broad-band emission source should be used. There are two accepted methods. *Method A* utilizes a tungsten white light source.[2] The output power of such sources is traceable to the National Metrology Institute (NMI). In the United Kingdom, the National Physical Laboratory also provides calibrated light bulbs. Several other vendors also provide NIST-traceable irradiance calibration standards. This method is applicable to all common laser excitation wavelengths listed in *Table 1*. In *Method B,* NIST standard reference materials (SRMs) are utilized.[3] Several doped-glass fluorescence standards are currently available.

Method A—The source should be placed at the sample location with the laser off and the response of the detector measured (using parameters appropriate for the instrument). The

[1] ASTM E1840-96 (2002) Standard Guide for Raman Shift Standards for Spectrometer Calibration, ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA, USA 19428-2959.

[2] NIST-traceable tungsten white light source statement: While the calibration of the Raman frequency (or Raman shift, cm^{-1}) axis using pure materials and an existing ASTM standard is well accepted, techniques for calibration of the Raman intensity axis are not. Intensity calibrations of Raman spectra can be accomplished with certified white light sources.

[3] NIST SRM 2241: Ray KG, McCreery RL. Raman intensity correction standard for systems operating with 785-nm excitation. Appl. Spectrosc. 1997, 51, 108–116.

output for the source used for calibration should be known. The ratio of the measured response to the true response should be determined and a correction file generated. This correction should be applied to all spectra acquired with the instrument. Most manufacturers will provide both appropriate calibration sources and software for this approach. If the manufacturer does not provide a procedure or method, the user can accomplish the task using a source obtained from NIST and appropriate software. If a manufacturer's method is used, attention must be paid to the calibration procedure and source validity. The user should obtain appropriate documentation from the manufacturer to ensure a qualified approach.

Method B—The fluorescence standard should be placed at the sample location. With the laser on, a spectrum of the SRM should be obtained (using parameters appropriate for the instrument). The output of the source used for calibration should be known. The ratio of the measured response to the true response should be determined and a correction file generated. This correction should be applied to all spectra acquired with the instrument. Most manufacturers will provide both appropriate calibration sources and software for this approach. If the manufacturer does not provide a procedure or method, the user can accomplish the task using a source obtained from NIST and appropriate software. If a manufacturer's method is used, attention must be paid to the calibration procedure and source validity. The user should obtain appropriate documentation from the manufacturer to ensure a qualified approach. [NOTE—*Method B* is currently appropriate for systems with 785-nm (SRM 2241), 532-nm (SRM 2242), and both 514.5-nm and 488-nm (SRM 2243) laser excitation. NIST is currently developing other SRMs that will be wavelength-specific for 1064-nm (SRM 2244) and 632.8-nm excitation (expected to be available in 2006).]

EXTERNAL CALIBRATION

Detailed functional validation employing external reference standards is recommended to demonstrate instrumental suitability for laboratory instruments, even for instruments that possess an internal calibration approach. The use of external reference standards does not obviate the need for internal quality control procedures; rather, it provides independent documentation of the fitness of the instrument to perform the specific analysis or purpose. For instruments installed in a process location or in a reactor where positioning of an external standard routinely is not possible, including those instruments that employ an internal calibration approach, the relative performance of an internal versus an external calibration approach should be periodically checked. The purpose of this test is to check for changes in components that might not be included in the internal calibration method (process lens, fiber-optic probe, etc.), e.g., photometric calibration of the optical system.

QUALIFICATION AND VERIFICATION OF RAMAN SPECTROMETERS

The suitability of a specific instrument for a given method is ensured by a thorough technology-suitability evaluation for the application; a routine, periodic instrument operational qualification; and the more frequent performance verification (see *Definition of Terms and Symbols*). The purpose of the technology-suitability evaluation is to ensure that the technology proposed is suitable for the intended application. The purpose of the instrument qualification is to ensure that the instrument to be used is suitable for its intended application and, when requalified periodically, continues to function properly over extended time periods. When the device is used for a specific qualitative or quantitative analysis, regular performance verifications are made. Because there are many different approaches to measuring Raman spectra, instrument operational qualification and performance verification often employ external standards that can be used on any instrument.

As with any spectrometric device, a Raman instrument needs to be qualified for both wavenumber (*x*-axis and shift from the excitation source) and photometric (signal axis) precision.

In performance verification, a quality-of-fit to an initial scan or group of scans (often referred to in nonscanning instruments as an accumulation) included in the instrumental qualification can be employed. In such an analysis, it is assumed that reference standard spectra collected on a new or a newly repaired, properly operating instrument represent the best available spectra. Comparison of spectra taken over time on identical reference standards (either the original standard or identical new standards [if stability of the reference standards is a concern]) forms the basis for evaluating the long-term stability of a Raman measurement system.

Frequency of Testing

Instrumental qualification is performed at designated intervals or following a repair or significant optical reconfiguration, such as the replacement of the laser, the detector or the notch or edge filters. Full instrument requalification might not be necessary when changing between sampling accessories such as a microprobe, a sample compartment, or a fixed fiber-optic probe. Performance verification tests may be sufficient in these cases; instrument-specific guidance from the vendor on qualification requirements should be followed. Tests include wavelength (*x*-axis and shift from the excitation source) and photometric (signal axis) precision. Instrument qualification tests require that specific application-dependent tolerances be met.

Performance verification is carried out on the instrument configured for the analytical measurements and is performed more frequently than instrument qualification. Performance verification includes measurement of the wavelength uncertainty and intensity-scale precision. Wavelength precision and intensity-scale precision tests may be needed prior to any data collection on a given day. Performance is verified by matching the current spectra to those collected during the previous instrument qualification.

Instrument Operational Qualification

It is important to note that the acceptance specifications given in both the *Instrument Operational Qualification* and *Performance Qualification* sections are applicable for general use; specifications for particular instruments and applications can vary depending on the analysis method used and the desired accuracy of the final result. ASTM standard reference materials are also specified, with the understanding that under some circumstances (specifically remote on-line applications) calibration using one of these materials may be impractical, and other suitably verified materials can be employed. At this juncture it is important to note that specific parameters such as spectrometer noise, limits of detection (LOD), limits of quantification (LOQ), and acceptable spectral bandwidth for any given application should be included as part of the analytical method development. Specific values for tests such as spectrometer noise and bandwidth will be dependent on the instrument chosen and the purpose required. As a result, specific instrument tests for these parameters are not dictated in this information chapter.

WAVELENGTH (*X*-AXIS) ACCURACY

It is important to ensure the accuracy of the wavelength axis via calibration to maintain the integrity of Raman peak positions. Wavelength calibration of a Raman spectrometer consists of two parts: primary wavelength axis and laser wavelength calibration. After both the primary wavelength axis and the laser wavelength are calibrated, instrument wavelength uncertainty can be determined. This can be accomplished using a Raman shift standard such as the ASTM shift standards or other suitably verified material. Selection of a standard with bands present across the full Raman spectral

range is recommended so that instrument wavelength uncertainty can be evaluated at multiple locations within the spectrum. The tolerance of wavelength precision that is required for a given measurement should be assessed during the method-development stage. [NOTE—For scanning dispersive instruments, calibration might need to be performed more frequently, and precision in both a scanning and static operation mode may need to be verified.]

PHOTOMETRIC PRECISION

Laser variation in terms of the total emitted photons occurring between two measurements can give rise to changes in the photometric precision of the instrument. Unfortunately, it is very difficult to separate changes in the photometric response associated with variations in the total emitted laser photons from the sample- and sampling-induced perturbations. This is one of the reasons why absolute Raman measurements are strongly discouraged and why the photometric precision specification is set relatively loosely. The tolerance of photometric precision required for a given measurement should be assessed during the method-development stage.

PERFORMANCE QUALIFICATION

The objective of performance qualification is to ensure that the instrument is performing within specified limits with respect to wavelength precision, photometric axis precision, and sensitivity. In certain cases when the instrument has been set up for a specific measurement (for example, installed in a process reactor), it might no longer be possible or desirable to measure the wavelength and photometric (signal) qualification reference standards identified above. Provided instrument operational qualification has shown that the equipment is fit for use, a single external performance verification standard can be used to reverify function on a continuing basis (for example, a routinely used process solvent signal, for both wavelength and photometric precision, following reactor cleaning). The performance verification standard should match the format of the samples in the current analysis as closely as possible and use similar spectral acquisition parameters. Quantitative measurements of an external performance verification standard spectrum check both the wavelength (*x*-axis and laser wavelength) and the photometric (signal) precision. Favorable comparison of a series of performance verification spectra demonstrates proper continued operation of the instrument.

WAVELENGTH PRECISION

The wavelength precision should be measured by collecting data for a single spectrum of the selected Raman shift standard for a period equal to that used in the photometric consistency test. When appropriate, powdered samples should be repacked between each set of measurements. Peak positions across the spectral range of interest are used to calculate precision. Performance is verified by matching the current peak positions to those collected during the previous instrument qualification and should not vary with a standard deviation of more than ± 0.3 cm^{-1}, although this specification can be adjusted according to the required accuracy of the measurement.

PHOTOMETRIC PRECISION

The photometric precision should be measured by collecting data for a single spectrum of a suitably verified reference standard material for a specified time. After suitable baseline correction, the areas of a number of bands across the spectral range of interest should be calculated by means of an appropriate algorithm. The area of the strongest band is set to 1, and all other envelopes are normalized to this band. Performance is verified by matching the current band areas to the respective areas collected during the previous instrument qualification. The areas should vary by no more than 10%, although this specification can be adjusted according to the required accuracy of the measurement.

LASER POWER OUTPUT PRECISION AND ACCURACY

This test is applicable only to Raman instruments with automatic, internal laser power meters. Instruments without laser power measurement should utilize a calibrated laser power meter from a reputable supplier. The laser output should be set to a representative output, dictated by the requirements of the analytical measurement and the laser power measured. The output should be measured and checked against the output measured at instrument qualification. The power (in milliwatts or watts) should vary by no more than 25% compared to the qualified level. If the power varies by more than this amount, the instrument should be serviced (as this variation might indicate, among other things, a gross misalignment of the system or the onset of failure of the laser).

For instruments with an automatic, internal laser power meter, the accuracy of the values generated from the internal power meter should be compared to a calibrated external laser power meter at an interval of not more than 12 months. The internally calculated value should be compared to that generated by the external power meter. Performance is verified by matching the current value to that generated during the previous instrument qualification. The manufacturer might provide software to facilitate this analysis. If the instrument design prevents the use of an external power meter, then the supplier should produce documentation to ensure the quality of the instrument and provide a recommended procedure for the above analysis to be accomplished during a scheduled service visit.

METHOD VALIDATION

Validation of Raman methods will follow the same protocols described in *Validation of Compendial Methods* ⟨1225⟩ in terms of accuracy, precision, etc. However, several of these criteria are affected by variables specific to Raman spectrometry. Fluorescence is the primary variable that can affect the suitability of a method. The presence of fluorescent impurities in samples can be quite variable and have little effect on the acceptability of a material. The method must be flexible enough to accommodate different sampling regimes that may be necessary to minimize the effects of these impurities.

Detector linearity must be confirmed over the range of possible signal levels. Fluorescence might drive both the signal baseline and the noise higher than that used in the validation, in which case the fluorescence must be decreased, or the method modified to accommodate the higher fluorescence levels. This is also true for the precision, limit of detection, and limit of quantification of the method, as increased baseline noise will negatively impact all of these values. Because fluorescence can also affect quantification caused by baseline shifts, acceptable quantification at different levels of photobleaching, when used, should also be confirmed.

The impact of the laser on the sample must be determined. Visual inspection of the sample and qualitative inspection of the Raman spectrum for measurements with differing laser powers and exposure times will confirm that the sample is not being altered (other than by photobleaching). Specific variables to confirm in the spectrum are shifts in peak position, changes in peak height and band width, and unexpected changes in background intensity.

Method precision must also encompass sample position. The sample presentation is a critical factor for both solids and liquids, and must be either tightly controlled or accounted for in the calibration model. Sample-position sensitivity can often be minimized by appropriate sample preparation or sample holder geometry, but will vary from instrument to instrument based on excitation and collection optical configuration.

DEFINITION OF TERMS AND SYMBOLS

CALIBRATION MODEL is a mathematical expression that relates the response from an analytical instrument to the properties of samples.

INSTRUMENT BANDPASS (OR RESOLUTION) is a measure of the capability of a spectrometer to separate radiation of similar wavelengths.

OPERATIONAL QUALIFICATION is the process by which it is demonstrated and documented that the instrument performs according to specifications, and that it can perform the intended task. This process is required following any significant change such as instrument installation, relocation, major repair, etc.

PERFORMANCE QUALIFICATION is the process of using one or more well-characterized and stable reference materials to verify consistent instrument performance. Qualification may employ the same or different standards for different performance characteristics.

RAMAN SPECTRA[4] are plots of the radiant energy, or number of photons, scattered by the sample through the indirect interaction between the molecular vibrations in the sample and monochromatic radiation of frequency much higher than that of the vibrations. The abscissa is usually the difference in wavenumber between the incident and scattered radiation.

(NORMAL) RAMAN SCATTERING[4] is the inelastic scattering of radiation that occurs because of changes in the polarizability, of the relevant bonds during a molecular vibration. Normal Raman spectra are excited by radiation that is not in resonance with electronic transitions in the sample.

RAMAN WAVENUMBER SHIFT[4],

$$\Delta\tilde{\nu}$$

is the wavenumber of the exciting line minus the wavenumber of the scattered radiation. SI unit: m^{-1}. Common unit: cm^{-1} = 100 m^{-1}.

$$\beta\Delta\tilde{\nu}$$

is positive for Stokes scattering and negative for anti-Stokes scattering.■2S (*USP30*)

[4] Chalmers, J., Griffiths, P., Eds. Handbook of Vibrational Spectroscopy; John Wiley & Sons, Ltd: New York, 2002.

BRIEFING

〈**1121**〉 **Nomenclature,** *USP 29* page 2988. It is proposed to update this general information chapter by adding the following new sections: (1) *General Nomenclature Forms,* (2) *Salt Nomenclature Policy,* and (3) *Policy for Postponement Schedules*. Other proposed changes are editorial in nature.

(NOM: W. Paul) RTS—C44903

Change to read:

The *USP* (or *NF*) titles

■for monograph articles■2S (*USP30*)
are legally recognized

■under the Federal Food, Drug, and Cosmetic Act■2S (*USP30*)
as the designations for use in labeling the articles to which they apply.

The value of designating each drug by one and only one nonproprietary[1] name is ~~obvious,~~

■important■2S (*USP30*)
in terms of achieving simplicity and uniformity in drug nomenclature. In support of the U.S. Adopted Names program (see *Mission and Preface* in *USP–NF*), of which the U.S. Pharmacopeial Convention is a cosponsor, the USP ~~Committee of Revision~~

■Council of Experts■2S (*USP30*)
gives consideration to the adoption of the U.S. Adopted Name, if any, as the official title for any compound that attains compendial recognition.

A compilation of the U.S. Adopted Names (USAN) published from the start of the USAN program in 1961, as well as other names for drugs, both current and retrospective, is provided in ~~*USAN and the USP Dictionary of Drug Names.*~~

■the *USP Dictionary of USAN and International Drug Names.*■2S (*USP30*)
This publication serves as a book of names useful for identifying and distinguishing all kinds of names for drugs, whether public, proprietary, chemical, or code-designated names.[2]

A nonproprietary name of a drug serves numerous and varied purposes, its principal function being to identify the substance to which it applies by means of a designation that may be used by the professional and lay public free from the restrictions associated with registered trademarks. Teaching in ~~pharmacy and medicine~~

■the health sciences■2S (*USP30*)
requires a common designation, especially for a drug that is available from several sources or is incorporated into a combination drug product; nonproprietary names facilitate communication among ~~physicians;~~

■healthcare providers;■2S (*USP30*)
nonproprietary names must be used as the titles of the articles recognized by official drug compendia; a nonproprietary name is essential to the pharmaceutical manufacturer as a means of protecting trade-

[1] The term "generic" has been widely used in place of the more accurate and descriptive term "nonproprietary" with reference to drug nomenclature.

[2] ~~*USAN and the USP Dictionary of Drug Names*~~

■*USP Dictionary of USAN and International Drug Names*■2S (*USP30*)
is obtainable on order from ~~the USAN Division, USP Convention, Inc.,~~

■U. S. Pharmacopeia, Customer Service Department,■2S (*USP30*)
12601 Twinbrook Parkway, Rockville, MD 20852.

mark rights in the brand name for the article concerned; and, finally, the manufacturer is obligated by federal law to include the established nonproprietary name in advertising and labeling.

Under the terms of the Drug Amendments of 1962 to the Federal Food, Drug, and Cosmetic Act, which became law October 10, 1962, the Secretary of Health and Human Services is authorized to designate an official name for any drug wherever deemed "necessary or desirable in the interest of usefulness and simplicity."[3]

The Commissioner of Food and Drugs and the Secretary of Health and Human Services published in the *Federal Register* regulations effective November 26, 1984, which state, in part:

"Sec. 299.4 Established names of drugs."

"(e) The Food and Drug Administration will not routinely designate official names under section 508 of the act. As a result, the established name under section 502(e) of the act will ordinarily be either the compendial name of the drug or, if there is no compendial name, the common ~~or~~

■and■2S (*USP30*)
usual name of the drug. Interested persons, in the absence of the designation by the Food and Drug Administration of an official name, may rely on as the established name for any drug the current compendial name or the USAN adopted name listed in *USAN and the USP Dictionary of Drug Names.*"[4]

It will be noted that the monographs on the biologics, which are produced under licenses issued by the Secretary of the U.S. Department of Health and Human Services, represent a special case. Although efforts continue toward achieving uniformity, there may be a difference between the respective title required by federal law and the USP title. Such differences are fewer than in past revisions of the Pharmacopeia. The USP title, where different from the FDA ~~Bureau of Biologics~~

■Center for Biologics Evaluation and Research■2S (*USP30*)
title, does not necessarily constitute a synonym for labeling purposes; the conditions of licensing the biologic concerned require that each such article be designated by the name appearing in the product license issued to the manufacturer. Where a USP title differs from the title in the federal regulations, the former has been adopted with a view to usefulness, simplicity, and conformity with the principles governing the selection of monograph titles generally.

Add the following:

■GENERAL NOMENCLATURE FORMS

Some monograph titles existing in the *USP–NF* do not conform to the formats outlined in this general information chapter. Typically, these monograph titles were adopted before the establishment of the title formats and nomenclature policies presented in this general information chapter. Such monograph titles may be subject to subsequent revision and should not be interpreted as precedents for other monograph titles.

Standardized forms of nomenclature have been devised in the interest of achieving uniformity for naming compendial articles. The general nomenclature forms that follow illustrate the terminology used throughout the official compendia for consistency in establishing titles of monographs on official pharmaceutical dosage forms and preparations. Examples are shown for the more frequently encountered categories of dosage forms.

For a variety of dosage forms, titles are in the following general form:

[DRUG][ROUTE OF ADMINISTRATION]
[DOSAGE FORM]

Examples:

Calcium Carbonate Oral Suspension
Cetylpyridinium Chloride Topical Solution
Dexamethasone Ophthalmic Suspension
Epinephrine Bitartrate Ophthalmic Solution
Isosorbide Dinitrate Sublingual Tablets
Miconazole Nitrate Topical Powder
Triple Sulfa Vaginal Cream

The term for route of administration is omitted for those dosage forms for which the route of administration is understood. The general form then becomes simply

[DRUG] [DOSAGE FORM]

Thus, capsules, tablets, and lozenges are administered via the oral route unless otherwise indicated by the title.

Examples:

Acetaminophen Capsules
Aminophylline Delayed-Release Tablets
Aspirin Extended-Release Tablets
Hexylresorcinol Lozenges
Meperidine Hydrochloride Tablets

Drugs that are injected may be administered via the intravenous, intramuscular, subcutaneous, etc., route; the route being specified in the labeling rather than in the name.

Examples:

Aurothioglucose Injectable Suspension
Epinephrine Injection
Fluorouracil Injection

[3] F.D.&C. Act, Sec. 508 [358].
[4] 53 Fed. Reg. 5369 (1988) amending 21 CFR § 299.4.

Hydrocortisone Acetate Injectable Suspension

Phytonadione Injectable Emulsion

Creams, ointments, lotions, and pastes are applied topically, unless otherwise indicated by the name.

Examples:

Benzoyl Peroxide Lotion

Betamethasone Dipropionate Cream

Estradiol Vaginal Cream

Nystatin Ointment

Zinc Oxide Paste

The term ''for'' is included in names, as appropriate, of preparations for which a solid drug substance must be dissolved or suspended in a suitable liquid to obtain a dosage form, and the general form becomes

[DRUG] FOR [ROUTE OF ADMINISTRATION][DOSAGE FORM]

Examples:

Ampicillin for Oral Suspension

Epinephrine Bitartrate for Ophthalmic Solution

Nafcillin for Injection

Spectinomycin for Injectable Suspension

In some instances, the drug is supplied in one dosage form for the preparation of the intended dosage form.

Examples:

Aspirin Effervescent Tablets for Oral Solution

Methadone Hydrochloride Tablets for Oral Suspension

Papain Tablets for Topical Solution

Systems are preparations of drugs in carrier devices that are applied topically or inserted into body cavities, from which drugs are released gradually over extended times, after which the carrier device is removed. The general form for a system is

[DRUG] [ROUTE] [SYSTEM]

Examples:

Nicotine Transdermal System

Progesterone Intrauterine Contraceptive System

The term ''Vaginal Inserts'', rather than ''Vaginal Tablets'' and ''Vaginal Capsules'', is used in the title of this type of vaginal preparation to avoid the potential for misuse of these products if only the term ''Tablets'' or ''Capsules'' were to appear in the title.

Example:

Clotrimazole Vaginal Inserts

The term ''Suppositories'' is used in the titles of preparations that are intended primarily for rectal administration. Suppositories that are intended for vaginal administration contain the term ''Vaginal Suppositories'' in the titles.

Examples:

Aspirin Suppositories

Miconazole Nitrate Vaginal Suppositories

Some drugs are available as concentrated solutions that are not intended for direct administration to humans or animals, but are to be diluted with suitable liquid vehicles to obtain the intended preparation. The general form for these preparations, which are not dosage forms, is

[DRUG][CONCENTRATE]

Examples:

Isosorbide Concentrate (used to prepare Isosorbide Oral Solution)

Glutaral Concentrate (used to prepare Glutaral Disinfectant Solution)

For products intended for parenteral administration, the use of the word ''Concentrate'' in the monograph title is restricted to one specific monograph, Potassium Chloride for Injection Concentrate. The word ''Concentrate'' should not appear in the monograph title for any other parenteral product; rather, this issue is to be addressed in the product labeling.

Some drugs are supplied as preparations that may be intermediates used for convenience in formulating finished dosage forms. The general form for such preparations, which are not finished dosage forms, is

[DRUG][PREPARATION]

Examples:

Vitamin E Preparation

Cranberry Liquid Preparation■2S (*USP30*)

Add the following:

▪SALT NOMENCLATURE POLICY

The USP follows the policy below for naming dosage form monographs:

> The term used in the title of a monograph for a dosage form formulated with a salt of an acid or base shall be the same as that used in expressing the strength of the article.
>
> Where the strength is expressed in terms of the salt, the same salt name is used in the monograph title.
>
> Where the strength is expressed in terms of the free acid or base, the same acid or base name is used in the monograph title.

With this policy, the dosage form monograph title uses the name of the molecule on which dosing and monitoring are based. Exceptions to the policy may rarely be made with suitable justification.

The application of this policy (1) is based on the strength that appears in FDA-approved labeling, (2) is intended for use in titles of monographs on dosage forms formulated from salts of organic acids and bases, (3) is not used in titles of dosage form monographs defined as containing esters, and (4) is not used in titles of drug substance monographs.

The *Salt Nomenclature Policy* is followed by USP in naming dosage forms that are newly admitted to the *United States Pharmacopeia.* Revising existing monographs on dosage forms to conform to the policy is not intended, except in cases where other revisions to the monograph would require labeling changes or where the USP Council of Experts determines that, for reasons such as safety, a nomenclature change is warranted.

When existing monographs are being revised or when new monographs that will require relabeling of the products are adopted, a delayed implementation of official dates of change of nomenclature and labeling is usually followed. Exceptions to the approach using a delayed implementation date are considered on an individual basis. For example, an earlier rather than a delayed implementation date may be considered in cases where public health and safety are an issue.■2S (*USP30*)

Add the following:

▪POLICY FOR POSTPONEMENT SCHEDULES

It is the practice of USP to postpone the official dates of nomenclature and labeling revisions for a reasonable time primarily to allow for product label changes to be made and to allow health practitioners and consumers time to become familiar with the new terminology. A postponement period of 18 months is usually applied when only one or a small number of products is affected. A postponement period of 30 months is usually applied when names or labeling of multisource products or multiproduct lines of a firm's preparations are being changed. A postponement period of 60 months is usually applied for title and labeling changes that affect excipients, because such changes would require relabeling of very large numbers of prescription-only and OTC preparations.

There may be exceptions to this postponement schedule where a shorter time is needed in order to specify nomenclature and labeling changes in cases where public health and safety are a concern.

The assignment of a postponement schedule is handled by the USP Expert Committee on Nomenclature. The postponement schedules are presented below. USP's implementation of a postponement schedule is automatic, unless an exception is sought. Exceptions to the postponement schedule are rarely made, and must have suitable justification as well as the ap-

proval of the Expert Committee on Nomenclature. Any questions or concerns regarding this postponement schedule may be addressed to the USP staff liaison assigned to the Expert Committee on Nomenclature.

18 months—Schedule for title and labeling changes for a drug product. One or few companies are involved. *Example:* Sterile [Drug] change to [Drug] for Injection.

30 months—Schedule for title and labeling changes for prescription-only and OTC products.

1. Extensive product line for a company. *Examples:* syrups and elixirs.
2. Several companies are involved. *Examples:* syrups and elixirs; lotions; sunscreens.

60 months—Schedule for title and labeling changes for excipient monographs. Ingredient names in numerous multisource products are affected.■2S (*USP30*)

BRIEFING

⟨**1150**⟩ **Pharmaceutical Stability,** *USP 29* page 2994. It is proposed to revise this general chapter to include *Controlled Cold Temperature,* which was proposed to be added in the *General Notices and Requirements* on page 721 of *PF* 31(3) [May–June 2005] under *Preservation, Packaging, Storage, and Labeling* (see *Storage Temperature and Humidity*) and will become official in the *Second Supplement* to *USP 29–NF 24* with an official date of August 1, 2006.

(P&S: D. Hunt) RTS—C45420

Change to read:

Controlled Room Temperature

▪and Controlled Cold Temperature■2S (*USP30*)

Controlled room temperature

▪and controlled cold temperature■2S (*USP30*)
(see *Storage Temperature and Humidity* in *Preservation, Packaging, Storage, and Labeling* under *General Notices and Requirements*) delineate the allowable tolerance in storage circumstances at any location in the chain of distribution (e.g., pharmacies, hospitals, and warehouses). These terminologies also allow patients or consumers to be counseled as to appropriate storage for the product. Products may be labeled either to store at controlled room temperature or to store at temperatures "up to 25°" where labeling is supported by long-term stability studies at the designated storage condition of 25°. *Controlled Room Temperature* limits the permissible excursions to those consistent with the maintenance of a mean kinetic temperature calculated to be not more than 25°.

▪Products may be labeled either to store at controlled cold temperature or to store at temperatures "up to 8°" where labeling is supported by long-term stability studies at the designated storage condition of 8°. *Controlled Cold Temperature* limits the permissible excursions to those consistent with the maintenance of a mean kinetic temperature calculated to be not more than 8°.■2S (*USP30*)
See *Mean Kinetic Temperature.* The common international guideline for long-term stability studies specifies 25 ± 2° at 60 ± 5% relative humidity. Accelerated studies are specified at 40 ± 2° and at 75 ± 5% relative humidity. Accelerated studies also allow the interpretation of data and information on short-term spikes in storage conditions in addition to the excursions allowed by controlled room temperature.

The term "room temperature" is used in different ways in different countries, and for products to be shipped outside the continental U.S. it is usually preferable for product labeling to refer to a maximum storage temperature or temperature range in degrees Celsius.

BRIEFING

⟨**1226**⟩ **Verification of Compendial Procedures,** page 555 of *PF* 31(2) [Mar.–Apr. 2005]. On the basis of numerous comments received following this general information chapter's initial publication and its presentation at the USP Annual Scientific Meeting in San Diego in September 2005, a newly proposed version is presented that attempts to incorporate these comments in order to provide general information on verifying the suitability of a compendial procedure under actual conditions of use, as stated in 21 CFR 211.194(a)(2). Requirements for compendial procedure verification are currently not addressed by regulatory authorities and standards-setting organizations; therefore the goal of this chapter is to clarify the topic and provide consistency between laboratories and regulatory agencies. This revised version provides a high-level view of the verification process. Although *Tables 1* and *2* were removed, a description of how the performance characteristics might be applied to method verification is mentioned. This would still provide the necessary guidance, while allowing the user the flexibility to determine which performance characteristics are most appropriate for the method being verified. Also included is language stating that this chapter is not intended for retroactive application to already successfully established laboratory procedures.

(GC: H. Pappa) RTS—C43714; 43045; 43047; 43068; 43100; 43101; 43141; 43164; 43180; 43287; 43314; 43315; 43316

In-Process Revision

Add the following:

■⟨1226⟩ VERIFICATION OF COMPENDIAL PROCEDURES

~~Calibration, validation, and traceability are core metrological components. The validation of analytical procedures is a standard practice in pharmaceutical analytical laboratories because it ensures the accuracy and reliability of generated data. General information chapter *Validation of Compendial Methods* ⟨1225⟩ provides guidance on characteristics that should be evaluated for various test categories and on the documentation that should accompany analytical procedures submitted for inclusion in *USP–NF*. Chapter ⟨1225⟩ does not provide guidance on verifying the suitability of compendial procedures. The intent of general information chapter ⟨1226⟩ is to provide guidance to laboratories on how to verify that a compendial procedure that is being performed for the first time will yield acceptable results utilizing the laboratories' personnel, equipment, and reagents. Verification consists of assessing selected *Analytical Performance Characteristics,* which are described in chapter ⟨1225⟩, to generate appropriate, relevant data rather than repeating the validation process.~~

~~Users of compendial analytical procedures are not required to validate these procedures when first used in their laboratories, but suitability should be established under actual conditions of use. In the United States, this requirement is established in 21 CFR 211.194(a)(2), which states that "the suitability of all testing methods used shall be verified under actual conditions of use." In cases where multiple sites or laboratories will perform the monograph test for the first time, one laboratory may verify the suitability of the procedure, and then conduct a procedure transfer to the other locations.~~

~~Microbiological procedures are not included in this chapter because they are covered in USP general chapters *Antimicrobial Effectiveness Testing* ⟨51⟩, *Microbial Limit Tests* ⟨61⟩, *Sterility Tests* ⟨71⟩, and *Validation of Microbial Recovery from Pharmacopeial Articles* ⟨1227⟩.~~

~~VERIFICATION PROCESS~~

~~Laboratory personnel should have the appropriate experience, knowledge, and training to understand and be able to perform the compendial procedure as written. An approved document should be available prior to performing the compendial procedure; this document describes the procedure to be verified, establishes the number and identity of lots or batches of articles that will be used in the verification test, details the analytical performance characteristics (see *Table 1*) to be evaluated, and specifies the range of results that will be considered acceptable. Any deviation from the recommendations in chapter ⟨1226⟩ should be justified in this documentation. Acceptance criteria should be established such that results meeting the requirements will provide confidence that the compendial procedure will perform suitably. Typically, the acceptance criteria would be more stringent than the compendial monograph specifications for the test.~~

~~Once the samples described in the verification document are analyzed, the data should be compared to the predetermined and approved acceptance criteria and the results documented. Documentation should include a summary of the analytical data, an assessment of the results and comparison to the acceptance criteria, and a conclusion as to the acceptability of the data as they relate to the ability of the laboratory analysts to successfully perform the compendial procedure in the particular laboratory. Once the results are shown to be acceptable, it can be concluded that the USP procedure will perform in the laboratory as intended.~~

~~If any of the acceptance criteria are not met, the source of the problem should be identified and corrective action, where appropriate, should be initiated (e.g., providing additional training for the laboratory analyst, or contacting USP staff for clarification of the procedure). Revisions to the verification document to include the implemented corrective actions should be made before the procedure is repeated. The initial unacceptable results, the most probable cause, and corrective actions implemented should be described in the final document.~~

If, after several attempts, the verification of the compendial procedure is not successful, and assistance from USP staff has not resolved the problem, it may be concluded that the procedure may not be suitable for use with the article being tested. It may then be necessary to develop and validate an alternate procedure and submit the data to USP with a recommendation to replace the current compendial procedure with the new procedure. In some situations it may be possible to revise the current procedure by adding the new procedure as an alternative to the current procedure.[+] The final internal verification documentation should summarize the inability to verify the compendial procedure and describe the action that was taken.

ANALYTICAL PERFORMANCE CHARACTERISTICS

The analytical performance characteristics that are typically included in the validation of procedures and that should be considered for the verification process are defined in general information chapter ⟨1225⟩.

Table 2 in chapter ⟨1225⟩ lists the analytical performance characteristics to be determined for several categories of assays to ensure that the procedure is validated. However, not all of the characteristics listed in chapter ⟨1225⟩, *Table 2,* need to be repeated for the verification of the compendial procedure in a laboratory. Depending on the type of test to be verified, different analytical performance characteristics should be studied.

Table 1 in this chapter includes examples of analytical performance characteristics that should be studied for various common analytical techniques applied to drug substances and excipients; corresponding information for dosage forms for each of the categories is presented in *Table 2* of this chapter. For several of the categories, the number of analytical performance characteristics to be studied for dosage forms is generally larger than that for excipients or drug substances because of the greater complexity of a drug product. Where the technique is not suitable for the category, no data elements are displayed in the table.

In addition to the analytical performance characteristics summarized in *Table 1,* the evaluation of other characteristics may be considered in order to provide further assurance that the procedure will continue to perform as intended when unplanned changes occur in analysts, equipment, reagent, or environmental conditions, or when deliberate adjustments are made in procedure parameters. The sensitivity of the procedure to these changes can be measured by a robustness study. An appropriate ruggedness study may be necessary if there is a possibility that the procedure will be used by more than one analyst or if the procedure is to be transferred to multiple company sites or laboratories. The design of the ruggedness study will depend on how the procedure will be used. The definition of ruggedness and robustness can be found in chapter ⟨1225⟩. Verification is not required for general tests such as residue on ignition, unless there is a reason to suspect that the compendial procedure is not appropriate for the article under test.

[+] Request for revision includes both new monograph or general chapters and suggested changes to existing monographs and general chapters. See the USP Guideline for Submitting Requests for Revision to the USP–NF.

Table 1. Data Elements for Verification of Drug Substances and Excipients

Technique	Category I	Category II		Category III	Category IV
		Quantitative	Limit Tests		
HPLC/GC	Precision	Precision Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity
Spectrophotometric/colorimetric	Precision	Precision Quantitation Limit	Specificity Detection Limit	—	Specificity
Titrimetric	Precision	Precision	—	—	—
TLC	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity
Gel Electrophoresis	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity

-

- *Category I:* Analytical procedures for quantitation of major components of drug substances or active ingredients (including preservatives) in finished dosage forms.
- *Category II:* Analytical procedures for determination of impurities in drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.
- *Category III:* Analytical procedures for determination of performance characteristics (e.g., dissolution, drug release).
- *Category IV:* Identification procedures.

Table 2. Data Elements for Verification of Dosage Forms

Technique	Category I	Category II		Category III	Category IV
		Quantitative	Limit Tests		
HPLC/GC	Precision Specificity Linearity Range	Precision Specificity Quantitation Limit	Specificity Detection Limit	Precision	Specificity
Spectrophotometric/colorimetric	Precision Linearity Range	Precision Quantitation Limit	Specificity Detection Limit	Precision	Specificity
Titrimetric	Precision Linearity Range	Precision	—	—	—
TLC	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity
Gel Electrophoresis	—	Specificity Quantitation Limit	Specificity Detection Limit	—	Specificity

-

- *Category I:* Analytical procedures for quantitation of major components of drug substances or active ingredients (including preservatives) in finished dosage forms.
- *Category II:* Analytical procedures for determination of impurities in drug substances or degradation compounds in finished pharmaceutical products. These procedures include quantitative assays and limit tests.
- *Category III:* Analytical procedures for determination of performance characteristics (e.g., dissolution, drug release).
- *Category IV:* Identification procedures.

In-Process Revision

The intent of this chapter is to provide general information to laboratories on the verification of compendial procedures that are being performed for the first time to yield acceptable results utilizing the laboratories' personnel, equipment, and reagents. This chapter is not intended for retroactive application to already successfully established laboratory procedures. The chapter *Validation of Compendial Procedures* ⟨1225⟩ provides general information on characteristics that should be evaluated for various test categories and on the documentation that should accompany analytical procedures submitted for inclusion in *USP–NF.* Verification consists of assessing selected analytical performance characteristics, such as those that are described in chapter ⟨1225⟩, to generate appropriate, relevant data rather than repeating the validation process.

Users of compendial analytical procedures are typically not required to validate these procedures when first used in their laboratories, but documented evidence of suitability should be established under actual conditions of use. In the United States, this requirement is established in 21 CFR 211.194(a)(2) of the current Good Manufacturing Practice regulations, which states that the ''suitability of all testing methods used shall be verified under actual conditions of use.''

Verification of microbiological procedures is not covered in this chapter because it is covered in USP general chapters *Antimicrobial Effectiveness* ⟨51⟩, *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩, *Sterility Tests* ⟨71⟩, and *Validation of Microbial Recovery from Pharmacopeial Articles* ⟨1227⟩.

VERIFICATION PROCESS

Laboratory personnel should have the appropriate experience, knowledge, and training to understand and be able to perform the compendial procedures as written. Acceptance criteria for verification should be established such that results meeting the requirements will provide confidence that the compendial procedure will perform suitably as intended.

If the verification of the compendial procedure is not successful, and assistance from USP staff has not resolved the problem, it may be concluded that the procedure may not be suitable for use with the article being tested in that laboratory. It may then be necessary to develop and validate an alternate procedure as allowed in the *General Notices*. The alternate procedure may be submitted to USP, along with the appropriate data, to support a proposal for inclusion or replacement of the current compendial procedure.

VERIFICATION REQUIREMENTS

Verification requirements should be based on an assessment of the complexity of both the procedure and the material to which the procedure is applied. Although complete revalidation of a compendial method is not required to verify the suitability of the method under actual conditions of use, some of the analytical performance characteristics listed in chapter ⟨1225⟩, *Table 2,* may be used for the verification process. Only those characteristics that are considered to be appropriate for the verification of the particular method need to be evaluated. This implies that a verification continuum exists in terms of which and how many analytical procedural characteristics need to be evaluated for any one USP procedure. The degree and extent of the verification process will depend on the level of training and experience of the laboratory personnel, on the type of procedure and its associated equipment or instrumentation, on the specific procedural steps, and on which article(s) are being tested.

As an example, an assessment of specificity is a key parameter in verifying that a compendial procedure is suitable for use in assaying drug substances and drug products. For instance, acceptable specificity for a chromatographic method may be verified by conformance with system suitability resolution requirements (if specified in the method). However, drug substances from different suppliers may have different

impurity profiles that are not addressed by the compendial test procedure. Similarly, the excipients in a drug product can vary widely among manufacturers and may have the potential to directly interfere with the procedure or cause the formation of impurities that are not addressed by the compendial procedure. In these cases, a more thorough assessment of specificity may be required to demonstrate suitability of the method for the particular drug substance or product. Other analytical performance characteristics such as an assessment of the limit of detection for an impurities procedure or precision for an assay procedure may be useful to demonstrate the suitability of the compendial method under actual conditions of use.

Verification is not required for common compendial test procedures that are routinely performed in a laboratory. Examples include, but are not limited to, loss on drying, residue on ignition, various wet chemical procedures such as acid value, and simple instrumental methods such as pH measurements, unless there is an indication that the compendial procedure is not appropriate for the article under test. However, for the application of already established routine procedures to compendial articles tested for the first time, it is recommended that consideration be given to any new or different sample handling or solution preparation requirements.■2S (*USP30*)

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

***n*-Butyl Chloride,** *USP 29* page 3116 and page 631 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to update the specifications of this reagent to reflect the materials currently available commercially.

(HDQ:M. Marques) RTS—C44724

Change to read:

***n*-Butyl Chloride** *(1-Chlorobutane),* C_4H_9Cl—**92.57**

■[*109-69-3*]■1S (*USP30*)
—Clear, colorless, volatile liquid.▲*USP29*[*Caution—Highly flammable.]* Practically insoluble in water. Miscible with alcohol and with ether.

~~*Assay*~~ ~~When examined by gas–liquid chromatography, it shows a purity of not less than 98%. The following conditions have been found suitable for assaying the article: a 3-mm × 1.8-m stainless steel column packed with phase G16 on support S1. Helium, flowing at a rate of about 40 mL per minute, is the carrier gas, the detector temperature is about 310°, the injection port temperature is about 230°, and the column temperature is programmed to rise at 10° per minute from 35° to 150°. A flame ionization detector is employed.~~

~~*Boiling range* ⟨721⟩: between 76° and 80°, within a 2° range.~~

~~*Refractive index* ⟨831⟩: between 1.4015 and 1.4035 at 20°.~~

~~*Acidity* Add phenolphthalein TS to 75 mL, and titrate with 0.1 N potassium hydroxide in methanol to a faint pink color that persists, with shaking, for 1.5 seconds: not more than 0.91 mL is required (about 0.005% as HCl).~~

~~*Water* ⟨921⟩: not more than 0.02%, determined by the *Titrimetric Method*.~~

~~*Residue after evaporation* Evaporate about 60 mL (50 g), accurately weighed, in a tared platinum dish on a steam bath, and dry at 105° for 1 hour: not more than 0.005% is found.~~

■Use HPLC grade.■2S (*USP30*)

BRIEFING

Casein, Hammersten. It is proposed to add this new reagent used to prepare the *Casein substrate* in the *Assay* test in the monograph for *Papain*.

(HDQ: M. Marques) RTS—C44880

Add the following:

■**Casein, Hammersten—**[*9000-71-9*].

[NOTE—A suitable grade is available from *www.emdchemicals.com*, catalog number CX0525-1.]■2S (*USP30*)

BRIEFING

Diaveridine. It is proposed to add this new reagent used in the test for *Chromatographic purity* in the *USP* monograph for *Trimethoprim*.

(HDQ: M. Marques) RTS—C46222

Add the following:

■**Diaveridine** *(5-([3,4-Dimethoxyphenyl]methyl)-2,4-pyrimidinediamine),* $C_{13}H_{16}N_4O_2$—**260.3**[*5355-16-8*]—Use a suitable grade.■2S (*USP30*)

BRIEFING

Eriochrome Black T–Sodium Chloride Indicator. It is proposed to add this new reagent to be used in the test for *Disodium acetate* in the Adoption Stage 6 proposal for *Edetate Calcium Disodium,* which also appears in this issue of *PF*.

(HDQ: M. Marques) RTS—C45162

Add the following:

■**Eriochrome Black T–Sodium Chloride Indicator—**Mix 0.1 g of eriochrome black T and 10 g of sodium chloride, and triturate until the mixture becomes homogenous.■2S (*USP30*)

BRIEFING

1-Nonyl Alcohol, *USP 29* page 3141. To facilitate the procurement of this reagent and other reagents appearing in this issue of *PF* (see related cross-references), it is proposed to include CAS numbers and relevant synonyms, as necessary.

(HDQ: M. Marques) RTS—43575-2

Change to read:

1-Nonyl Alcohol *(1-Nonanol),* $CH_3(CH_2)_8OH$—**144.25**

■[*143-08-8*]■2S (*USP30*)

—Colorless liquid.

Assay—Use a suitable gas chromatograph equipped with a flame-ionization detector, helium being used as the carrier gas at a flow rate of about 40 mL per minute. The following conditions have been found suitable: a 3.2-mm × 1.83-m stainless steel column packed with 20% phase G16 on support S1A; the injection port, column, and detector temperatures are maintained at about 250°, 160°, and 310°, respectively. Not less than 97% of $C_9H_{20}O$ is found.

Refractive index ⟨831⟩: between 1.432 and 1.434 at 20°.

BRIEFING

Octadecyl Silane, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-3

Change to read:

Octadecyl Silane

■—[*18623-11-5*]■2S (*USP30*)
—This reagent is formed *in situ* by reaction of the column support with a suitable silylating agent such as octadecyl trichlorosilane.

BRIEFING

Octanophenone, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-4

Change to read:

Octanophenone, $C_{14}H_{20}O$—**204.31**

■[*1674-37-9*]■2S (*USP30*)
—Colorless liquid.

Assay—

MOBILE PHASE—Prepare a filtered and degassed mixture of acetonitrile and water (7 : 3).

PROCEDURE—Inject about 20 µL into a suitable liquid chromatograph (see *Chromatography* ⟨621⟩) equipped with a 254-nm detector and a 4.6-mm × 15.0-cm column that contains packing L1. The flow rate is about 2 mL per minute. The area of the $C_{14}H_{20}O$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: 1.5043 at 20°.

BRIEFING

Orange G, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-5

Change to read:

Orange G *(the sodium salt of azobenzene-betanaphthol disulfonic acid),* $C_6H_5N{:}NC_{10}H_4(OH)(SO_3Na)_2$-2,6,8—**452.37**

■[*1936-15-8*]■2S (*USP30*)
—Orange to brick-red powder or dark red crystals. Readily soluble in water, yielding an orange-yellow solution; slightly soluble in alcohol; insoluble in ether and in chloroform. The addition of tannic acid TS to its 1 in 500 solution causes no precipitation *(acid color)*. The addition of hydrochloric acid to a mixture of 500 mg of zinc dust and 10 mL of its 1 in 500 solution produces decolorization. When filtered, the colorless filtrate, on standing exposed to air, does not regain its original color *(presence of azo-group)*. When heated, orange G does not deflagrate (distinction from *nitro colors*). The addition of barium or calcium chloride TS to a concentrated solution of orange G produces a colored, crystalline precipitate. The addition of hydrochloric acid to its 1 in 500 solution produces no change; the addition of sodium hydroxide TS to a similar solution produces a yellowish red to a Bordeaux color but no precipitation. Orange G dissolves in sulfuric acid with an orange to yellowish-red color. No change in color results upon diluting the solution cautiously with water.

BRIEFING

Orcinol, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-6

Change to read:

Orcinol *(5-Methylresorcinol),* $C_7H_8O_2 \cdot H_2O$—**142.15**

■[*6153-39-5*]■2S (*USP30*)
—White to light tan crystals.

Assay—Transfer about 60 mg, accurately weighed, to a 100-mL volumetric flask, dissolve in methanol, dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask and dilute with methanol to volume, and mix. Using a suitable spectrophotometer, 1-cm cells, and methanol as the blank, record the absorbance of the solution at the wavelength of maximum absorbance at about 273 nm. From the observed absorbance, calculate the absorptivity (see *Spectrophotometry and Light-Scattering* ⟨851⟩): the absorptivity is not less than 13.2, corresponding to not less than 98% of $C_7H_8O_2 \cdot H_2O$.

Melting range ⟨741⟩: between 58° and 61°.

In-Process Revision

BRIEFING

Osmium Tetroxide, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-7

Change to read:

Osmium Tetroxide *(Osmic Acid; Perosmic Anhydride),* OsO_4—**254.23**

■[*20816-12-0*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Oxalic Acid, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-8

Change to read:

Oxalic Acid, $H_2C_2O_4 \cdot 2H_2O$—**126.07**

■[*6153-56-6*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

3,3′-Oxydipropionitrile, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-9

Change to read:

3,3′-Oxydipropionitrile, $O(CH_2CH_2CN)_2$—**124.14**[

■1656-48-0]■2S *(USP30)*
—Clear, colorless to slightly yellow liquid. Refractive index: about 1.446 at 20°.

Boiling range: between 174° and 176° at 10 mm of mercury.

BRIEFING

Palladium Chloride, *USP 29* page 3142—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-9

Change to read:

Palladium Chloride, $PdCl_2$—**177.33**

■[*7647-10-1*]■2S *(USP30)*
—Brown, crystalline powder. Soluble in water, in alcohol, in acetone, and in diluted hydrochloric acid.

Assay—Dissolve 80 mg, accurately weighed, in 10 mL of diluted hydrochloric acid, dilute with water to 50 mL, and add 25 mL of a 1 in 100 solution of dimethylglyoxime in alcohol. Allow to stand for 1 hour, and filter. Check for complete precipitation with the dimethylglyoxime solution. Ignite the precipitate in a tared platinum crucible at 850° for 2 hours, cool, and weigh the palladium. The weight of the residue is not less than 59.0% of the weight of the test specimen.

BRIEFING

Pancreatin, *USP 29* page 3143—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-10

Change to read:

Pancreatin

■—[*8049-47-6*]■2S *(USP30)*
—Use a grade of pancreatin which meets the USP requirements for amylase, lipase, and protease activities specified for the official substance.

BRIEFING

***Para*-aminobenzoic Acid,** *USP 29* page 3143—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-11

Change to read:

***Para*-aminobenzoic Acid** *(p-Aminobenzoic Acid),* $H_2NC_6H_4COOH$—**137.14**

■[*150-13-0*]■2S *(USP30)*
—White or slightly yellow ▲▲*USP29* crystals or crystalline powder, becoming discolored on exposure to air or light. One g dissolves in 170 mL of water, in 9 mL of boiling water, in 8 mL of alcohol, and in 50 mL of ether. Freely soluble in solutions of alkali hydroxides

and carbonates; soluble in warm glycerin; sparingly soluble in diluted hydrochloric acid; slightly soluble in chloroform. Store in tight, light-resistant containers.

Assay—Accurately weigh about 300 mg, previously dried at 105° for 2 hours, and transfer to a beaker or casserole. Add 5 mL of hydrochloric acid and 50 mL of water, and stir until dissolved. Cool to about 15°, add about 25 g of crushed ice, and slowly titrate with 0.1 M sodium nitrite VS until a glass rod dipped into the titrated solution produces an immediate blue ring when touched to starch iodide paper. When the titration is complete, the endpoint is reproducible after the mixture has been allowed to stand for 1 minute. Each mL of 0.1 M sodium nitrite is equivalent to 13.71 mg of $C_7H_7NO_2$. Not less than 98.5% is found.

Melting range ⟨741⟩: between 186° and 189°.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.2% of its weight.

Residue on ignition (Reagent test): not more than 0.1%.

BRIEFING

Paraformaldehyde, *USP 29* page 3143—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-12

Change to read:

Paraformaldehyde, $(CH_2O)_n$

■—[*30525-89-4*]■2S (*USP30*)
—Fine, white powder. ▲*USP29*

Assay—Transfer about 1 g, accurately weighed, to a 250-mL conical flask containing 50.0 mL of 1 N sodium hydroxide VS, and mix by swirling. Immediately, and slowly, add 50 mL of hydrogen peroxide TS, previously neutralized to bromothymol blue, through a small funnel placed in the neck of the flask. After the reaction moderates, rinse the funnel and inner wall of the flask with water, allow the solution to stand for 30 minutes, add bromothymol blue TS, and titrate the excess alkali with 1 N sulfuric acid VS. Each mL of 1 N sodium hydroxide is equivalent to 30.03 mg of HCHO: not less than 95% is found.

Residue on ignition: not more than 0.1%.

Solubility in ammonia—Dissolve 5 g in 50 mL of ammonia TS: a practically clear, colorless solution results.

Reaction—Shake 1 g with 20 mL of water for about 1 minute, and filter: the filtrate is neutral to litmus.

BRIEFING

Pentadecane, *USP 29* page 3143—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-13

Change to read:

Pentadecane, $C_{15}H_{32}$—**212.41**

■[*629-62-9*]■2S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; and the column temperature is maintained at 180° and programmed to rise 10° per minute to 280°. The area of the $C_{15}H_{32}$ peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.430 and 1.434 at 20°.

BRIEFING

Pentane, *USP 29* page 3143—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-14

Change to read:

Pentane *(n-Pentane),* C_5H_{12}—**72.15**

■[*109-66-0*]■2S (*USP30*)
—Clear, colorless, *flammable* liquid. Very slightly soluble in water. Miscible with alcohol, with ether, and with many organic solvents. Specific gravity: about 0.62.

Boiling range (Reagent test)—Not less than 95% distils between 34° and 36°.

BRIEFING

Pepsin, *USP 29* page 3143—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-15

Change to read:

Pepsin

■—[*9001-75-6*]■2S (*USP30*)
—Use *Pepsin* (*Enzyme Preparations*) FCC, having an activity of 1.0 to 1.17 Pepsin units per mg. Pepsin of higher activity may be reduced to this activity by admixture with pepsin of lower activity or with lactose.

BRIEFING

Perchloric Acid, *USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-16

Change to read:

Perchloric Acid *(70 Percent Perchloric Acid),* $HClO_4$—**100.46**

■[*7601-90-3*]■2S *(USP30)*
—Use ACS reagent grade (containing between 70.0% and 72.0% of $HClO_4$).

BRIEFING

Periodic Acid, *USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-17

Change to read:

Periodic Acid, H_5IO_6—**227.94**

■[*10450-60-9*]■2S *(USP30)*
—White to pale yellow crystals. Very soluble in water. Undergoes slow decomposition to iodic acid. Use ACS reagent grade.

BRIEFING

Phenacetin, *USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-18

Change to read:

Phenacetin

■—[*62-44-2*]■2S *(USP30)*
—Use a suitable grade.

BRIEFING

1,10-Phenanthroline,*USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-19

Change to read:

1,10-Phenanthroline *(Orthophenanthroline),* $C_{12}H_8N_2 \cdot H_2O$—**198.22**

■[*5144-89-8*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Phenol, *USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43576-20

Change to read:

Phenol

■—[*108-95-2*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Phenoxybenzamine Hydrochloride, *USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-1

Change to read:

Phenoxybenzamine Hydrochloride *[N-(2-Chloroethyl)-N-(1-methyl-2-phenoxyethyl)benzylamine Hydrochloride],* $C_{18}H_{22}ClNO \cdot HCl$—**340.29**

■[*63-92-3*]■2S *(USP30)*
—White, crystalline powder.

Melting range ⟨741⟩: between 137° and 140°.

Absorptivity—Its absorptivity, 1%, 1 cm, in the range of 272 nm to 290 nm, in chloroform solution is about 178.

BRIEFING

2-Phenoxyethanol, *USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-2

Change to read:

2-Phenoxyethanol, $C_6H_5OCH_2CH_2OH$—**138.16**

■[*122-99-6*]■2S *(USP30)*
—Colorless, slightly viscous liquid. Soluble in water. Miscible with alcohol, with acetone, and with glycerin. Density: about 1.107.

Assay—To 2 g, accurately weighed, add 10 mL of a freshly prepared solution made by dissolving 25 g of acetic anhydride in 100 g of anhydrous pyridine. Swirl to mix the liquids, heat on a steam bath for 45 minutes, add 10 mL of water, heat for 2 additional minutes, and cool. Add 10 mL of normal butyl alcohol, shake vigorously, add phenolphthalein TS, and titrate with 1 N sodium hydroxide VS. Perform a blank test using the same quantities of the same reagents, and in the same manner, and make any necessary correction. Each mL of 1 N sodium hydroxide is equivalent to 138.2 mg of $C_8H_{10}O_2$. Not less than 99% is found.

Phenol—Add 0.2 mL of it to 20 mL of water, mix, and to 5 mL of the mixture add 0.2 mL of Millon's reagent. Warm the solution at 60° for 90 seconds, and allow to stand: no pink or red color is produced within 1 minute.

BRIEFING

Phenyl Isocyanate, *USP 29* page 3144—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-3

Change to read:

Phenyl Isocyanate, C_6H_5NCO—**119.12**

■[*103-71-9*]■2S (*USP30*)
—Clear, colorless to straw-yellow liquid of medium volatility. *[Caution—Phenyl Isocyanate is a violent lacrimator, and the vapor is highly toxic. Handle with care.]*

Assay—Transfer 250 mg, accurately weighed, to a glass-stoppered, 250-mL flask. Exercise care to avoid loss by volatilization, and avoid breathing the vapor. Add 20 mL of butylamine solution (25 g of butylamine diluted to 1000 mL with dioxane previously dried over potassium hydroxide pellets), insert the stopper in the flask, and allow to stand for 15 minutes. Add a few drops of methyl red TS and 25 mL of water, and titrate the excess amine with 0.1 N sulfuric acid VS. Perform a blank titration on 20 mL of the butylamine solution (see *Residual Titrations* ⟨541⟩). Subtract the volume of 0.1 N sulfuric acid consumed in the test specimen titration from that consumed in the blank titration. Each mL of 0.1 N sulfuric acid, representing this difference, is equivalent to 11.91 mg of C_6H_5NCO: not less than 97.0% of C_6H_5NCO is found.

BRIEFING

***dl*-Phenylalanine,** *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-4

Change to read:

***dl*-Phenylalanine,** $C_9H_{11}NO_2$—**165.19**

■[*150-30-1*]■2S (*USP30*)
—Use a suitable grade.

BRIEFING

Phenylhydrazine, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-5

Change to read:

Phenylhydrazine, $C_6H_5NHNH_2$—**108.14**

■[*100-63-0*]■2S (*USP30*)
—A colorless, or slightly yellowish, highly refractive liquid. [NOTE—Protect from light, and distill under reduced pressure shortly prior to use.]

Congealing temperature ⟨651⟩: not below 16°.

Insoluble matter—Shake 1 mL with 20 mL of diluted acetic acid: the resulting solution is clear or practically so.

Residue on ignition (Reagent test)—Ignite 1 mL with 0.5 mL of sulfuric acid: the residue weighs not more than 1 mg (0.1%).

BRIEFING

Phenylhydrazine Hydrochloride, *USP 29* page 3145 and page 660 of *PF* 32(2) [Mar.–Apr. 2006]—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-6

Change to read:

Phenylhydrazine Hydrochloride, $C_6H_5NHNH_2 \cdot HCl$—**144.60**

■[*59-88-1*]■2S (*USP30*)
—White or yellowish crystals or powder. Soluble in water and in alcohol. Store in tight containers, protected from light.

~~*Melting range* ⟨741⟩: between 242° and 246°, with slight darkening.~~

~~*Solubility*—Separate 500-mg portions dissolve in 10 mL of water and in 10 mL of alcohol, respectively, to yield solutions that are clear and complete or practically so.~~

~~*Residue on ignition* (Reagent test)—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 1 mg (0.1%).~~

■Use a suitable grade with a content of not less than 99%.■1S (*USP30*)

In-Process Revision

BRIEFING

3-Phenylphenol, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-7

Change to read:

3-Phenylphenol *(m-Phenylphenol),* $C_6H_5C_6H_4OH$—**170.21**

■[*580-51-8*]■2S (*USP30*)
—White to off-white, crystalline powder.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography*⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with G1; the injection port temperature is maintained at 250°; the column temperature is maintained at 150° and programmed to rise 15° per minute to 250°; and the detector temperature is maintained at 310°. The area of the 3-phenylphenol peak is not less than 98% of the total peak area.

Melting range ⟨741⟩: between 76° and 79°.

BRIEFING

Phloroglucinol, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-8

Change to read:

Phloroglucinol, $C_6H_3(OH)_3 \cdot 2H_2O$—**162.14**

■[*6099-90-7*]■2S (*USP30*)
—White or yellowish-white crystals or a crystalline powder. Soluble in alcohol and in ether; slightly soluble in water.

Insoluble in alcohol—Dissolve 1 g in 20 mL of alcohol: a clear and complete solution results.

Melting range, *Class Ia*⟨741⟩: between 215° and 219°.

Residue on ignition (Reagent test)—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 1 mg (0.1%).

Diresorcinol—Heat to boiling a solution of 100 mg in 10 mL of acetic anhydride, cool the solution, and superimpose it upon 10 mL of sulfuric acid: no violet color appears at the zone of contact of the liquids.

BRIEFING

Phosphomolybdic Acid,*USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-9

Change to read:

Phosphomolybdic Acid, approximately $20MoO_3 \cdot P_2O_5 \cdot 51H_2O$—**3939.49**

■[*11104-88-4*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Phosphoric Acid, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-10

Change to read:

Phosphoric Acid, H_3PO_4—**98.00**

■[*7664-38-2*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Phosphorus Pentoxide,*USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-11

Change to read:

Phosphorus Pentoxide *(Phosphoric Anhydride),* P_2O_5—**141.94**

■[*1314-56-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Phthalazine, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-12

Change to read:

Phthalazine, $C_8H_6N_2$—**130.15**

■[*253-52-1*]■2S (*USP30*)
—Yellow to tan crystals.

Melting range ⟨741⟩: between 89° and 92°.

BRIEFING

Phthalic Acid, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-13

Change to read:

Phthalic Acid, $C_8H_6O_4$—**166.13**

■[*88-99-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Phthalic Anhydride, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-14

Change to read:

Phthalic Anhydride, $C_8H_4O_3$—**148.12**

■[*85-44-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Phthalimide, *USP 29* page 3145—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-15

Change to read:

Phthalimide, $C_8H_5NO_2$—**147.13**

■[*85-41-6*]■2S (*USP30*)
—White powder.

Assay—

MOBILE PHASE—Prepare a mixture of isooctane and methyl-*tert*-butyl ether (88 : 12).

PROCEDURE—Inject about 20 µL into a suitable liquid chromatograph (see *Chromatography*⟨621⟩) equipped with a 230-nm detector and a 4.6-mm × 15-cm column that contains packing L3. The flow rate is about 2 mL per minute. The area of the $C_8H_5NO_2$ peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 233° and 235°, with decomposition.

BRIEFING

2-Picoline, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-16

Change to read:

2-Picoline, C_6H_7N—**93.13**

■[*109-06-8*]■2S (*USP30*)
—Colorless to yellowish liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography*⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 2-mm × 2-m glass column packed with 20% liquid phase G16 on 80- to 100-mesh support S1C; the injection port temperature is maintained at 140°; the detector temperature is maintained at 300°; the column temperature is maintained at 90° and programmed to rise 3° per minute to 140°. The area of the C_6H_7N peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: 1.500 ± 0.002 at 20°.

BRIEFING

Picric Acid, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-17

Change to read:

Picric Acid *(2,4,6-Trinitrophenol; Trinitrophenol),* $C_6H_2(OH)(NO_2)_3$-1,2,4,6—**229.10**

■[*88-89-1*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Picrolonic Acid, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-18

Change to read:

Picrolonic Acid *(3-Methyl-4-nitro-1-(p-nitrophenyl)-5-pyrazolone),* $C_{10}H_8N_4O_5$—**264.19**

■[*550-74-3*]■2S (*USP30*)
—Yellow to brownish-yellow, crystalline powder. Slightly soluble in water; soluble in alcohol, in chloroform, in ether, in benzene, and in solutions of alkali hydroxides.

Melting range ⟨741⟩: between 115° and 117°.

Residue on ignition (Reagent test): negligible, from 200 mg.

In-Process Revision

Sensitiveness—Dissolve 25 mg in 10 mL of warm water containing 0.1 mL of glacial acetic acid, and filter the solution, if necessary. Dissolve 100 mg of calcium chloride in 250 mL of water, and mix. Heat 1 mL of the calcium chloride solution in a test tube to about 60°, then add to it 1 mL of the picrolonic acid solution: a bulky precipitate forms in 5 minutes or less.

BRIEFING

Pipemidic Acid, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-19

Change to read:

Pipemidic Acid *(8-Ethyl-3,8-dihydro-5-oxo-2-(1-piperazinyl)pyrido[2,3-d]-pyrimidine-6-carboxylic acid),* $C_{14}H_{17}N_5O_3$—**303.3**

■[*51940-44-4*]■2S (*USP30*)
—Use a suitable grade.

BRIEFING

Piperidine, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43583-20

Change to read:

Piperidine, $C_5H_{11}N$—**85.15**

■[*110-89-4*]■2S (*USP30*)
—Colorless liquid. Miscible with water and with alcohol. Specific gravity: about 0.860.

Congealing range ⟨651⟩: between 12° and 15°.

Boiling range (Reagent test)—Not less than 95% distills between 104° and 106°.

Refractive index: about 1.454.

BRIEFING

Platinic Chloride, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-1

Change to read:

Platinic Chloride *(Chloroplatinic Acid),* $H_2PtCl_6 \cdot 6H_2O$—**517.90**

■[*16941-12-1*]■2S (*USP30*)
—Use ACS reagent grade Chloroplatinic Acid.

BRIEFING

Polyethylene Glycol 600, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-2

Change to read:

Polyethylene Glycol 600

■—[*25322-68-3*]■2S (*USP30*)
—A clear, practically colorless, viscous liquid condensation polymer represented by $H(OCH_2CH_2)_nOH$, in which *n* varies from 12 to 14. Its average molecular weight is about 600.

It meets the requirements of all of the tests under *Polyethylene Glycol* (*NF* monograph) except *Limit of ethylene glycol and diethylene glycol.*

BRIEFING

Polyethylene Glycol 20,000, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-3

Change to read:

Polyethylene Glycol 20,000

■—[*25322-68-3*]■2S (*USP30*)
—Molecular weight range: 15,000–20,000. Hard, white, waxy solid, usually supplied in flake form. Soluble in water with subsequent gel formation.

Viscosity of 25% solution ⟨911⟩—Add 50.0 g of test specimen to a 250-mL wide-mouth, screw-cap jar containing 150.0 g of water. Attach the cap securely to the jar, and roll on a mechanical roller until the test specimen is completely dissolved, in 2 to 4 hours. Allow the solution to stand until all air bubbles have disappeared. Another 2 to 4 hours may be required. Adjust the temperature of the solution to 37.8 ± 0.1°, and determine the kinematic viscosity on a suitable viscosimeter of the Ubbelohde type. The viscosity is not less than 100 centistokes.

pH ⟨791⟩: between 6.5 and 8.0 in a solution (1 in 20). [NOTE—A five-fold dilution of the test solution prepared for the *Viscosity of 25% solution* test may be used.]

Residue on ignition ⟨281⟩: not more than 0.7%, the use of sulfuric acid being omitted.

BRIEFING

Polyvinyl Alcohol, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-4

Change to read:

Polyvinyl Alcohol, $(C_2H_4O)_n$

■—[*9002-89-5*]■2S (*USP30*)
—White powder. Soluble in water; insoluble in organic solvents.

pH ⟨791⟩: between 5.0 and 8.0, in a solution (1 in 25).

Loss on drying—Dry it at 110° to constant weight: it loses not more than 5% of its weight.

Residue on ignition: not more than 0.75%.

[NOTE—Suitable grades are available as catalog number U 232, from J.T. Baker Chemical Co., www.jtbaker.com.]

BRIEFING

Potassium Acetate, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-5

Change to read:

Potassium Acetate, $KC_2H_3O_2$—**98.14**

■[*127-08-2*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Bicarbonate, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-6

Change to read:

Potassium Bicarbonate, $KHCO_3$—**100.12**

■[*298-14-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Biphthalate, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-7

Change to read:

Potassium Biphthalate *(Acid Potassium Phthalate; Phthalic Acid Monopotassium Salt; Potassium Hydrogen Phthalate Acidimetric Standard),* $KHC_6H_4(COO)_2$—**204.22**

■[*877-24-7*]■2S (*USP30*)
—Use ACS reagent grade Potassium Hydrogen Phthalate, Acidimetric Standard.

BRIEFING

Potassium Bisulfate, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-8

Change to read:

Potassium Bisulfate, $KHSO_4$—**136.17**

■[*7646-93-7*]■2S (*USP30*)
—Fused, white, deliquescent masses or granules. Very soluble in water. When ignited, it evolves SO_3 and H_2O, changing first to potassium pyrosulfate, then to sulfate.

Acidity—Dissolve 4 g, accurately weighed, in 50 mL of water, add phenolphthalein TS, and titrate with 1 N alkali: it contains between 34% and 36%, calculated as H_2SO_4.

Insoluble matter and *ammonium hydroxide precipitate*—Dissolve 10 g in 100 mL of water, add methyl red TS, render slightly alkaline with ammonia TS, boil for 1 minute, and digest on a steam bath for 1 hour. Pass through a tared filtering crucible, wash thoroughly, and dry at 105° for 2 hours: the precipitate weighs not more than 1 mg (0.01%).

For the following tests, prepare a *Test solution* as follows. Dissolve 6 g in 45 mL of water, add 2 mL of hydrochloric acid, boil gently for 10 minutes, cool, and dilute with water to 60 mL.

Heavy metals (Reagent test)—To 30 mL of *Test solution* add phenolphthalein TS, and neutralize with ammonia TS. Add 0.5 mL of glacial acetic acid, dilute with water to 40 mL, and add 10 mL of hydrogen sulfide TS: any brown color produced is not darker than that of a control containing 10 mL of *Test solution* and 0.02 mg of added Pb (0.001%).

Iron ⟨241⟩—To 5 mL of *Test solution* add 2 mL of hydrochloric acid, and dilute with water to 47 mL: the solution shows not more than 0.01 mg of Fe (0.002%).

BRIEFING

Potassium Bromate, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-9

Change to read:

Potassium Bromate, $KBrO_3$—**167.00**

■[*7758-01-2*]■2S (*USP30*)
—Use ACS reagent grade.

In-Process Revision

BRIEFING

Potassium Bromide, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-10

Change to read:

Potassium Bromide, KBr—**119.00**

■[*7758-02-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Carbonate, Anhydrous, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-11

Change to read:

Potassium Carbonate, Anhydrous, K_2CO_3—**138.21**

■[*584-08-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Chlorate, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-12

Change to read:

Potassium Chlorate, $KClO_3$—**122.55**

■[*3811-04-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Chloride, *USP 29* page 3146—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-13

Change to read:

Potassium Chloride, KCl—**74.55**

■[*7447-40-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Chromate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-14

Change to read:

Potassium Chromate, K_2CrO_4—**194.19**

■[*7789-00-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Cyanide, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-15

Change to read:

Potassium Cyanide, KCN—**65.12**

■[*151-50-8*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Dichromate,*USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-16

Change to read:

Potassium Dichromate, $K_2Cr_2O_7$—**294.18**

■[*7778-50-9*]■2S (*USP30*)
—Use ACS reagent grade.
[NOTE—Potassium dichromate of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Washington, DC, www.nist.gov, as standard sample No. 136.]

BRIEFING

Potassium Ferricyanide,*USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-17

Change to read:

Potassium Ferricyanide, $K_3Fe(CN)_6$—**329.24**

■[*13746-66-2*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Ferrocyanide,*USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-18

Change to read:

Potassium Ferrocyanide, $K_4Fe(CN)_6 \cdot 3H_2O$—**422.39**

■[*13943-58-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Hydroxide,*USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-19

Change to read:

Potassium Hydroxide, KOH—**56.11**

■[*1310-58-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Iodate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43593-20

Change to read:

Potassium Iodate, KIO_3—**214.00**

■[*7758-05-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Iodide, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-1

Change to read:

Potassium Iodide, KI—**166.00**

■[*7681-11-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Nitrate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-2

Change to read:

Potassium Nitrate, KNO_3—**101.10**

■[*7757-79-1*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Nitrite, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-3

In-Process Revision

Change to read:

Potassium Nitrite, KNO_2—**85.10**

■[*7758-09-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Perchlorate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-4

Change to read:

Potassium Perchlorate, $KClO_4$—**138.55**

■[*7778-74-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Periodate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-5

Change to read:

Potassium Periodate *(Potassium meta-Periodate),* KIO_4—**230.00**

■[*7790-21-8*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Permanganate,*USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-6

Change to read:

Potassium Permanganate, $KMnO_4$—**158.03**

■[*7722-64-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Persulfate,*USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-7

Change to read:

Potassium Persulfate, $K_2S_2O_8$—**270.32**

■[*7727-21-1*]■2S (*USP30*)
—Use ACS reagent grade Potassium Peroxydisulfate.

BRIEFING

Potassium Phosphate, Dibasic, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-8

Change to read:

Potassium Phosphate, Dibasic *(Dipotassium Hydrogen Phosphate; Dipotassium Phosphate),* K_2HPO_4—**174.18**

■[*7758-11-4*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Phosphate, Monobasic, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43596-9

Change to read:

Potassium Phosphate, Monobasic *(Potassium Biphosphate; Potassium Dihydrogen Phosphate),* KH_2PO_4—**136.09**

■[*7778-77-0*]■2S (*USP30*)
—Use ACS reagent grade.
[NOTE—Certified Potassium Dihydrogen Phosphate is available from the National Institute of Standards and Technology, Washington, DC, www.nist.gov, as standard sample No. 186.]

BRIEFING

Potassium Phosphate, Tribasic, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-1

Change to read:

Potassium Phosphate, Tribasic, K_3PO_4—**212.27**

■[*7778-53-2*]■2S (*USP30*)
—Deliquescent, orthorhombic crystals. Use ACS reagent grade.

BRIEFING

Potassium Pyroantimonate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-2

Change to read:

Potassium Pyroantimonate *(Potassium hexahydroxyantimonate),* $KSbO_3 \cdot 3H_2O$—**262.90**

■[*10090-54-7*]■2S (*USP30*)
—White crystals or a white, crystalline powder. Sparingly soluble in water. Use a suitable grade.

BRIEFING

Potassium Pyrophosphate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-3

Change to read:

Potassium Pyrophosphate, $K_4P_2O_7$—**330.34**

■[*7320-34-5*]■2S (*USP30*)
—Colorless, deliquescent granules. Freely soluble in water; insoluble in alcohol.

BRIEFING

Potassium Pyrosulfate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-4

Change to read:

Potassium Pyrosulfate

■—[*7790-62-7*]■2S (*USP30*)
—Usually available as a mixture of potassium pyrosulfate ($K_2S_2O_7$) and potassium bisulfate ($KHSO_4$). Use ACS reagent grade.

BRIEFING

Potassium Sodium Tartrate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-5

Change to read:

Potassium Sodium Tartrate, $KNaC_4H_4O_6 \cdot 4H_2O$—**282.22**

■[*304-59-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Sulfate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-6

Change to read:

Potassium Sulfate, K_2SO_4—**174.26**

■[*7778-80-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Potassium Tellurite, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-7

Change to read:

Potassium Tellurite *(Potassium Tellurate IV),* K_2TeO_3—**253.79**

■[*7790-58-1*]■2S (*USP30*)
—White, granular powder. Soluble in water. Its solution is alkaline.

Assay—Weigh accurately about 120 mg, transfer to a beaker, and dissolve in a mixture of 10 mL of nitric acid, 10 mL of sulfuric acid, and 25 mL of water. Heat to boiling, and boil until copious fumes of sulfur trioxide are evolved. Cool, cautiously add 100 mL of water, heat to boiling, add 6 g of sodium fluoride, and titrate the hot solution with 0.1 N potassium permanganate VS. Each mL of 0.1 N potassium permanganate is equivalent to 12.69 mg of K_2TeO_3. Not less than 98% is found.

Chloride (Reagent test)—One g shows not more than 0.1 mg of Cl (0.01%).

BRIEFING

Potassium Thiocyanate, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-8

Change to read:

Potassium Thiocyanate, KSCN—**97.18**

■[*333-20-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Propionaldehyde, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-9

Change to read:

Propionaldehyde, C_3H_6O—**58.08**

■[*123-38-6*]■2S (*USP30*)
—Use a suitable grade.

BRIEFING

Propionic Anhydride, *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-10

Change to read:

Propionic Anhydride, $C_6H_{10}O_3$—**130.14**

■[*123-62-6*]■2S (*USP30*)
—Colorless liquid. ▲*USP29* Is decomposed by water. Soluble in methanol, in alcohol, in ether, and in chloroform.

Assay—Accurately weigh about 350 mg into a tared, glass-stoppered flask containing 50 mL of dimethylformamide previously neutralized to the thymol blue endpoint with 0.1 N sodium methoxide in methanol VS. Titrate with 0.1 N sodium methoxide in methanol VS to the thymol blue endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium methoxide is equivalent to 13.014 mg of $C_6H_{10}O_3$. Not less than 97.0% is found.

Refractive index ⟨831⟩**:** between 1.4035 and 1.4045 at 20°.

BRIEFING

***n*-Propyl Alcohol,** *USP 29* page 3147—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-11

Change to read:

***n*-Propyl Alcohol** *(1-Propanol),* $CH_3CH_2CH_2OH$—**60.10**

■[*71-23-8*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Purine, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-12

Change to read:

Purine, $C_5H_4N_4$—**120.11**

■[*120-73-0*]■2S (*USP30*)
—White to off-white powder.

Assay—When it is examined by thin-layer chromatography, with the use of plates coated with chromatographic silica gel mixture and a developing system consisting of butyl alcohol, water, and glacial acetic acid (60 : 25 : 15), a single spot is exhibited.

Melting range ⟨741⟩: between 214° and 217°.

BRIEFING

Pyrazole, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-13

Change to read:

Pyrazole, $C_3H_4N_2$

■—[*288-13-1*]■2S (*USP30*)
—White to pale yellow crystals or crystalline powder. Soluble in water, in alcohol, and in ether.

Melting range ⟨741⟩: between 67° and 71°.

BRIEFING

Pyrene, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-14

Change to read:

Pyrene, $C_{16}H_{10}$—**202.25**

■[*129-00-0*]■2S (*USP30*)
—White to light yellow crystals.

Assay—Transfer about 9 mg, accurately weighed, to a 100-mL volumetric flask, dissolve in methanol, dilute with methanol to volume, and mix. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with methanol to volume, and mix. Using a suitable spectrophotometer, 1-cm cells, and methanol as the blank, record the absorbance of the solution at the wavelength of maximum absorbance at about 238 nm. From the observed absorbance, calculate the absorptivity (see *Spectrophotometry and Light-Scattering* ⟨851⟩): the absorptivity is not less than 432.9, corresponding to not less than 98% of $C_{16}H_{10}$.

Melting range ⟨741⟩: between 149° and 153° over a 2° range.

BRIEFING

Pyridine, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-15

Change to read:

Pyridine, C_5H_5N—**79.10**

■[*110-86-1*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Pyridine, Dried, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-16

Change to read:

Pyridine, Dried

■—[*110-86-1*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Pyridoxal Hydrochloride, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-17

Change to read:

Pyridoxal Hydrochloride, $C_8H_9NO_3 \cdot HCl$—**203.62**

■[*65-22-5*]■2S (*USP30*)
—White to slightly yellow crystals or crystalline powder. Gradually darkens on exposure to air or sunlight. One g dissolves in about 2 mL of water and in about 25 mL of alcohol. Insoluble in acetone, in chloroform, and in ether. Its solutions are acid (pH about 3).

Melting range ⟨741⟩: between 171° and 175° with some decomposition.

Residue on ignition (Reagent test): not more than 0.1%.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.

Nitrogen content (Reagent test)—Determine by the Kjeldahl method, using a test specimen previously dried at 105° for 2 hours: between 6.7% and 7.1% of N is found.

Chloride content—Accurately weigh about 500 mg, previously dried at 105° for 2 hours, and dissolve in 50 mL of water. Add 3 mL of nitric acid and 50.0 mL of 0.1 N silver nitrate VS, then add 5 mL of nitrobenzene, shake for about 2 minutes, add ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS: each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of Cl. Between 17.2% and 17.7% is found.

BRIEFING

Pyridoxal 5-Phosphate,*USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-18

Change to read:

Pyridoxal 5-Phosphate, 4-$CHOC_5HN$-2-CH_3, 3-OH, 5-$CH_2PO_4H_2 \cdot H_2O$—**265.16**

■[*41468-25-1*]■2S (*USP30*)
—Light yellow powder. Use a suitable grade.

BRIEFING

Pyridoxamine Dihydrochloride, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-19

Change to read:

Pyridoxamine Dihydrochloride, $C_8H_{12}N_2O_2 \cdot 2HCl$—**241.11**

■[*524-36-7*]■2S (*USP30*)
—White to slightly yellow crystals or crystalline powder. Gradually darkens on exposure to air or sunlight. One g dissolves in about 1 mL of water and in about 60 mL of alcohol. Insoluble in chloroform and in ether. Its solutions are acid.

Melting range ⟨741⟩: between 225° and 230°, with some decomposition.

Residue on ignition (Reagent test): not more than 0.15%.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.

Nitrogen content (Reagent test)—Determine by the Kjeldahl method, using a test specimen previously dried at 105° for 2 hours: between 11.3% and 11.8% of N is found.

Chloride content—Determine as directed in the test for *Chloride content* under *Pyridoxal Hydrochloride:* between 29.1% and 29.6% of Cl is found.

BRIEFING

1-(2-Pyridylazo)-2-naphthol, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43597-20

Change to read:

1-(2-Pyridylazo)-2-naphthol, $C_{15}H_{11}N_3O$—**249.27**

■[*85-85-8*]■2S (*USP30*)
—Stable, orange-red crystals. Soluble in alcohol and in hot solutions of dilute alkalies; slightly soluble in water.

Melting range ⟨741⟩: between 140° and 142°.

Sensitiveness—Add 0.1 mL of a 1 in 1000 solution of it in alcohol to a mixture of 10 mL of water and 1 mL of a buffer solution prepared by mixing 80 mL of 0.2 M acetic acid and 20 mL of sodium acetate solution (8.2 in 100), and mix. To this solution add 1 mL of a mixture of 1 mL of cupric sulfate TS and 2 mL of water, and mix: the color changes from yellow to red.

BRIEFING

Pyrogallol, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-1

Change to read:

Pyrogallol, $C_6H_3(OH)_3$—**126.11**

■[*87-66-1*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Pyrrole, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-2

Change to read:

Pyrrole, C_4H_5N—**67.09**

■[*109-97-7*]■2S (*USP30*)
—Clear liquid, colorless when freshly distilled, becoming yellow in a few days. ▲▲*USP29* Specific gravity: about 0.94. Insoluble in water; soluble in alcohol, in benzene, and in ether.

Boiling range (Reagent test)—Not less than 90% distills between 128° and 132°.

BRIEFING

Pyruvic Acid, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-3

Change to read:

Pyruvic Acid, $CH_3COCOOH$—**88.06**

■[*127-17-3*]■2S (*USP30*)
—Colorless to light yellow liquid. Miscible with water, with alcohol, and with ether.

Refractive index ⟨831⟩: about 1.43 at 20°.

Assay—Accurately weigh about 1 g, transfer to a suitable container, and add 100 mL of water. Mix, add phenolphthalein TS, and titrate with 0.5 N sodium hydroxide VS. Each mL of 0.5 N sodium hydroxide is equivalent to 44.03 mg of $CH_3COCOOH$: not less than 98% of $CH_3COCOOH$ is found.

BRIEFING

Quinhydrone, *USP 29* page 3148—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-4

Change to read:

Quinhydrone, $C_6H_4(OH)_2 \cdot C_6H_4O_2$—**218.21**

■[*106-34-3*]■2S (*USP30*)
—Green crystals having a metallic luster. Slightly soluble in cold water; soluble in hot water, in alcohol, and in ether.

Assay—Transfer about 450 mg, accurately weighed, to a glass-stoppered flask, add 50 mL of 1 N sulfuric acid and 3 g of potassium iodide, insert the stopper in the flask, and shake until dissolved. Titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Each mL of 0.1 N sodium thiosulfate is equivalent to 5.405 mg of quinone ($C_6H_4O_2$). Between 49.0% and 51.0% is found.

Alcohol-insoluble matter—Dissolve 10 g in 100 mL of hot alcohol, filter through a suitable tared crucible of fine porosity, and wash with hot alcohol until the last washing is colorless. Dry at 105°, cool in a desiccator, and weigh: the residue weighs not more than 1.0 mg (0.010%).

Residue on ignition (Reagent test): not more than 0.050%, a 2.0-g test specimen being used. Save the residue.

Sulfate—Transfer 1 g to a platinum crucible, add 10 mL of hot water and 0.5 g of sodium carbonate, evaporate to dryness, and ignite, protected from the sulfur in the flame, until the residue is nearly white. Cool, add 20 mL of water and 1 mL of 30 percent hydrogen peroxide, boil gently for a few minutes, add 2 mL of hydrochloric acid, and evaporate on a steam bath to dryness. Cool, dissolve the residue in 20 mL of water, filter, and to the filtrate add 1 mL of 1 N hydrochloric acid and 3 mL of barium chloride TS: any turbidity produced within 10 minutes does not exceed that in a control containing 0.2 mg of added SO_4 and 0.5 mg of sodium carbonate, 1 mL of 30 percent hydrogen peroxide, and 2 mL of hydrochloric acid previously evaporated on a steam bath to dryness (0.02%).

Heavy metals—To the residue retained from the test for *Residue on ignition* add 2 mL of hydrochloric acid and 0.5 mL of nitric acid, and evaporate on a steam bath to dryness. Dissolve the residue in 30 mL of hot water containing 1 mL of 1 N hydrochloric acid, cool, dilute with water to 40 mL, and mix. Dilute 20 mL of this solution (retain the rest of the solution) with water to 25 mL, adjust to a pH between 3.0 and 4.0 by the addition of 1 N acetic acid or 6 N ammonium hydroxide as necessary, dilute with water to 40 mL, and add 10 mL of freshly prepared hydrogen sulfide TS: any brown color produced does not exceed that in a control containing 0.02 mg of added Pb (0.002%).

Iron ⟨241⟩—To 10 mL of the solution retained from the test for *Heavy metals* add 2 mL of hydrochloric acid, and dilute with water to 47 mL: the solution shows not more than 0.01 mg of Fe (0.002%).

BRIEFING

Resazurin (Sodium), *USP 29* page 3149—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-5

Change to read:

Resazurin (Sodium), $C_{12}H_6NNaO_4$—**251.17**

■[*62758-13-8*]■2S (*USP30*)
—A brownish-purple, crystalline powder. One g dissolves in 100 mL of water, forming a deep-violet-colored solution.

Hydrogen sulfide and other compounds containing the thiol group decolorize solutions of resazurin sodium, forming dihydroresorufin. When the decolorized solution is shaken in the presence of air, a rose color develops as a result of the formation of resorufin.

BRIEFING

Rhodamine B, *USP 29* page 3149—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-6

Change to read:

Rhodamine B *(Tetraethylrhodamine),* $C_{28}H_{31}ClN_2O_3$—**479.01**

■[*81-88-9*]■2S (*USP30*)
—Green crystals or a reddish-violet powder. Very soluble in water, yielding a bluish-red solution that is strongly fluorescent when dilute. Very soluble in alcohol; slightly soluble in dilute acids and in alkali solutions. In strong acid solution, it forms a pink complex with antimony that is soluble in isopropyl ether.

Clarity of solution—Its solution (1 in 200) is complete and clear.

Residue on ignition (Reagent test)—Ignite 1 g with 1 mL of sulfuric acid: the residue weighs not more than 2 mg (0.2%).

BRIEFING

Rose Bengal Sodium, *USP 29* page 3149—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-7

Change to read:

Rose Bengal Sodium *(Disodium Salt of 4,5,6,7-Tetrachloro-2′,4′,5′,7′-tetraiodofluorescein),* $C_{20}H_2Cl_4I_4Na_2O_5$—**1017.64**

■[632-69-9]■2S (*USP30*)
—Fine, rose-colored crystals or crystalline powder. ▲▲*USP29* Soluble in water.

[NOTE—Render commercially available material suitably pure by the following treatment. Dissolve 8 g in 200 mL of water, and adjust to a pH between 10 and 11, using short-range pH indicator paper.

In-Process Revision

Add 200 mL of acetone, while stirring gently, then add dilute hydrochloric acid (1 in 10), while continuing to stir, until the pH of the solution reaches 4.0. Add 400 mL more of water, with stirring, and continue the stirring for 5 minutes. Filter the crystals on a filtering funnel, and return the crystals to the beaker used for crystallization. Recrystallize three more times in the same manner, and dry the crystals at 110° for 12 hours. Store in an amber bottle in a refrigerator at a temperature between 2° and 8°. Prepare this reagent fresh monthly.]

Chromatographic purity—Dissolve 100 mg of rose bengal sodium, prepared as described above, in 100 mL of water, and apply 10 µL of the solution on suitable chromatographic paper. Develop the chromatogram by ascending chromatography, using a mixture of 1 part of dilute alcohol (1 in 4) and 1 part of dilute stronger ammonia water (1 in 12). Examine the chromatogram in daylight and under UV light (360 nm): no colored or fluorescent spot is visible other than the rose bengal sodium spot.

[NOTE—A suitable grade is available commercially as "Silica Gel H".]

BRIEFING

Ruthenium Red, *USP 29* page 3149—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-7

Change to read:

Ruthenium Red *(Ruthenium Oxychloride, Ammoniated),* $Ru_2(OH)_2Cl_4 \cdot 7NH_3 \cdot 3H_2O$—**551.23**

■[*11103-72-3*]■2S (*USP30*)
—A brownish-red to dark purple powder. Soluble in water.

BRIEFING

Safranin O, *USP 29* page 3149—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-8

Change to read:

Safranin O

■—[*477-73-6*]■2S (*USP30*)
—Dark red powder consisting of a mixture of 3,7-diamino-2,8-dimethyl-5-phenylphenazinium chloride, $C_{20}H_{19}ClN_4$—350.85, and 3,7-diamino-2,8-dimethyl-5-*o*-tolylphenazinium chloride, $C_{21}H_{21}ClN_4$—364.88—Sparingly soluble in 70 percent alcohol yielding a clear red solution with a yellowish-red fluorescence.

Identification—

A: To 10 mL of a 0.5% w/v solution add 5 mL of hydrochloric acid: a bluish violet solution is produced.

B: To 10 mL of a 0.5% w/v solution add 5 mL of sodium hydroxide solution (1 in 5): a brownish-red precipitate is produced.

C: To 100 mg add 5 mL of sulfuric acid: a green solution is produced, which, on dilution, changes to blue and finally to red.

Absorption characteristics—Dissolve 50 mg in 250 mL of 50 percent alcohol. Dilute 3 mL of this solution with 50 percent alcohol to 200 mL. Determine the absorbance, in a 1-cm cell, with a suitable spectrophotometer. The absorbance maximum is in the range of 530 to 533 nm; the ratio $(P - 15)/(P + 15)$ is between 1.10 and 1.32, in which P is the wavelength of maximum absorbance.

[NOTE—A suitable grade is available as catalog number 10,214-8 from Sigma-Aldrich, www.sigma-aldrich.com.]

BRIEFING

Salicylaldehyde, *USP 29* page 3149—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-9

Change to read:

Salicylaldehyde, $2\text{-}HOC_6H_4CHO$—**122.12**

■[*90-02-8*]■2S (*USP30*)
—Clear, colorless to yellowish-green liquid. Specific gravity: about 1.17. Slightly soluble in water; soluble in alcohol and in ether. May contain a stabilizer.

Assay—When examined by gas-liquid chromatography, using suitable apparatus and conditions, it shows a purity of not less than 98%.

Congealing temperature ⟨651⟩: between 1.0° and 3.0°.

Refractive index ⟨831⟩: between 1.573 and 1.574 at 20°.

BRIEFING

Selenious Acid, *USP 29* page 3150—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-10

Change to read:

Selenious Acid *(Selenous Acid),* H_2SeO_3—**128.97**

■[*7783-00-8*]■2S (*USP30*)
—Colorless or white crystals, efflorescent in dry air and hygroscopic in moist air. Soluble in water and in alcohol.

Assay—Accurately weigh about 100 mg, transfer to a glass-stoppered flask, and dissolve in 50 mL of water. Add 10 mL of potassium iodide solution (3 in 10) and 5 mL of hydrochloric acid, mix, insert the stopper in the flask, and allow to stand for 10 minutes. Dilute with 50 mL of water, add 3 mL of starch TS, and titrate with 0.1 N sodium thiosulfate VS until the color is no longer diminished, then titrate with 0.1 N iodine VS to a blue color. Subtract the volume of 0.1 N iodine solution from the volume of 0.1 N sodium thiosulfate to give the volume of 0.1 N thiosulfate equivalent to selenious acid. Each mL of 0.1 N sodium thiosulfate is equivalent to 3.225 mg of H_2SeO_3: not less than 93% is found.

Insoluble matter—Dissolve 1 g in 5 mL of water: the solution is clear and complete.

Residue on ignition (Reagent test): not more than 1.0 mg (0.01%), from 10 g.

Selenate and *sulfate*—Dissolve 500 mg in 10 mL of water, and add 0.1 mL of hydrochloric acid and 1 mL of barium chloride TS: no turbidity or precipitate is formed within 10 minutes.

BRIEFING

Selenium, *USP 29* page 3150—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-11

Change to read:

Selenium, Se—**At. Wt. 78.96**

■[*7782-49-2*]■2S *(USP30)*
—Dark-red amorphous, or bluish-black, crystalline powder. Soluble in solutions of sodium and potassium hydroxides or sulfides; insoluble in water.

Residue on ignition (Reagent test)—One g yields not more than 2 mg (0.2%).

Heavy metals—To the *Residue on ignition* add 3 mL of hydrochloric acid and 2 mL of nitric acid, evaporate on a steam bath to dryness, take up the residue in a mixture of 2 mL of diluted hydrochloric acid and 50 mL of hot water, cool, filter, and wash the filter with sufficient water to make 100 mL of filtrate (*Test Solution*). To a 30-mL aliquot of the *Test Solution* add 10 mL of water and 10 mL of hydrogen sulfide TS: the color produced is not darker than that of a *Control Solution* prepared from 3 mL of *Standard Lead Solution* (see *Heavy Metals* ⟨231⟩; 0.03 mg of Pb), 0.2 mL of 1 N hydrochloric acid, 37 mL of water, and 10 mL of hydrogen sulfide TS (0.01%).

Iron ⟨241⟩—To 20 mL of the *Test Solution* prepared in the test for *Heavy metals* add 2 mL of hydrochloric acid, and dilute with water to 47 mL: the solution shows not more than 0.01 mg of Fe (0.005%).

Nitrogen—

STANDARD NITROGEN SOLUTION—Dissolve 382 mg of ammonium chloride in water to make 1 L. Each mL of this solution contains the equivalent of 0.1 mg of nitrogen (N).

PROCEDURE—Heat 1.0 g with 10 mL of sulfuric acid in a Kjeldahl flask until the test specimen is dissolved and the volume of acid is reduced to about 5 mL. Cool, cautiously dilute with 100 mL of water, render strongly alkaline with sodium hydroxide solution (3 in 10), and distill about 75 mL of the solution into 5 mL of water containing 2 drops of 1 N hydrochloric acid. Dilute the distillate with water to 250 mL. To a 50-mL aliquot of the solution add 1 mL of sodium hydroxide solution (1 in 10) and 2 mL of mercuric–potassium iodide TS: the color produced is not darker than that produced by 0.1 mL of *Standard nitrogen solution* (0.01 mg of N) treated in the same manner as the test specimen (0.005%).

Sulfur—To 1.0 g in a beaker add, successively, 5 mL of nitric acid, then 10 mL of hydrochloric acid, and evaporate on a steam bath to dryness. Add 10 mL of hydrochloric acid, and slowly evaporate again to dryness. Take up the residue in 30 mL of dilute hydrochloric acid (1 in 30), filter, and wash the filter with water to make about 100 mL of the filtrate. Heat the filtrate to boiling, and add slowly, with stirring, 5 mL of barium chloride TS. Digest on the steam bath for 4 hours. Pass through a fine-porosity filter paper, wash the precipitate until it is free from chloride, ignite, and weigh. The weight of the barium sulfate residue, multiplied by 0.1374, represents sulfur (S). Not more than 0.5 mg of S is found (0.05%).

BRIEFING

Selenomethionine, *USP 29* page 3150—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-12

Change to read:

Selenomethionine, $C_5H_{11}NO_2Se$—**196.11**

■[*1464-42-2*]■2S *(USP30)*
—*[Caution—Handle with care, as this reagent is highly toxic.]*

Assay—Weigh accurately about 750 mg, dissolve in 100 mL of methanol, add crystal violet TS, and titrate with 0.1 N perchloric acid to a blue-green endpoint. Each mL of 0.1 N perchloric acid is equivalent to 19.61 mg of $C_5H_{11}NO_2Se$: between 97.0% and 103.0%, calculated on the as-is basis, is found.

Melting range ⟨741⟩: about 260°, with decomposition.

Nitrogen content ⟨461⟩—Determine by the Kjeldahl method: between 6.8% and 7.4%, calculated on the as-is basis, is found.

BRIEFING

Silicic Acid, *USP 29* page 3151—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-13

Change to read:

Silicic Acid, $SiO_2 \cdot xH_2O$—(anhydrous) **60.08**

■[*1343-98-2*]■2S *(USP30)*
—White, amorphous powder. Insoluble in water and in acids; soluble in hot solutions of strong alkalies.

Residue on ignition (Reagent test): not less than 80.0%.

Nonvolatile with hydrofluoric acid—Heat 500 mg with 1 mL of sulfuric acid and 10 mL of hydrofluoric acid in a platinum crucible to dryness, and ignite to constant weight: the weight of the residue does not exceed 1.0 mg (0.2%).

Chloride (Reagent test)—One g shows not more than 0.05 mg of Cl (0.005%).

Sulfate (Reagent test)—Boil 2 g with 20 mL of dilute hydrochloric acid (1 in 40), filter, neutralize the filtrate with ammonia TS, and dilute with water to 20.0 mL. A 10-mL aliquot of the solution shows not more than 0.1 mg of SO_4 (0.01%).

Heavy metals (Reagent test)—Boil 2.5 g with 50 mL of dilute hydrochloric acid (1 in 10) for 5 minutes, filter while hot, and evaporate the filtrate on a steam bath to dryness. Take up the residue in 20 mL of dilute hydrochloric acid (1 in 500), digest for 5 minutes, cool, add water to make 100 mL, and filter. To 40 mL of the filtrate add 10 mL of hydrogen sulfide TS: any color produced is not darker than that produced by adding 10 mL of hydrogen sulfide TS to a control containing 0.03 mg of Pb (0.003%).

Iron ⟨241⟩—To 20 mL of the filtrate obtained in the test for *Heavy metals* add 1 mL of hydrochloric acid, and dilute with water to 47 mL: the solution shows not more than 0.015 mg of Fe (0.003%).

In-Process Revision

BRIEFING

Silicon Carbide, *USP 29* page 3151—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-14

Change to read:

Silicon Carbide, SiC—**40.10**

■[*409-21-2*]■2S (*USP30*)
—In small clean chips, suitable for use in promoting ebullition.

BRIEFING

Silicotungstic Acid, *n*-Hydrate,*USP 29* page 3151—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43599-15

Change to read:

Silicotungstic Acid, *n*-Hydrate *(Tungstosilicic Acid),* $H_4Si(W_3O_{10})_4 \cdot nH_2O$—**2878.17** (anhydrous)

■[*12520-88-6*]■2S (*USP30*)
—Green powder.

Assay—Dissolve about 1 g, accurately weighed, in 25 mL of dilute hydrochloric acid (1 in 5). Add 50 mL of a solution of 5 g of cinchonine in dilute hydrochloric acid (1 in 2). Warm on a steam bath for about 30 minutes. Cool, filter through a tared crucible, and ignite at 800° to constant weight. The weight of the residue multiplied by 1.047 is equal to the weight of silicotungstic acid dihydrate in the sample taken. Not less than 98% is found.

BRIEFING

Silver Diethyldithiocarbamate, *USP 29* page 3151—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-1

Change to read:

Silver Diethyldithiocarbamate, $(C_2H_5)_2NCS_2Ag$—**256.14**

■[*1470-61-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Silver Nitrate, *USP 29* page 3151—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-2

Change to read:

Silver Nitrate, $AgNO_3$—**169.87**

■[*7783-99-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Silver Oxide, *USP 29* page 3151—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-3

Change to read:

Silver Oxide, Ag_2O—**231.74**

■[*20667-12-3*]■2S (*USP30*)
—Brownish-black, heavy ▲▲*USP29* powder. Slowly decomposes on exposure to light. Absorbs carbon dioxide when moist. Practically insoluble in water; freely soluble in dilute nitric acid and in ammonia; insoluble in alcohol. Store in well-closed containers; do not expose to ammonia fumes or easily oxidizable substances.

Assay—Dissolve about 500 mg, previously dried at 120° for 3 hours and accurately weighed, in a mixture of 20 mL of water and 5 mL of nitric acid. Dilute with 100 mL of water, add 2 mL of ferric ammonium sulfate TS, and titrate with 0.1 N ammonium thiocyanate VS to a permanent reddish-brown color. Each mL of 0.1 N ammonium thiocyanate is equivalent to 11.59 mg of Ag_2O: not less than 99.7% of Ag_2O is found.

Loss on drying—Dry it at 120° for 3 hours: it loses not more than 0.25% of its weight.

Nitrate—To 500 mg add 30 mg of sodium carbonate and 2 mL of phenoldisulfonic acid TS, mix, and heat on a steam bath for 15 minutes. Cool, *cautiously* add 20 mL of water, render alkaline with ammonia TS, and dilute with water to 30 mL: any color produced by the test solution is not darker than that produced in a control containing 0.01 mg of NO_3 (0.002%).

Substances insoluble in nitric acid—Dissolve 5 g in a mixture of 5 mL of nitric acid and 10 mL of water, dilute with water to about 65 mL, and filter any undissolved residue on a tared filtering crucible (retain the filtrate for the test for *Substances not precipitated by hydrochloric acid*). Wash the crucible with water until the last washing shows no opalescence with 1 drop of hydrochloric acid, and dry at 105° to constant weight: the residue weighs not more than 1 mg (0.02%).

Substances not precipitated by hydrochloric acid—Dilute the filtrate obtained in the test for *Substances insoluble in nitric acid* with water to 250 mL, heat to boiling, and add, dropwise, sufficient hydrochloric acid to precipitate all of the silver (about 5 mL), avoiding any great excess. Cool, dilute with water to 300 mL, and allow to stand overnight. Filter, evaporate 200 mL of the filtrate in a suitable tared porcelain dish to dryness, and ignite: the residue weighs not more than 1.7 mg (0.05%).

Alkalinity—Heat 2 g with 40 mL of water on a steam bath for 15 minutes, cool, and dilute with water to 50 mL. Filter, discarding the first 10 mL of the filtrate. To 25 mL of the subsequent filtrate add 2 drops of phenolphthalein TS, and titrate with 0.02 N hydrochloric acid VS to the disappearance of any pink color: not more than 0.20 mL is required (0.016% as NaOH).

BRIEFING

Sodium, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-4

Change to read:

Sodium, Na—**At. Wt. 22.98977**

■[*7440-23-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Acetate, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-5

Change to read:

Sodium Acetate, $NaC_2H_3O_2 \cdot 3H_2O$—**136.08**

■[*127-09-3*]■2S (*USP30*)
—Use ACS reagent grade Sodium Acetate Trihydrate.

BRIEFING

Sodium Acetate, Anhydrous, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-6

Change to read:

Sodium Acetate, Anhydrous, $NaC_2H_3O_2$—**82.03**

■[*127-09-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Arsenite, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-7

Change to read:

Sodium Arsenite, $NaAsO_2$—**129.91**

■[*7784-46-5*]■2S (*USP30*)
—White, crystalline ▲*USP29* powder. Soluble in water; slightly soluble in alcohol.

Assay—Transfer about 5.5 g, accurately weighed, to a 500-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Pipet 25 mL of this solution into a suitable container, add 50 mL of water and 5 g of dibasic sodium phosphate, swirl to dissolve, and titrate with 0.1 N iodine VS, adding 3 mL of starch TS as the endpoint is approached. Each mL of 0.1 N iodine is equivalent to 3.746 mg of As. Between 57.0% and 60.5% is found (equivalent to 98.8% to 104.9% of $NaAsO_2$).

Chloride (Reagent test)—One g shows not more than 0.10 mg of Cl (0.01%).

Heavy metals—Dissolve 200 mg in 8 mL of dilute hydrochloric acid (3 in 8), and evaporate on a steam bath to dryness. Dissolve the residue in 5 mL of dilute hydrochloric acid (2 in 5), and again evaporate to dryness. Dissolve the residue in 10 mL of water, and add 2 mL of diluted acetic acid and 10 mL of hydrogen sulfide TS. Any brown color produced is not darker than that of a control containing 0.01 mg of added Pb (0.005%).

Iron—Dissolve 1 g in 20 mL of dilute hydrochloric acid (1 in 5), and add, dropwise, a slight excess of bromine TS. Boil the solution to remove the excess bromine, cool, dilute with water to 40 mL, and add 10 mL of ammonium thiocyanate solution (3 in 10). Any red color produced is not darker than that of a control containing 0.02 mg of added Fe (0.02%).

Sulfide—Dissolve 1 g in 20 mL of water, and add 5 drops of lead acetate TS: no brown color is produced (about 0.0005%).

Sulfate (Reagent test, *Method II*)—Dissolve 5 g in 100 mL of water, add methyl orange TS, neutralize with 1 N hydrochloric acid, add 3 mL of the acid in excess, and filter: the filtrate yields not more than 3 mg of residue (0.02%).

BRIEFING

Sodium Azide, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-8

Change to read:

Sodium Azide, NaN_3—**65.01**

■[*26628-22-8*]■2S (*USP30*)
—White powder.

Assay—[Caution—Sodium azide is a potent poison. Its conjugate acid HN_3 is more toxic than hydrogen cyanide and is readily liberated from neutral aqueous solutions. Contact of NaH_3 or hydrazoic acid (HN_3)with certain metals may produce explosive salts. Work in a well-ventilated hood, and handle the sample with care.] Dissolve about 100 mg, accurately weighed, in 50 mL of water, and add 3 drops of phenolphthalein. Adjust the pH, if

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necessary, to 7.0, and add 35.0 mL of 0.1 N perchloric acid. Pipet, while stirring, 2.5 mL of 1.0 M sodium nitrite into the solution, and stir for 15 seconds. Titrate rapidly to the phenolphthalein endpoint with 0.1 N sodium hydroxide. The endpoint should be reached in less than 4 minutes after addition of perchloric acid because HN_3 is readily volatile. Calculate the percentage of azide by the formula:

$$[(N_P)(V_P) - (N_S)(V_S)](65.01)(100)/2C$$

where N_P is the normality of perchloric acid solution; V_P is the volume of perchloric acid, in mL, taken; N_S is the normality of sodium hydroxide solution; V_S is the volume, in mL, of sodium hydroxide taken; 65.01 is the molecular weight of sodium azide; and C is the weight, in mg, of sodium azide. Not less than 98.5% of NaN_3 is found.

BRIEFING

Sodium Bicarbonate, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-9

Change to read:

Sodium Bicarbonate, $NaHCO_3$—**84.01**

■[*144-55-8*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Bisulfite, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-10

Change to read:

Sodium Bisulfite

■—[*7631-90-5*]■2S (*USP30*)
—Use ACS reagent grade Sodium Metabisulfite.

BRIEFING

Sodium Bitartrate, *USP 29* page 3152—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-11

Change to read:

Sodium Bitartrate, $NaHC_4H_4O_6 \cdot H_2O$—**190.08**

■[*526-94-3*]■2S (*USP30*)
—White crystals or a crystalline powder. Soluble in cold water.

Assay—Dissolve about 500 mg, accurately weighed, in 30 mL of water, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS: each mL of 0.1 N sodium hydroxide is equivalent to 19.01 mg of $NaHC_4H_4O_6 \cdot H_2O$. Between 99% and 100.5% is found.

Insoluble matter(Reagent test): not more than 1 mg, from 10 g (0.01%).

Chloride (Reagent test)—One g shows not more than 0.2 mg of Cl (0.02%).

Heavy metals (Reagent test)—Dissolve 4 g in 25 mL of water, add 2 drops of phenolphthalein TS, and then add ammonia TS, dropwise, until the solution is slightly pink. Add 4 mL of 1 N hydrochloric acid, dilute with water to 40 mL, and add 10 mL of hydrogen sulfide TS: any brown color produced is not darker than that of a control containing 0.04 mg of added Pb (0.001%).

Sulfate (Reagent test, *Method I*)—One g shows not more than 0.2 mg of SO_4 (0.02%).

BRIEFING

Sodium Borate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-12

Change to read:

Sodium Borate *(Borax; Sodium Tetraborate),* $Na_2B_4O_7 \cdot 10H_2O$—**381.37**

■[*1330-43-4*]■2S (*USP30*)
—Use ACS reagent grade.

[NOTE—Certified Borax is available from the National Institute of Standards and Technology, Washington, DC, www.nist.gov, as standard sample No. 187.]

BRIEFING

Sodium Borohydride, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-13

Change to read:

Sodium Borohydride, $NaBH_4$—**37.83**

■[*16940-66-2*]■2S (*USP30*)
—White, crystalline solid. Freely soluble in water; soluble (with reaction) in methanol. Its solutions are rapidly decomposed by boiling.

Assay—

POTASSIUM IODATE SOLUTION (0.25 N)—Dissolve 8.917 g, previously dried at 110° to constant weight and accurately weighed, in water to make 1000.0 mL.

PROCEDURE—Dissolve about 500 mg, accurately weighed, in 125 mL of sodium hydroxide solution (1 in 25) in a 250-mL volumetric flask, dilute with the sodium hydroxide solution to volume, and mix. Pipet 10 mL of the solution into a 250-mL iodine flask, add 35.0 mL of *Potassium iodate solution*, and mix. Add 2 g of potassium iodide, mix, add 10 mL of dilute sulfuric acid (1 in 10), insert the stopper in the flask, and allow to stand in the dark for 3 minutes. Titrate the solution with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Calculate the amount, in mg, of $NaBH_4$ in the specimen titrated by the formula:

$$([(35.0)(0.25)] - 0.1V)4.729$$

in which V is the volume, in mL, of 0.1 N sodium thiosulfate used in the titration. Not less than 98% is found.

BRIEFING

Sodium Bromide, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-14

Change to read:

Sodium Bromide, NaBr—**102.89**

■[*7647-15-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Carbonate, Anhydrous, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-15

Change to read:

Sodium Carbonate, Anhydrous, Na_2CO_3—**105.99**

■[*497-19-8*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Chloride, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-16

Change to read:

Sodium Chloride, NaCl—**58.44**

■[*7647-14-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Chromate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-17

Change to read:

Sodium Chromate, $Na_2CrO_4 \cdot 4H_2O$—**234.03**

■[*7775-11-3*]■2S ▲(*USP30*)
—Lemon-yellow ▲*USP29* crystals. Soluble in water.

Assay—Accurately weigh about 300 mg, and dissolve in 10 mL of water contained in a 500-mL flask. Add 3 g of potassium iodide and 10 mL of diluted sulfuric acid, and dilute with 350 mL of oxygen-free and carbon dioxide-free water. Titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached. Each mL of 0.1 N sodium thiosulfate consumed is equivalent to 7.802 mg of $Na_2CrO_4 \cdot 4H_2O$. Not less than 99% is found.

Insoluble matter (Reagent test): not more than 1 mg, from 20 g dissolved in 150 mL of water (0.005%).

Aluminum—Dissolve 20 g in 140 mL of water, filter, and add 5 mL of glacial acetic acid to the filtrate. Add stronger ammonia water until alkaline, and digest for 2 hours on a steam bath. Pass through hardened filter paper, wash thoroughly, ignite, and weigh: the residue weighs not more than 0.8 mg (0.002%).

Calcium—Determine as directed in the test for calcium for ACS reagent grade Potassium Chromate (0.005%).

Chloride—Determine as directed in the test for chloride for ACS reagent grade Potassium Chromate (about 0.005%).

Sulfate—Determine as directed in the test for sulfate for ACS reagent grade Potassium Dichromate, but add 4.5 mL of hydrochloric acid to the water used to dissolve the test specimen: the residue weighs not more than 2.4 mg (0.01%).

BRIEFING

Sodium Cobaltinitrite,*USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-18

Change to read:

Sodium Cobaltinitrite, $Na_3Co(NO_2)_6$—**403.94**

■[*13600-98-1*]■2S (*USP30*)
—Use ACS reagent grade.

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BRIEFING

Sodium Cyanide, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-19

Change to read:

Sodium Cyanide, NaCN—**49.01**

■[*1433-33-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium 1-Decanesulfonate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-6

Change to read:

Sodium 1-Decanesulfonate—

■[*13419-61-9*]—■2S (*USP30*)
Use a suitable grade.

BRIEFING

Sodium Dichromate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43600-20

Change to read:

Sodium Dichromate, $Na_2Cr_2O_7 \cdot 2H_2O$ (for chromic acid cleaning mixture)298.00

■ [*7789-12-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Diethyldithiocarbamate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-1

Change to read:

Sodium Diethyldithiocarbamate, $(C_2H_5)_2NCS_2Na \cdot 3H_2O$—**225.31**

■[*20624-25-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Dodecyl Sulfate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-2

Change to read:

Sodium Dodecyl Sulfate *(Sodium Lauryl Sulfate),* $C_{12}H_{25}SO_4Na$—**288.38**[

■151-21-3]■2S (*USP30*)
—Light yellow, crystalline powder.

BRIEFING

Sodium Ferrocyanide, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-3

Change to read:

Sodium Ferrocyanide, $Na_4Fe(CN)_6 \cdot 10H_2O$—**484.06**

■[*13601-19-9*]■2S (*USP30*)
—Yellow crystals or granules. Freely soluble in water.

Assay—Dissolve 2 g, accurately weighed, in 400 mL of water, add 10 mL of sulfuric acid, and titrate with 0.1 N potassium permanganate VS. Each mL of 0.1 N potassium permanganate is equivalent to 48.41 mg of $Na_4Fe(CN)_6 \cdot 10H_2O$. Not less than 98% is found.

Insoluble matter (Reagent test): not more than 1 mg, from 10 g (0.01%).

Chloride (Reagent test)—Dissolve 1 g in 75 mL of water, add a solution prepared by dissolving 1.2 g of cupric sulfate in 25 mL of water, mix, and allow to stand for 15 minutes. To 20 mL of the decanted, clear liquid add 2 mL of nitric acid and 1 mL of silver nitrate TS: any turbidity produced does not exceed that of a control containing 0.02 mg of Cl, 2 mL of nitric acid, 1 mL of silver nitrate TS, and sufficient cupric sulfate to match the color of the Test solution.

Sulfate—Dissolve 5 g in 100 mL of water without heating, filter, and to the filtrate add 0.25 mL of glacial acetic acid and 5 mL of barium chloride TS: no turbidity is produced in 10 minutes (about 0.01% as SO_4).

BRIEFING

Sodium Fluoride, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-4

Change to read:

Sodium Fluoride, NaF—**41.99**

■[*7681-49-4*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

Sodium Glycocholate,*USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-5

Change to read:

Sodium Glycocholate, $C_{26}H_{42}NNaO_6$—**487.60**

■[*863-57-0*]■2S ▲*(USP30)*
—White to tan ▲*USP29* powder. Is hygroscopic. Freely soluble in water and in alcohol.

Specific rotation ⟨781⟩: between +28° and +31°, calculated on the dried basis (it is rendered anhydrous by drying at 100° for 2 hours), determined at 20° in a solution containing 10 mg per mL.

Nitrogen, Method I ⟨461⟩: between 2.6% and 3.2% of N is found, calculated on the dried basis.

BRIEFING

Sodium 1-Heptanesulfonate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-7

Change to read:

Sodium 1-Heptanesulfonate *(1-Heptanesulfonic Acid Sodium Salt),* $C_7H_{15}NaO_3S$—**202.25**

■[*22767-50-6*]■2S *(USP30)*
—Use a suitable grade.

BRIEFING

Sodium 1-Hexanesulfonate, *USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-8

Change to read:

Sodium 1-Hexanesulfonate *(1-Hexanesulfonic Acid Sodium Salt),* $C_6H_{13}NaO_3S$—**188.22**

■[*2832-45-3*]■2S *(USP30)*
—Use a suitable grade.

BRIEFING

Sodium Hydrosulfite,*USP 29* page 3153—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-9

Change to read:

Sodium Hydrosulfite *(Sodium Dithionite),* $Na_2S_2O_4$—**174.11**

■[*7775-14-6*]■2S *(USP30)*
—White or grayish-white crystalline powder. Soluble in water; slightly soluble in alcohol. Gradually oxidizes in air, more readily when in solution, to bisulfite, acquiring an acid reaction. Is affected by light.

Assay—Accurately weigh about 1 g, dissolve it in a mixture of 10 mL of formaldehyde TS and 10 mL of water contained in a small glass-stoppered flask, and allow to stand for 30 minutes with frequent agitation. Transfer the solution to a 250-mL volumetric flask, add 150 mL of water and 3 drops of methyl orange TS, and then add, dropwise, 1 N sulfuric acid to a slightly acid reaction. Dilute with water to 250 mL, and mix. To 50.0 mL of the dilution add 2 drops of phenolphthalein TS and just sufficient 0.1 N sodium hydroxide to produce a slight, pink color, then titrate with 0.1 N iodine, adding 3 mL of starch TS as the indicator. Then discharge the blue color of the solution with 1 drop of 0.1 N sodium thiosulfate, and titrate with 0.1 N sodium hydroxide VS to a pink color: each mL of 0.1 N sodium hydroxide is equivalent to 3.482 mg of $Na_2S_2O_4$. Not less than 88% is found.

Sulfide—Add sodium hydroxide solution (1 in 10) to lead acetate TS until the precipitate dissolves. Add 5 drops of this solution to a solution of 1 g of the sodium hydrosulfite in 10 mL of water: no immediate darkening is observed.

Heavy metals—Dissolve 1 g in 10 mL of water, add 10 mL of hydrochloric acid, and evaporate on a steam bath to dryness. Dissolve the residue in 20 mL of water and 0.5 mL of diluted hydrochloric acid, filter, and add to the filtrate 10 mL of hydrogen sulfide TS: no darkening is produced. Render the solution alkaline with ammonia TS: a slight, greenish color may be produced, but not a dark or white precipitate.

Suitability for riboflavin assay—To each of 2 or more tubes add 10 mL of water and 1.0 mL of a standard riboflavin solution containing 20 µg of riboflavin in each mL, and mix. To each tube add 1.0 mL of glacial acetic acid, mix, add with mixing, 0.5 mL of potassium permanganate solution (1 in 25), and allow to stand for 2 minutes. Then to each tube add, with mixing, 0.5 mL of hydrogen peroxide TS: the permanganate color is destroyed within 10 seconds. Shake the tubes vigorously until excess oxygen is expelled. If gas bubbles

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remain on the sides of tubes after foaming has ceased, remove the bubbles by tipping the tubes so that the solution flows slowly from end to end. In a suitable fluorometer, measure the fluorescence of the solution. Then add, with mixing, 8.0 mg of sodium hydrosulfite: the riboflavin is completely reduced in not more than 5 seconds.

BRIEFING

Sodium Hydroxide, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-10

Change to read:

Sodium Hydroxide, NaOH—**40.00**

■[*1310-73-2*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Hypochlorite Solution, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-11

Change to read:

Sodium Hypochlorite Solution

■—[*7681-52-9*]■2S (*USP30*)
—A solution of sodium hypochlorite (NaOCl) in water. Usually yellow to yellowish-green in color. Has an odor of chlorine. Is affected by light and gradually deteriorates. Store it in light-resistant containers, preferably below 25°. *[Caution—This solution is corrosive and may evolve gases that are corrosive and toxic. It is a powerful oxidant that can react violently with reducing agents. Is irritating and corrosive to skin and mucous membranes.]*

Assay—Transfer about 3 mL to a tared, glass-stoppered iodine flask, and weigh accurately. Add 50 mL of water, 2 g of potassium iodide, and 10 mL of acetic acid, insert the stopper in the flask, and allow to stand in the dark for 10 minutes. Remove the stopper, rinse the walls of the flask with a few mL of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is neared. Each mL of 0.1 N sodium thiosulfate consumed is equivalent to 3.723 mg of NaOCl: not less than 5.25% is found. If it is desired to calculate the percentage of available chlorine, note that each mL of 0.1 N sodium thiosulfate consumed is equivalent to 3.545 mg of available chlorine.

Calcium—Transfer 10.0 g to a 150-mL beaker, dissolve in 10 mL of water, and add 5 mL of hydrochloric acid and 2 g of potassium iodide. Heat the mixture for 5 minutes, cool, and add 2 mL of 30 percent hydrogen peroxide. Evaporate to dryness, cool, and add 2 mL of hydrochloric acid and 2 mL of 30 percent hydrogen peroxide. Rinse the inner walls of the beaker with a few mL of water, and evaporate to dryness. Take up the residue in 20 mL of water, and filter if necessary. To the filtrate add ammonium hydroxide until the solution is just alkaline, then add 4 drops of ammonium hydroxide and 5 mL of ammonium oxalate TS: any turbidity produced within 15 minutes does not exceed that in a blank containing 0.1 mg of added Ca carried through the entire procedure (0.001%).

Phosphate (Reagent test)—Transfer 2 g to a beaker, and add 5 mL of hydrochloric acid and 2 g of potassium iodide. Heat the solution for 5 minutes, and cool. Add 2 mL of 30 percent hydrogen peroxide, and evaporate the solution to dryness. Rinse the walls of the beaker with a few mL of water, and add 2 mL of hydrochloric acid and 2 mL of 30 percent hydrogen peroxide. Evaporate again to dryness: the residue shows not more than 0.01 mg of PO_4 (5 ppm).

BRIEFING

Sodium Metabisulfite, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-12

Change to read:

Sodium Metabisulfite, $Na_2S_2O_5$—**190.11**

■[*7681-57-4*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Metaperiodate,*USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-13

Change to read:

Sodium Metaperiodate, $NaIO_4$—**213.89**

■[*7790-28-5*]■2S (*USP30*)
—Use ACS reagent grade Sodium Periodate.

BRIEFING

Sodium Methoxide, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-14

Change to read:

Sodium Methoxide, CH_3ONa—**54.02**

■[*124-41-4*]■2S (*USP30*)
—Fine, white powder. Reacts violently with water with evolution of heat. Soluble in alcohol and in methanol.

Assay—Transfer about 220 mg to a tared, glass-stoppered flask, and weigh accurately. Dissolve the test specimen in about 10 mL of methanol, then add 100 mL of water slowly, with stirring. Add phenolphthalein TS, and titrate with 0.1 N hydrochloric acid VS to a

colorless endpoint: each mL of 0.1 N hydrochloric acid VS is equivalent to 5.402 mg of CH_3ONa. Not less than 98.0% is found.

BRIEFING

Sodium Molybdate, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-15

Change to read:

Sodium Molybdate, $Na_2MoO_4 \cdot 2H_2O$—**241.95**

■[*7631-95-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Nitrate, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-16

Change to read:

Sodium Nitrate, $NaNO_3$—**84.99**

■[*7631-99-4*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Nitrite, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-17

Change to read:

Sodium Nitrite, $NaNO_2$—**69.00**

■[*7632-00-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Nitroferricyanide, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-18

Change to read:

Sodium Nitroferricyanide *(Sodium Nitroprusside),* $Na_2Fe(NO)(CN)_5 \cdot 2H_2O$—**297.95**

■[*13755-38-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium 1-Octanesulfonate, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-19

Change to read:

Sodium 1-Octanesulfonate, $C_8H_{17}NaO_3S$—**216.27**

■[*5324-84-5*]■2S (*USP30*)
—Use a suitable grade.

BRIEFING

Sodium Oxalate, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43601-20

Change to read:

Sodium Oxalate, $Na_2C_2O_4$—**134.00**

■[*62-76-0*]■2S (*USP30*)
—Use ACS reagent grade.
[NOTE—Sodium Oxalate of a quality suitable as a primary standard is available from the Office of Standard Reference Materials, National Institute of Standards and Technology, Washington, DC, www.nist.gov, as standard sample No. 40.]

In-Process Revision

BRIEFING

Sodium (tri) Pentacyanoamino Ferrate, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-1

Change to read:

Sodium (tri) Pentacyanoamino Ferrate *[Trisodium Aminepentacyanoferrate (3-)],* $Na_3[Fe(CN)_5NH_3]$—**271.93**

■[*14099-05-9*]■2S (*USP30*)
—Yellow to tan powder. Soluble in water.

Solubility—Dissolve 500 mg in 50 mL of water, and allow to stand for 1 hour: the solution is clear and free from foreign matter.

Sensitivity—

1,1-DIMETHYLHYDRAZINE STANDARD SOLUTION—Place 500 mL of water in a 1-L volumetric flask, and add from a buret 1.27 mL of anhydrous 1,1-dimethylhydrazine. Dilute with water to volume, and mix. Pipet 10 mL of this solution into a 100-mL volumetric flask, and dilute with water to volume. Each mL of this solution contains the equivalent of 100 µg of 1,1-dimethylhydrazine.

BUFFER SOLUTION—Transfer 4.8 g of citric acid monohydrate to a 1-L volumetric flask, dissolve in water, add 14.6 g of sodium phosphate, swirl to dissolve, and dilute with water to volume.

TEST PREPARATION—Dissolve 100 mg of sodium (tri)pentacyanoamino ferrate in 100 mL of water.

PROCEDURE—Into each of five 25-mL volumetric flasks pipet 0 mL, 0.25 mL, 0.50 mL, 1.0 mL, and 1.5 mL, respectively, of *1,1-Dimethylhydrazine standard solution;* to each add 15 mL of *Buffer solution,* and swirl to mix. To each flask, add by pipet 2 mL of *Test preparation,* mix, dilute with *Buffer solution* to volume, and allow to stand for 1 hour. Using a suitable spectrophotometer, 1-cm cells, and the solution containing no *1,1-Dimethylhydrazine standard solution* as the blank, determine the absorbances of the remaining solutions at 500 nm. Plot the observed absorbance as the ordinate versus the concentration of standard as the abscissa on coordinate paper, and draw the curve of best fit. The plot is linear and the absorbance of the 150-µg solution is not less than 0.65.

BRIEFING

Sodium 1-Pentanesulfonate, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-2

Change to read:

Sodium 1-Pentanesulfonate, $C_5H_{11}NaO_3S \cdot H_2O$—**192.21**

■[*22767-49-3*]■2S (*USP30*)
—White, crystalline solid. Soluble in water.

Solubility—One g, dissolved in 25 mL of water, yields a clear and complete solution.

Water, Method I ⟨921⟩: not more than 2.0%.

BRIEFING

Sodium Perchlorate, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-3

Change to read:

Sodium Perchlorate, $NaClO_4 \cdot H_2O$—**140.46**

■[*7601-89-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Peroxide, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-4

Change to read:

Sodium Peroxide, Na_2O_2—**77.98**

■[*1313-60-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Phosphate, Dibasic, *USP 29* page 3154—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-5

Change to read:

Sodium Phosphate, Dibasic *(Disodium Phosphate; Disodium Hydrogen Phosphate; Sodium Phosphate, Dibasic, Heptahydrate),* $Na_2HPO_4 \cdot 7H_2O$—**268.07**

■[*7782-85-6*]■2S (*USP30*)
—Use ACS reagent grade Sodium Phosphate, Dibasic, Heptahydrate.

BRIEFING

Sodium Phosphate, Dibasic, Anhydrous, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-6

Change to read:

Sodium Phosphate, Dibasic, Anhydrous *(Anhydrous Disodium Hydrogen Phosphate)* (for buffer solutions), Na_2HPO_4—**141.96**

■[*7558-79-4*]■2S (*USP30*)
—Use ACS reagent grade Sodium Phosphate, Dibasic, Anhydrous.

BRIEFING

Sodium Phosphate Dibasic, Dodecahydrate. It is proposed to add this new reagent used to prepare the *Phosphate buffer* in the test for *Related compounds* under *Citalopram Tablets.*

(HDQ: M. Marques) RTS—C45954

Add the following:

■**Sodium Phosphate Dibasic, Dodecahydrate** *(Disodium Hydrogen Phosphate, Dodecahydrate),* $Na_2HPO_4.12H_2O$—**358.14**[*10039-32-4*]—Use a suitable grade with a content of between 98.0% and 102.0% of $Na_2HPO_4 \cdot 12H_2O$.■2S (*USP30*)

BRIEFING

Sodium Phosphate, Monobasic, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-7

Change to read:

Sodium Phosphate, Monobasic *(Sodium Biphosphate; Sodium Dihydrogen Phosphate; Acid Sodium Phosphate; Monosodium Orthophosphate),* $NaH_2PO_4 \cdot H_2O$—**137.99**

■[*10049-21-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Phosphate, Tribasic, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-8

Change to read:

Sodium Phosphate, Tribasic, $Na_3PO_4 \cdot 12H_2O$—**380.12**

■[*7601-54-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Pyrophosphate,*USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-9

Change to read:

Sodium Pyrophosphate, $Na_4P_2O_7 \cdot 10H_2O$—**265.90**

■[*7722-88-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Pyruvate, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-10

Change to read:

Sodium Pyruvate, CH_3COCO_2Na—**110.04**

■[*113-24-6*]■2S (*USP30*)
—White to practically white powder or crystalline solid. Soluble in water.

Assay—Transfer about 300 mg, accurately weighed, to a high-form titration beaker, add 150 mL of glacial acetic acid, and stir until dissolved. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using a glass electrode and a calomel electrode modified to use 0.1 N tetramethylammonium chloride in methanol as the electrolyte. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 11.00 mg of CH_3COCO_2Na: not less than 98.0% is found.

Solubility—Dissolve 1.5 g in 25 mL of water: the solution is clear and complete.

Free acid—Dissolve 10 g in 150 mL of water, and titrate with 0.5 N sodium hydroxide VS, determining the endpoint potentiometrically: not more than 2.8 mL of 0.5 N sodium hydroxide is consumed (about 1% as $C_3H_4O_3$).

In-Process Revision

BRIEFING

Sodium Salicylate, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-11

Change to read:

Sodium Salicylate—

■[*54-21-7*]■2S (*USP30*)
—It complies with the specifications under *Sodium Salicylate* (USP monograph), and in addition meets the requirements of the following test.

Nitrate—Dissolve 100 mg in 5 mL of water, and superimpose the solution upon 5 mL of sulfuric acid: no brownish-red color appears at the junction of the two liquids.

BRIEFING

Sodium Selenite, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-12

Change to read:

Sodium Selenite, Na_2SeO_3—**172.94**

■[*10102-18-8*]■2S (*USP30*)
—White, odorless, crystalline powder, usually partially hydrated. Freely soluble in water; insoluble in alcohol.

Assay—Accurately weigh about 180 mg, previously dried at 120° to constant weight, and dissolve it in 50 mL of water in a glass-stoppered flask. Add, successively, 3 g of potassium iodide and then 5 mL of hydrochloric acid, insert the stopper, and allow to stand for 10 minutes. Add 50 mL of water, 50.0 mL of 0.1 N sodium thiosulfate VS, and 3 mL of starch TS, and immediately titrate with 0.1 N iodine VS to a blue color. Perform a blank determination. The difference in volumes of 0.1 N iodine is equivalent to 4.323 mg of Na_2SeO_3. Between 98% and 101% is found.

Solubility—One g in 10 mL of water shows not more than a faint haze.

Carbonate—To 500 mg add 1 mL of water and 2 mL of diluted hydrochloric acid: no effervescence is produced.

Chloride (Reagent test)—A 500-mg portion shows not more than 0.05 mg of Cl (0.01%).

Nitrate (Reagent test)—A 200-mg portion dissolved in 3 mL of water shows not more than 0.02 mg of NO_3 (0.01%).

Selenate and *sulfate* (*as* SO_4)—To 500 mg in a small evaporating dish add 20 mg of sodium carbonate and 10 mL of hydrochloric acid. Slowly evaporate the solution on a steam bath under a hood to dryness. Wash the sides of the dish with 5 mL of hydrochloric acid, and again evaporate to dryness. Dissolve the residue in a mixture of 15 mL of hot water and 1 mL of hydrochloric acid. Proceed as directed under *Sulfate in Reagents* (Reagent test, *Method I*), beginning with "Filter the solution." The test specimen shows no more turbidity than that produced by 0.15 mg of SO_4 (0.03%).

BRIEFING

Sodium Sulfate, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-13

Change to read:

Sodium Sulfate *(Glauber's Salt),* $Na_2SO_4 \cdot 10H_2O$—**322.20**

■[*7727-73-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Sulfate, Anhydrous, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-14

Change to read:

Sodium Sulfate, Anhydrous, Na_2SO_4—**142.04**

■[*7757-82-6*]■2S (*USP30*)
—Use ACS reagent grade.

For use in assaying alkaloids by gas–liquid chromatography, it conforms to the following additional test.

Suitability for alkaloid assays—Transfer about 10 mg of atropine, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with alcohol to volume. Pipet 3 mL of the solution into each of two 60-mL separators, and add to each 10 mL of water, 1 mL of 1 N sodium hydroxide, and 10 mL of chloroform. Shake thoroughly, and allow the layers to separate. Filter the organic phase from one separator through phase-separating paper, previously washed with 5 mL of chloroform, supported in a funnel, and collect the filtrate in a suitable container. Add 10 mL of chloroform to the separator, shake thoroughly, and filter the organic layer through the same phase-separating paper, collecting and combining the filtrates in the same container. Designate the combined filtrates as *Solution A*. Filter the organic phase from the second separator through 30 g of the Anhydrous Sodium Sulfate, supported on a pledget of glass wool in a small funnel, and previously washed with chloroform, and collect the filtrate in a suitable container. Add 10 mL of chloroform to the separator, shake thoroughly, and filter the organic layer through the same portion of anhydrous sodium sulfate, collecting and combining the two filtrates in the same container. Designate the combined filtrates as *Solution B*. Evaporate the two solutions in vacuum to a volume of about 1 mL. Inject an accurately measured volume of *Solution A* into a suitable gas chromatograph, and record the peak height. Repeat the determination with a second accurately measured volume of *Solution A,* record the peak height, and obtain the average of the two results. In a similar manner, determine the peak height of two portions of *Solution B,* and obtain the average of the results. The average value obtained for *Solution B* is within 5.0% of the value obtained for *Solution A*.

Under typical conditions, the gas chromatograph contains a 4-mm × 1.2-m glass column packed with 3% phase G3 on packing S1A. After curing and conditioning, the column temperature is maintained at 210°, the injector port temperature at 225°, and the detector block temperature at 240° during the determinations. The carrier gas is helium, flowing at a rate of 60 mL per minute.

BRIEFING

Sodium Sulfide, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-16

Change to read:

Sodium Sulfide, $Na_2S \cdot 9H_2O$—**240.18**

■[*1313-84-4*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Sulfite, Anhydrous, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-17

Change to read:

Sodium Sulfite, Anhydrous *(Exsiccated Sodium Sulfite),* Na_2SO_3—**126.04**

■[*7753-83-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Tartrate, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-18

Change to read:

Sodium Tartrate, $Na_2C_4H_4O_6 \cdot 2H_2O$—**230.08**

■[*6106-24-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Tetraphenylborate, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-15

Change to read:

Sodium Tetraphenylborate, $NaB(C_6H_5)_4$—**342.22**

■[*143-66-8*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Thioglycolate,*USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43614-20

Change to read:

Sodium Thioglycolate *(Sodium Thioglycollate),* $HSCH_2COONa$—**114.10**

■[*367-51-1*]■2S (*USP30*)
—A white, crystalline powder. ~~having a slight, characteristic odor.~~

■■2S (*USP30*)
Very soluble in water; slightly soluble in alcohol. Is hygroscopic, and oxidizes in air. Store in tight, light-resistant containers. It should not be used if it is pale yellow or darker in color.

Assay—Accurately weigh about 250 mg, and dissolve in 50 mL of oxygen-free water. Add 5 mL of diluted hydrochloric acid, boil for 2 minutes, cool, and titrate the solution with 0.1 N iodine VS, adding 3 mL of starch TS toward the end: each mL of 0.1 N iodine is equivalent to 11.41 mg of $HSCH_2COONa$. Not less than 75% is found.

Insoluble matter—A solution of 1 g in 10 mL of water is clear, and practically complete.

Sulfide—Dissolve 500 mg in 10 mL of water in a small flask, add 2 mL of hydrochloric acid, then place a strip of filter paper, moistened with lead acetate TS, over the mouth of the flask, and bring the solution to a boil: the lead acetate paper is not darkened.

BRIEFING

Sodium Thiosulfate, *USP 29* page 3155—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-1

In-Process Revision

Change to read:

Sodium Thiosulfate, $Na_2S_2O_3 \cdot 5H_2O$—**248.19**

■[*10102-17-7*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sodium Tungstate, *USP 29* page 3156—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-2

Change to read:

Sodium Tungstate, $Na_2WO_4 \cdot 2H_2O$—**329.85**

■[*10213-10-2*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Stannous Chloride, *USP 29* page 3156—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-3

Change to read:

Stannous Chloride, $SnCl_2 \cdot 2H_2O$—**225.65**

■[*7772-99-8*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Starch, Soluble, *USP 29* page 3156—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-4

Change to read:

Starch, Soluble (for iodimetry)

■—[*9005-84-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Stearic Acid, *USP 29* page 3156—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-5

Change to read:

Stearic Acid, $C_{18}H_{36}O_2$—**284.48**

■[*57-11-4*]■2S (*USP30*)
—Hard, white crystals or amorphous, white powder. Freely soluble in chloroform and in ether; soluble in alcohol and in solvent hexane.

Congealing temperature ⟨651⟩: between 67° and 69°.

Acid value ⟨401⟩: between 196 and 199.

Iodine value ⟨401⟩: not more than 1.

Saponification value ⟨401⟩: between 197 and 200.

Palmitic acid—Determine as directed in the *Assay* under *Stearic Acid* (*NF* monograph): not more than 5.0% is found.

BRIEFING

Stearyl Alcohol, *USP 29* page 3156—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-6

Change to read:

Stearyl Alcohol *(1-Octadecanol),* $C_{18}H_{38}O$—**270.49**

■[*112-92-5*]■2S (*USP30*)
—White flakes, granules, or crystals. Soluble in alcohol, in ether, in acetone, and in benzene; insoluble in water.

Melting range ⟨741⟩: between 56° and 58°.

Other requirements—It conforms to the tests for *Acid value, Iodine value,* and *Hydroxyl value* under *Stearyl Alcohol* (*NF* monograph).

BRIEFING

Strontium Acetate, *USP 29* page 3156—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-7

Change to read:

Strontium Acetate, $Sr(CH_3COO)_2 \cdot ½H_2O$—**214.72**

■[*543-94-2*]■2S (*USP30*)
—White, crystalline powder. Soluble in 3 parts of water; slightly soluble in alcohol.

Assay—Ignite about 3 g, accurately weighed, in a platinum crucible, protecting from sulfur in the flame. Cool, transfer the crucible with the residue to a beaker, and add 50 mL of water and

40.0 mL of 1 N hydrochloric acid VS. Boil gently for 30 minutes or longer, if necessary; filter; wash with hot water until the washings are neutral; add methyl red TS; and titrate the excess acid with 1 N sodium hydroxide VS. Each mL of 1 N hydrochloric acid is equivalent to 107.4 mg of $Sr(CH_3COO)_2 \cdot \frac{1}{2}H_2O$: not less than 99% is found.

Insoluble matter(Reagent test): not more than 2 mg, from 10 g (0.02%).

Free alkali or free acid—Dissolve 3 g in 30 mL of water, and add 3 drops of phenolphthalein TS: no pink color is produced. Titrate with 0.1 N sodium hydroxide VS to a pink color: not more than 0.30 mL of the 0.1 N sodium hydroxide is required.

Barium—Dissolve 1 g in 10 mL of water, and add 1 drop of glacial acetic acid and 5 drops of potassium dichromate solution (1 in 10): no turbidity is produced within 2 minutes (about 0.02%).

Calcium—Ignite 1 g until completely carbonized. Warm the residue with a mixture of 3 mL of nitric acid and 10 mL of water, filter, wash with 5 mL of water, and evaporate the filtrate on a steam bath to dryness. Powder the residue, and dry it at 120° for 3 hours. Reflux the dried powder with 15 mL of dehydrated alcohol for 10 minutes, cool in ice, and filter. Repeat the extraction with 10 mL of dehydrated alcohol. Evaporate the combined filtrates to dryness, add 0.5 mL of sulfuric acid, and ignite: the weight of the residue is not more than 10 mg (0.3% of Ca).

Chloride (Reagent test)—One g shows not more than 0.1 mg of Cl (0.01%).

Heavy metals (Reagent test): 0.001%.

Iron ⟨241⟩—Dissolve 1.0 g in 45 mL of water, and add 2 mL of hydrochloric acid: the solution shows not more than 0.01 mg of Fe (0.001%).

Alkali salts—Dissolve 2 g in 80 mL of water, heat to boiling, add an excess of ammonium carbonate TS, boil for 5 minutes, dilute with water to 100 mL, and filter. Evaporate 50 mL of the filtrate, and ignite: the residue, after correcting for the ignition residue from half the volume of the clear ammonium carbonate TS used above, is not more than 3 mg (0.3%).

Nitrate—Dissolve 1 g in 10 mL of water, add 0.10 mL of indigo carmine TS, and then add 10 mL of sulfuric acid: the blue color persists for 5 minutes (about 0.01% of NO_3).

BRIEFING

Strontium Hydroxide,*USP 29* page 3156—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-8

Change to read:

Strontium Hydroxide *(Strontium Hydroxide Octahydrate),* $Sr(OH)_2 \cdot 8H_2O$—**265.76**

■[*18480-07-4*]■2S (*USP30*)
—White, crystalline, free-flowing powder. Sparingly soluble in water. May absorb carbon dioxide from the air. Keep tightly closed.

Assay and *carbonate*—Accurately weigh about 5 g, dissolve in 200 mL of warm carbon dioxide-free water in a glass-stoppered, 500-mL flask, add phenolphthalein TS, and titrate with 1 N hydrochloric acid VS to determine the hydroxide alkalinity. Then add methyl orange TS, and titrate with 1 N hydrochloric acid VS. Each mL of 1 N hydrochloric acid required to reach the phenolphthalein endpoint is equivalent to 132.9 mg of $Sr(OH)_2 \cdot 8H_2O$, and each additional mL of 1 N hydrochloric acid VS required to reach the methyl orange endpoint is equivalent to 73.8 mg of $SrCO_3$. Not less than 95.0% of $Sr(OH)_2 \cdot 8H_2O$ and not more than 3.0% of $SrCO_3$ are found.

Chloride (Reagent test)—Dissolve 1.0 g in 100 mL of water, and filter if necessary: 1.0 mL of the solution shows not more than 0.01 mg of Cl (0.1%).

Calcium (Reagent test)—

TEST SOLUTION—Dissolve 5.0 g in water, and dilute with water to 100 mL.

SAMPLE SOLUTION—Dilute 10.0 mL of the *Test solution* with water to 100 mL.

CONTROL SOLUTION—To 10.0 mL of the *Test solution* add 0.50 mg of calcium ion (Ca), and dilute with water to 100 mL.

PROCEDURE—Determine the background emission at 416.7 nm: the limit is 0.1%.

Iron—Dissolve 1 g in warm water, and dilute with water to 100 mL. To 20 mL of this solution add 2 mL of hydrochloric acid and 0.1 mL of 0.1 N potassium permanganate, allow to stand for 5 minutes, and add 3 mL of ammonium thiocyanate solution (3 in 10). Any red color produced is not darker than that of a control containing 0.03 mg of added Fe (0.015%).

Heavy metals—Dissolve 2.0 g in 14 mL of dilute hydrochloric acid (1 in 6), and evaporate on a steam bath to dryness. Take up the residue in 25 mL of water, filter, and dilute with water to 100 mL *(Test solution).* To 5.0 mL of the *Test solution* add 0.02 mg of lead (Pb), and dilute with water to 30 mL, to provide the standard. For the test specimen, use 30 mL of the *Test solution.* Adjust each solution with diluted acetic acid or ammonia TS to a pH between 3.0 and 4.0 (using short-range pH paper), dilute with water to 40 mL, and add 10 mL of freshly prepared hydrogen sulfide TS: any brown color developed in the sample solution is not darker than that in the control solution (0.004%).

BRIEFING

Strychnine Sulfate, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-9

Change to read:

Strychnine Sulfate, $(C_{21}H_{22}N_2O_2)_2 \cdot H_2SO_4 \cdot 5H_2O$—**856.98**

■[*60-41-3*]■2S (*USP30*)
—Colorless or white crystals, or a white, crystalline powder. Its solutions are levorotatory. One g dissolves in about 35 parts of water, in 85 mL of alcohol, and in about 220 mL of chloroform. Insoluble in ether.

Solubility—A solution of 500 mg in 25 mL of water is complete, clear, and colorless.

Residue on ignition (Reagent test): not more than 0.1%.

Brucine—To 100 mg add 1 mL of dilute nitric acid (1 in 2): a yellow color may be observed, but not a red or reddish-brown color.

In-Process Revision

BRIEFING

Sudan III, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-10

Change to read:

Sudan III, $C_{22}H_{16}N_4O$—**352.39**

■[*85-86-9*]■2S (*USP30*)
—Red to red-brown powder. Use a suitable grade.

Assay—When tested by thin-layer chromatography (see *Chromatography* ⟨621⟩) with the use of plates coated with chromatographic silica gel mixture and a developing system consisting of a mixture of hexane and ethyl acetate (80 : 20), and examined under short-wavelength UV light, a single spot is exhibited, with trace impurities.

BRIEFING

Sudan IV, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-11

Change to read:

Sudan IV, $C_{24}H_{20}N_4O$—**380.44**

■[*85-83-6*]■2S (*USP30*)
—Brown to reddish-brown powder.

Assay—Transfer about 25 mg, accurately weighed, to a 100-mL volumetric flask. Dissolve in chloroform, dilute with chloroform to volume, and mix. Dilute 2.0 mL of the resulting solution with chloroform to 50.0 mL. Determine the absorbance of this solution in 1-cm cells at the wavelength of maximum absorbance at about 520 nm, with a suitable spectrophotometer, using chloroform as the blank. Calculate the percentage of Sudan IV in the test specimen taken by the formula:

$$(100A) / (85C)$$

in which A is the absorbance at 520 nm and C is the concentration of the test specimen in g per L. Not less than 90% is found.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 10% of its weight.

BRIEFING

Sulfamic Acid, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-12

Change to read:

Sulfamic Acid, HSO_3NH_2—**97.09**

■[*5329-14-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sulfanilamide, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-13

Change to read:

Sulfanilamide, $C_6H_8N_2O_2S$—**172.21**

■[*63-74-1*]■2S (*USP30*)
—Use USP Sulfanilamide Melting Point RS.

BRIEFING

Sulfanilic Acid, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-14

Change to read:

Sulfanilic Acid, p-$NH_2C_6H_4SO_3H \cdot H_2O$—**191.21**

■[*121-57-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sulfosalicylic Acid,*USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-15

Change to read:

Sulfosalicylic Acid, $C_6H_3(COOH)(OH)(SO_3H)$-1,2,5 $\cdot 2H_2O$—**254.22**

■[*97-05-2*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sulfuric Acid, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-16

Change to read:

Sulfuric Acid, H_2SO_4—**98.08**

■[*7664-93-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Sulfuric Acid, Fuming, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-17

Change to read:

Sulfuric Acid, Fuming, H_2SO_4 plus free SO_3 having a nominal content of 15%, 20%, or 30% of free SO_3—

■ [*8014-95-7*]—■2S (*USP30*)
Use ACS reagent grade (containing between 15.0% and 18.0%, between 20.0% and 23.0%, or between 30.0% and 33.0% of free SO_3).

BRIEFING

Sulfurous Acid, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-18

Change to read:

Sulfurous Acid, H_2SO_3—**82.08**

■[*7782-99-2*]■2S (*USP30*)
—A water solution of sulfur dioxide. Use ACS reagent grade.

BRIEFING

Tannic Acid, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-19

Change to read:

Tannic Acid *(Tannin)*

■—[*1401-55-4*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Tetrabutylammonium Bromide, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43617-20

Change to read:

Tetrabutylammonium Bromide, $(C_4H_9)_4NBr$—**322.37**

■[*1643-19-2*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Tetrabutylammonium Hydrogen Sulfate, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-1

Change to read:

Tetrabutylammonium Hydrogen Sulfate, $C_{16}H_{37}NO_4S$—**339.54**

■[*32503-27-8*]■2S (*USP30*)
—White, crystalline powder. Soluble in alcohol yielding a slightly hazy, colorless solution.

Assay—Dissolve about 170 mg, accurately weighed, in 40 mL of water. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 33.95 mg of $C_{16}H_{37}NO_4S$. Not less than 97.0% is found.

Melting range ⟨741⟩**:** between 169° and 173°.

In-Process Revision

BRIEFING

Tetrabutylammonium Hydroxide, 1.0 M in Methanol, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-2

Change to read:

Tetrabutylammonium Hydroxide, 1.0 M in Methanol

■—[*2052-49-5*]■2S (*USP30*)
—Use a suitable grade.

BRIEFING

Tetrabutylammonium Hydroxide, 40 Percent in Water, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-3

Change to read:

Tetrabutylammonium Hydroxide, 40 Percent in Water, $[CH_3(CH_2)_3]_4NOH$—**259.47**

■[*2052-49-5*]■2S (*USP30*)
—Use a suitable grade.

BRIEFING

Tetrabutylammonium Iodide, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-4

Change to read:

Tetrabutylammonium Iodide, $(C_4H_9)_4NI$—**369.37**

■[*311-28-4*]■2S (*USP30*)
—White, shiny, crystalline flakes. Soluble in alcohol and in ether; slightly soluble in water.

Assay—Dissolve 200 mg, accurately weighed, in 40 mL of boiling water with vigorous stirring, and cool to room temperature. Stir the solution by mechanical means, add 5 mL of 2 N nitric acid, and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically, using a glass–silver electrode system and adding the titrant in 0.1-mL increments as the endpoint is approached. Perform a complete blank determination, and make any necessary correction. Each mL of 0.1 N silver nitrate is equivalent to 36.94 mg of $(C_4H_9)_4NI$: not less than 99.0% is found.

Melting range ⟨741⟩: between 146° and 147°.

BRIEFING

Tetrabutylammonium Phosphate, *USP 29* page 3157—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-5

Change to read:

Tetrabutylammonium Phosphate, $(C_4H_9)_4NH_2PO_4$—**339.46**

■[*5574-97-0*]■2S (*USP30*)
—White to off-white powder. Soluble in water.

Assay—Dissolve about 1.5 g, accurately weighed, in 100 mL of water. Without delay, titrate with 0.5 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 169.7 mg of $(C_4H_9)_4NH_2PO_4$. Not less than 97.0% is found.

BRIEFING

Tetracosane, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-6

Change to read:

Tetracosane, $C_{24}H_{50}$—**338.66**

■[*646-31-1*]■2S (*USP30*)
—White powder.

Melting range ⟨741⟩: between 51° and 53°.

BRIEFING

Tetradecane, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-7

Change to read:

Tetradecane, $C_{14}H_{30}$—**198.39**

■[*629-59-4*]■2S (*USP30*)
—Clear, colorless liquid.

Assay—When examined by gas-liquid chromatography, it shows a purity of not less than 98%. The following conditions have been found suitable for assaying the reagent: a 3-mm × 2.4-m stainless steel column packed with phase G16 on support S1; the carrier gas is helium, flowing at a rate of 27.5 mL per minute; the column temperature is maintained at 250°, the injection port is maintained at 200°, and the detector is maintained at 280°. A flame-ionization detector is employed.

Melting range, Class II ⟨741⟩: between 4° and 8°, within a 2° range.

Refractive index ⟨831⟩: between 1.4280 and 1.4300 at 20°.

BRIEFING

Tetraethylene Glycol, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-8

Change to read:

Tetraethylene Glycol, $C_8H_{18}O_5$—**194.23**

■[*112-60-7*]■2S (*USP30*)
—Nearly colorless liquid. Refractive index: about 1.46.

Assay—When examined by gas–liquid chromatography, using suitable gas chromatographic apparatus and conditions, it shows a purity of not less than 90%.

Boiling range (Reagent test): between 177° and 187°, at a pressure of 9 mm of Hg.

BRIEFING

Tetraethylenepentamine, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-9

Change to read:

Tetraethylenepentamine, $C_8H_{23}N_5$—**189.31**

■[*112-57-2*]■2S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 280°. The area of the $C_8H_{23}N_5$ peak is not less than 30% of the total peak area.

Refractive index ⟨831⟩: between 1.503 and 1.507 at 20°.

BRIEFING

Tetraheptylammonium Bromide, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-10

Change to read:

Tetraheptylammonium Bromide, $(C_7H_{15})_4NBr$—**490.70**

■[*4368-51-8*]■2S (*USP30*)
—White, flaky powder.

Melting range ⟨741⟩: between 89° and 91°.

BRIEFING

Tetrahydrofuran, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-11

Change to read:

Tetrahydrofuran, C_4H_8O—**72.11**

■[*109-99-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Tetrahydro-2-furancarboxylic Acid, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-12

Change to read:

Tetrahydro-2-furancarboxylic Acid *(± Tetrahydro-2-furoic Acid),* $C_5H_8O_3$—**116.12**

■[*16874-33-2*].■2S (*USP30*)

Assay—Inject an appropriate sample dissolved in acetone into a gas chromatograph (see *Chromatography* ⟨621⟩) that is equipped with a flame-ionization detector and contains a 0.53-mm × 30-m capillary column coated with a layer of G25. The carrier gas is helium, flowing at a rate of 9 mL per minute. The chromatograph is programmed as follows. Initially the column temperature is equilibrated at 150°, then the temperature is increased at a rate of 10° per minute to 250°. The injection port temperature is maintained at 240°, and the detector is maintained at 265°. The area of the tetrahydro-2-furancarboxylic acid peak is not less than 97% of the total peak area.

Refractive index ⟨831⟩: 1.4600.

Boiling range: between 128° and 129° at a pressure of 13 mm of Hg.

Density: 1.209.

In-Process Revision

BRIEFING

1,2,3,4-Tetrahydronaphthalene, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-13

Change to read:

1,2,3,4-Tetrahydronaphthalene, $C_{10}H_{12}$—**132.21**

■[*119-64-2*]■2S (*USP30*)
—Colorless liquid.
Refractive index ⟨831⟩: 1.5401 at 20°.

BRIEFING

Tetramethylammonium Bromide, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-14

Change to read:

Tetramethylammonium Bromide, $(CH_3)_4NBr$—**154.05**

■[*64-20-0*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Tetramethylammonium Chloride, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-15

Change to read:

Tetramethylammonium Chloride, $(CH_3)_4NCl$—**109.60**

■[*75-57-0*]■2S (*USP30*)
—Colorless crystals. Soluble in water and in alcohol; insoluble in chloroform.

Assay—Transfer about 200 mg, accurately weighed, to a beaker, add 50 mL of water and 10 mL of diluted nitric acid, swirl to dissolve the test specimen, add 50.0 mL of 0.1 N silver nitrate VS, and mix. Add 2 mL of ferric ammonium sulfate TS and 5 mL of nitrobenzene, shake, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS: each mL of 0.1 N silver nitrate is equivalent to 10.96 mg of $(CH_3)_4NCl$. Not less than 98% is found.

BRIEFING

Tetramethylammonium Hydroxide, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-16

Change to read:

Tetramethylammonium Hydroxide, $(CH_3)_4NOH$—**91.15**

■[*75-59-2*]■2S (*USP30*)
—Available as an approximately 10% or approximately 25% aqueous solution, or as the crystalline pentahydrate. Is clear and colorless. ▲▲*USP29* Tetramethylammonium hydroxide is a stronger base than ammonia and rapidly absorbs carbon dioxide from the air. Store in tight containers.

Assay—Accurately weigh a glass-stoppered flask containing about 15 mL of water. Add a quantity of a solution of tetramethylammonium hydroxide, equivalent to about 200 mg of $(CH_3)_4NOH$, and again weigh. Add methyl red TS, and titrate the solution with 0.1 N hydrochloric acid VS: each mL of 0.1 N hydrochloric acid is equivalent to 9.115 mg of $(CH_3)_4NOH$.

Residue on evaporation—Evaporate 5 mL of solution on a steam bath, and dry at 105° for 1 hour: the weight of the residue is equivalent to not more than 0.02% of the weight of the test specimen.

Ammonia and other amines—Accurately weigh a quantity of solution, corresponding to about 300 mg of $(CH_3)_4NOH$, in a low-form weighing bottle tared with 5 mL of water. Add a slight excess of 1 N hydrochloric acid (about 4 mL), evaporate on a steam bath to dryness, and dry at 105° for 2 hours: the weight of the tetramethylammonium chloride so obtained, multiplied by 0.8317, represents the quantity, in mg, of $(CH_3)_4NOH$ in the portion of test specimen taken and corresponds to within 0.2% above or below that found in the *Assay.*

BRIEFING

Tetramethylammonium Hydroxide, Pentahydrate, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-17

Change to read:

Tetramethylammonium Hydroxide, Pentahydrate, $(CH_3)_4NOH \cdot 5H_2O$—**181.23**

■[*10424-65-4*]■2S (*USP30*)
—White to off-white crystals. Is hygroscopic. Strong base. Keep well-closed. Soluble in water and in methanol.

Assay—Accurately weigh about 800 mg, dissolve in 100 mL of water, and titrate with 0.1 N hydrochloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N hydrochloric acid is equivalent to 18.22 mg of $(CH_3)_4NOH \cdot 5H_2O$: not less than 98% is found.

BRIEFING

Tetramethylammonium Hydroxide Solution in Methanol, *USP 29* page 3158—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-18

Change to read:

Tetramethylammonium Hydroxide Solution in Methanol

■—[*75-59-2*]■2S (*USP30*)
—A solution in methanol of tetramethylammonium hydroxide [$(CH_3)_4NOH$—91.15]. Is generally available in concentrations of 10% and 25%. The following specifications apply specifically to the 25% concentration; for other concentrations, appropriate adjustments in the procedures may be necessary.

Assay—Accurately weigh about 1 g of the solution, and dilute with water to about 50 mL. Add phenolphthalein TS, and titrate with 0.1 N hydrochloric acid VS to the disappearance of the pink color: each mL of 0.1 N hydrochloric acid VS is equivalent to 91.15 mg of $(CH_3)_4NOH$. Between 23% and 25% is found.

Clarity—A portion of it in a test tube is clear, or only slightly turbid, when viewed transversely.

BRIEFING

Tetramethylammonium Nitrate, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-19

Change to read:

Tetramethylammonium Nitrate, $(CH_3)_4NNO_3$—**136.15**

■[*1941-24-8*]■2S (*USP30*)
—White crystals. Freely soluble in water.

BRIEFING

4,4′-Tetramethyldiaminodiphenylmethane, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43621-20

Change to read:

4,4′-Tetramethyldiaminodiphenylmethane *[(4,4′-Methylenebis(N,N-dimethylaniline)],* $[(CH_3)_2NC_6H_4]_2CH_2$—**254.38**

■[*101-61-1*]■2S (*USP30*)
—Off-white crystals.

Melting range ⟨741⟩: between 87° and 90°.

BRIEFING

Tetramethylsilane, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-1

Change to read:

Tetramethylsilane, $(CH_3)_4Si$—**88.23**

■[*75-76-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Theobromine, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-2

Change to read:

Theobromine, $C_7H_8N_4O_2$—**180.17**

■[*83-67-0*]■2S (*USP30*)
—White, crystalline solid. Very slightly soluble in water and in alcohol; almost insoluble in benzene, in ether, and in chloroform.

Assay—Dissolve about 34 mg, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 18.02 mg of $C_7H_8N_4O_2$. Not less than 95% is found.

BRIEFING

Thiazole Yellow, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-3

Change to read:

Thiazole Yellow *(CI Direct Yellow 9; Clayton Yellow; Titan Yellow),* $C_{28}H_{19}N_5Na_2O_6S_4$—**695.74**

■[*1829-00-1*]■2S (*USP30*)
—Yellowish-brown powder. Soluble in water and in alcohol to yield in each instance a yellow solution; soluble in dilute alkali to yield a brownish-red solution. Protect from light.

Solubility—A 200-mg portion mixed with 50 mL of water shows not more than a faint haze.

Residue on ignition—Accurately weigh about 1.5 g, previously dried at 105° for 2 hours, and ignite until thoroughly charred. Cool, add 2 mL of nitric acid and 2 mL of sulfuric acid, ignite gently to expel excess acids, then at 600° to 800° to constant weight: the residue of sodium sulfate (Na_2SO_4) is between 19.8% and 21.5% of the weight of the test specimen (theory is 20.4%).

Sensitiveness to magnesium—Add 0.2 mL of a solution (1 in 10,000) and 2 mL of 1 N sodium hydroxide to a mixture of 9.5 mL of water and 0.5 mL of a solution prepared by dissolving 1.014 g of clear crystals of magnesium sulfate in water, diluting with water to 100 mL, then diluting 10 mL of the resulting solution with water to 1 L: a distinct pink color is produced within 10 minutes.

BRIEFING

Thioacetamide, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-3

Change to read:

Thioacetamide, C_2H_5NS—**75.13**

■[*62-55-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

2-Thiobarbituric Acid, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-4

Change to read:

2-Thiobarbituric Acid, $C_4H_4N_2O_2S$—**144.15**

■[*504-17-6*]■2S (*USP30*)
—White leaflets. Slightly soluble in water.
Melting temperature ⟨741⟩: 236°, with decomposition.

BRIEFING

2,2′-Thiodiethanol, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-5

Change to read:

2,2′-Thiodiethanol, $(HOCH_2CH_2)_2S$—**122.19**

■[*111-48-8*]■2S (*USP30*)
—Pale yellow to colorless liquid.

Assay—A suitable gas chromatograph equipped with a flame-ionization detector is used. The following conditions have been found suitable: a 4.0-mm × 1.83-m glass column is packed with 10% phase G25 on support S1A; the column, injection port, and detector temperatures are maintained at 200°, 250°, and 310°, respectively. Not less than 98% of $C_4H_{10}O_2S$ is found.
Refractive index ⟨831⟩: between 1.4250 and 1.4270, at 20°.

BRIEFING

Thiourea, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-7

Change to read:

Thiourea, $(NH_2)_2CS$—**76.12**

■[*62-56-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Thorium Nitrate, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-8

Change to read:

Thorium Nitrate, $Th(NO_3)_4 \cdot 4H_2O$—**552.12**

■[*13823-29-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Thromboplastin, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-9

Change to read:

Thromboplastin

■—[*9035-58-9*]■2S (*USP30*)
—Buff-colored powder, or opalescent or turbid suspension. It exhibits thrombokinase activity derived from the acetone-extracted brain and/or lung tissue of freshly killed rabbits. It may contain sodium chloride and calcium chloride in suitable proportions, and it may contain a suitable antimicrobial agent. ~~It may have the characteristic odor of dried animal tissue.~~

■■2S (*USP30*)
It is used in suspension form for the determination of the prothrombin time and activity of blood. Its thrombokinase activity is such that it gives a clotting time of 11 to 16 seconds with normal human plasma and the proper concentration of calcium ions. Store in tight containers, preferably at a temperature below 5°.

Loss on drying ⟨731⟩—[NOTE—This test is applicable only to the dry form.] Dry it in vacuum at 60° for 6 hours: it loses not more than 5.0% of its weight.

BRIEFING

Thymol, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-10

Change to read:

Thymol, $C_6H_3[CH_3][OH][CH(CH_3)_2]1,3,4$—**150.22**

■[*89-83-3*]■2S (*USP30*)
—Colorless, often large, crystals, or a white, crystalline powder. ▲▲*USP29* Is affected by light. Has greater density than water, but when liquefied by fusion is less dense than water. Its alcohol solutions are neutral to litmus. One g dissolves in about 1000 mL of water, in 1 mL of alcohol, in 1 mL of chloroform, in 1.5 mL of ether, and in about 2 mL of olive oil. Soluble in glacial acetic acid and in fixed or volatile oils. Store in tight, light-resistant containers.

Melting range ⟨741⟩**:** between 48° and 51°, but when melted it remains liquid at a considerably lower temperature.

Nonvolatile matter—Volatilize 2 g on a steam bath, and dry at 105° to constant weight: the residue weighs not more than 1 mg (0.05%).

BRIEFING

Tin, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-11

Change to read:

Tin, Sn—At. Wt. **118.71**

■[*7440-31-5*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Titanium Tetrachloride,*USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-12

Change to read:

Titanium Tetrachloride, $TiCl_4$—**189.68**

■[*7550-45-0*]■2S (*USP30*)
—Clear, colorless liquid. Fumes in air. *[Caution—It reacts violently with water.]*

Assay—Accurately weigh 0.75 g into 100 mL of 2 N sulfuric acid contained in a Smith weighing buret. Pour the solution through a zinc–mercury reduction column into 50 mL of 0.1 N ferric ammonium sulfate VS. Elute with 100 mL of 2 N sulfuric acid and 100 mL of water. Add 10 mL of phosphoric acid, and titrate with 0.1 N potassium permanganate VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N potassium permanganate is equivalent to 18.97 mg of $TiCl_4$. Not less than 99.5% is found.

Boiling range (Reagent test): between 135° and 140°.

BRIEFING

Titanium Trichloride, *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-13

Change to read:

Titanium Trichloride *(Titanous Chloride),* $TiCl_3$—**154.23**

■[*7705-07-9*]■2S (*USP30*)
—Black, hygroscopic powder, unstable in air. Soluble in water, the solution depositing titanic acid on exposure to air. Is available usually as 15% to 20%, dark violet-blue, aqueous solutions. Store the solution in tightly closed, glass-stoppered bottles, protected from light.

BRIEFING

***o*-Tolidine,** *USP 29* page 3159—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-14

Change to read:

***o*-Tolidine** *(4,4′-Diamino-3,3′-dimethylbiphenyl),* $(NH_2)(CH_3)C_6H_3 \cdot C_6H_3(CH_3)(NH_2)$4,3,3′,4′—**212.29**

■[*119-93-7*]■2S *(USP30)*
—White to reddish crystals or crystalline powder. Slightly soluble in water; soluble in alcohol, in ether, and in dilute acids. Preserve in well-closed containers, protected from light. *[Caution—Avoid contact with o-tolidine and mixtures containing o-tolidine, and conduct all tests in a well-ventilated fume hood.]*

Melting range ⟨741⟩: between 129° and 131°.

BRIEFING

Tolualdehyde, *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-15

Change to read:

Tolualdehyde *(o-Tolualdehyde),* C_8H_8O—**120.15**

■[*529-20-4*]■2S *(USP30)*
—Use a suitable grade.

BRIEFING

***p*-Tolualdehyde,** *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-16

Change to read:

***p*-Tolualdehyde,** C_8H_8O—**120.15**

■[*104-87-0*]■2S *(USP30)*
—Colorless to yellow, clear liquid.

Assay—When examined by gas–liquid chromatography, the following conditions have been found suitable: a 3-mm × 1.8-m stainless steel column packed with a 5% phase G4 on support S1; nitrogen, having a flow rate of about 12 mL per minute, is the carrier gas; the detector and column temperatures are maintained at about 125°, and the injection port temperature is maintained at about 205°. A flame-ionization detector is employed, and the specimen is a 5% solution in carbon disulfide. It shows a purity of not less than 98%.

Refractive index ⟨831⟩: between 1.544 and 1.546, at 20°.

BRIEFING

Toluene, *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-17

Change to read:

Toluene *(Toluol),* $C_6H_5CH_3$—**92.14**

■[*108-88-3*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

***p*-Toluenesulfonic Acid,** *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-18

Change to read:

***p*-Toluenesulfonic Acid,** $CH_3C_6H_4SO_3H \cdot H_2O$—**190.22**

■[*6192-52-5*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

***p*-Toluic Acid,** *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43653-20

Change to read:

***p*-Toluic Acid,** $CH_3C_6H_4COOH$—**136.15**

■[*99-94-5*]■2S *(USP30)*
—White, crystalline powder. Sparingly soluble in hot water; very soluble in alcohol, in methanol, and in ether.

Assay—Transfer about 650 mg, accurately weighed, to a suitable container, dissolve in 125 mL of alcohol, add 25 mL of water, and mix. Titrate with 0.5 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 68.07 mg of $C_8H_8O_2$: not less than 98% is found.

Melting range ⟨741⟩: over a range of 2° that includes 181°.

BRIEFING

***o*-Toluidine,** *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-1

Change to read:

***o*-Toluidine** *(2-Aminotoluene; 2-Methylaniline),* $C_6H_4(CH_3)(NH_2)1,2$—**107.15**

■[*95-53-4*]■2S *(USP30)*
—Light yellow liquid becoming reddish brown on exposure to air and light. Soluble in alcohol, in ether, and in dilute acids; slightly soluble in water. Preserve in well-closed containers, protected from light.

Specific gravity ⟨841⟩: 1.008 at 20°.

Boiling range (Reagent test): between 200° and 202°.

BRIEFING

p*-Toluidine,USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-2

Change to read:

***p*-Toluidine,** C_7H_9N—**107.15**

■[*106-49-0*]■2S *(USP30)*
—White to beige crystals or flakes.

Freely soluble in alcohol, in acetone, in methanol, and in dilute acids; slightly soluble in water.

Assay—Dissolve 400 mg, accurately weighed, in 100 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 10.72 mg of $CH_3C_6H_4NH_2$. Not less than 98%, calculated on the dried basis, is found.

Loss on drying—Weigh accurately about 1 g, and dry at 30° to constant weight: it loses not more than 2% of its weight.

BRIEFING

***n*-Triacontane,** *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-3

Change to read:

***n*-Triacontane,** $C_{30}H_{62}$—**422.81**

■[*638-68-6*]■2S *(USP30)*
—Use a suitable grade.

BRIEFING

Tributyl Phosphate, *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-4

Change to read:

Tributyl Phosphate *(Tri-n-butyl Phosphate),* $(C_4H_9)_3PO_4$—**266.31**

■[*126-73-8*]■2S *(USP30)*
—Clear, almost colorless liquid. Slightly soluble in water. Miscible with common organic solvents. Specific gravity: about 0.976.

Refractive index ⟨831⟩: between 1.4205 and 1.4225.

BRIEFING

Tributyrin, *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-5

Change to read:

Tributyrin *(Glyceryl Tributyrate),* $C_{15}H_{26}O_6$—**302.36**

■[*60-01-5*]■2S *(USP30)*
—Colorless, oily liquid. Very soluble in alcohol and in ether; insoluble in water.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, nitrogen being used as the carrier gas. The following conditions have been found suitable: a 3-mm × 1.8-m stainless steel column containing phase G4 on support S1A; the injection port temperature is maintained at 270°; and the detector temperature is maintained at 300°. The area of the tributyrin peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: between 1.4345 and 1.4365 at 20°.

Acid content—Transfer 1.0 g, accurately weighed, to a beaker, add 75 mL of methanol, and dissolve by stirring. When dissolution is complete, add 25 mL of water, and titrate with 0.05 N potassium hydroxide VS, using phenolphthalein TS as the indicator. Perform a blank determination, and make any necessary correction. Each mL of 0.05 N potassium hydroxide is equivalent to 88.1 mg of butyric acid: not more than 0.5% is found.

BRIEFING

Trichloroacetic Acid, *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-6

Change to read:

Trichloroacetic Acid, CCl_3COOH—**163.39**

■[*76-03-9*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Trichlorofluoromethane, *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-7

Change to read:

Trichlorofluoromethane, CCl_3F—**137.37**

■[*75-69-4*]■2S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: a 2.0-mm × 1.8-m glass column packed with 10% G1 phase on support S1A; the injection port temperature is maintained at 50°; the detector temperature is maintained at 300°; and the column temperature is maintained at 0° and programmed to rise 3° per minute to 50°. The area of the CCl_3F peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.380 and 1.384 at 20°.

BRIEFING

***n*-Tricosane,** *USP 29* page 3160—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-8

Change to read:

***n*-Tricosane,** $C_{23}H_{48}$—**324.63**

■[*638-67-5*]■2S (*USP30*)
—Colorless or white, more or less translucent mass, showing a crystalline structure. ▲*USP29* Has a slightly greasy feel. Insoluble in water and in alcohol; soluble in chloroform, in ether, in volatile oils, and in most warm fixed oils; slightly soluble in dehydrated alcohol. Boils at about 380°.

Melting range ⟨741⟩**:** between 47° and 49°.

Suitability—Determine its suitability for use in the test for *Related compounds* under *Propoxyphene Hydrochloride* (*USP* monograph) as follows. Dissolve a suitable quantity in chloroform to yield a solution containing 20 µg per mL. Following the directions given in the test for *Related compounds* under *Propoxyphene Hydrochloride,* inject a suitable volume of the solution into the chromatograph, and record the chromatogram. Concomitantly record the chromatogram from the *Standard preparation* prepared as directed in the test for *Related compounds:* only one main peak is obtained from the *n*-tricosane solution, and no minor peaks are observed at, or near, the peak positions obtained for propoxyphene, acetoxy, or carbinol in the chromatogram from the *Standard preparation*.

BRIEFING

Triethylamine, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-9

Change to read:

Triethylamine, $(C_2H_5)_3N$—**101.19**

■[*121-44-8*]■2S (*USP30*)
—Colorless liquid. ▲*USP29* Slightly soluble in water. Miscible with alcohol, with ether, and with cold water. Store in well-closed containers.

Boiling range (Reagent test): between 89° and 90°.

Absorbance—To 1 mL in a 50-mL volumetric flask add 10 mL of methanol and 1 mL of hydrochloric acid, and add chloroform to volume. The absorbance of this solution, determined at the wavelength of maximum absorbance at about 285 nm, with a suitable spectrophotometer, does not exceed 0.01. [NOTE—If the absorbance exceeds 0.01, purify the triethylamine as follows. Reflux 100 mL with 20 mL of water and 2 g of sodium hydrosulfite for not less than 8 hours, wash with water, dry by refluxing, using a Dean-Stark trap, and distill, collecting only the first 75 mL of the filtrate. Store over anhydrous sodium carbonate or anhydrous potassium carbonate.]

BRIEFING

Triethylamine Hydrochloride, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-10

Change to read:

Triethylamine Hydrochloride, $C_6H_{15}N \cdot HCl$—**137.65**

■[*554-68-7*]■2S (*USP30*)
—White to off-white powder.

Assay—Transfer about 35 mg, accurately weighed, to a suitable beaker, add 50 mL of glacial acetic acid, and dissolve by stirring. Add 5 mL of mercuric acetate TS, with stirring. When solution is complete, titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank titration, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 13.77 mg of $C_6H_{15}N \cdot HCl$. Not less than 97.5% of $C_6H_{15}N \cdot HCl$ is found.

Melting point ⟨741⟩: between 256° and 259°, with decomposition.

BRIEFING

Triethylene Glycol, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-11

Change to read:

Triethylene Glycol, $C_6H_{14}O_4$—**150.17**

■[*112-27-6*]■2S (*USP30*)
—Colorless to pale yellow liquid. Is hygroscopic. Miscible with water, with alcohol, and with toluene.

Assay—Inject an appropriate test specimen into a suitable gas chromatograph equipped with a flame-ionization detector (see *Chromatography* ⟨621⟩), helium being used as the carrier gas. The following conditions have been found suitable: a 3-mm × 1.85-m stainless steel column packed with support S2; the injection port, column, and detector temperatures are maintained at 250°, 230°, and 310°, respectively. The area of the $C_6H_{14}O_4$ peak is not less than 97% of the total peak area.

Refractive index ⟨831⟩: between 1.4550 and 1.4570, at 20°.

BRIEFING

Trifluoroacetic Acid, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-12

Change to read:

Trifluoroacetic Acid, $C_2HF_3O_2$—**114.02**

■[*76-05-1*]■2S (*USP30*)
—Colorless liquid. Miscible with ether, with acetone, with ethanol, with benzene, with carbon tetrachloride, and with hexane.

Assay—Dissolve about 300 mg, accurately weighed, in 25 mL of water and 25 mL of alcohol. Titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 N sodium hydroxide is equivalent to 11.40 mg of $C_2HF_3O_2$. Not less than 99% is found.

BRIEFING

Trifluoroacetic Anhydride, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-14

Change to read:

Trifluoroacetic Anhydride, $(F_3CCO)_2O$—**210.03**

■[*407-25-0*]■2S (*USP30*)
—Colorless liquid. Boils between 40° and 42°. Extremely volatile. Avoid exposure to air or water.

Assay—Transfer about 0.8 g, accurately weighed, to a glass-stoppered flask containing 50 mL of methanol. Add 500 mg of phenolphthalein, and titrate with 0.1 N sodium methoxide VS to a pink endpoint. Calculate *A* by the formula:

$$V / W$$

in which *V* is the volume, in mL, of 0.1 N sodium methoxide and *W* is the weight, in mg, of test specimen. To a second glass-stoppered flask containing 50 mL of a mixture of dimethylformamide and water (1 : 1) transfer 0.4 g, accurately weighed, of the specimen under test, add 500 mg of phenolphthalein, and titrate with 0.1 N sodium hydroxide VS to a pink endpoint. Calculate *B* by the formula:

$$V^1 / W^1$$

in which V^1 is the volume, in mL, of 0.1 N sodium hydroxide and W^1 is the weight, in mg, of test specimen. Calculate the percentage of $(F_3CCO)_2O$ by the formula:

$$2100.3(B - A)$$

Not less than 97% is found. If 2*A* is greater than *B*, calculate the percentage of F_3CCOOH by the formula:

$$1140.3(2A - B)$$

BRIEFING

2,2,2-Trifluoroethanol, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-15

Change to read:

2,2,2-Trifluoroethanol, CF_3CH_2OH—**100.04**

■[*75-89-8*]■2S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 100°; the detector temperature is maintained at 150°; and the column temperature is maintained at 0° and programmed to rise 10° per minute to 150°. The area of the CF_3CH_2OH peak is not less than 99% of the total peak area.

Boiling range: between 77° and 80°.

In-Process Revision

BRIEFING

5-(Trifluoromethyl)uracil, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-16

Change to read:

5-(Trifluoromethyl)uracil, $C_5H_3F_3N_2O_2$—**180.08**

■[*54-20-6*]■2S *(USP30)*
—White to off-white powder.

Assay—When tested by thin-layer chromatography, with the use of plates coated with chromatographic silica gel mixture, a developing system consisting of chloroform, methanol, and acetic acid (17 : 2 : 1), and examined visually and under long-wavelength UV light, a single spot is exhibited.

BRIEFING

Trimethylacethydrazide Ammonium Chloride, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-17

Change to read:

Trimethylacethydrazide Ammonium Chloride *(Betaine Hydrazide Chloride; Girard Reagent T),* $[(CH_3)_3N^+CH_2CONHNH_2]Cl^-$—**167.64**

■[*123-46-6*]■2S *(USP30)*
—Colorless or white crystals. Freely soluble in water. One g dissolves in about 25 mL of alcohol. Insoluble in chloroform and in ether. Hygroscopic.

Melting range ⟨741⟩: between 185° and 192°, determined after recrystallization from hot alcohol, if necessary.

Residue on ignition (Reagent test)—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 10 mg (1%).

BRIEFING

2,2,4-Trimethylpentane,*USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-18

Change to read:

2,2,4-Trimethylpentane *(Isooctane),* C_8H_{18}—**114.23**

■[*540-84-1*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

2,4,6-Trimethylpyridine, *USP 29* page 3161—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-19

Change to read:

2,4,6-Trimethylpyridine *(5-Collidine),* $C_8H_{11}N$—**121.18**

■[*108-75-8*]■2S *(USP30)*
—Clear, colorless liquid. ▲▲*USP29* Soluble in cold water and less soluble in hot water; soluble in alcohol, in chloroform, and in methanol. Miscible with ether.

Assay—Inject an appropriate test specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩), helium being used as a carrier gas. The following conditions have been found suitable: a 3-mm × 1.85-m stainless steel column containing phase G16 on support S1A; the injection port, column, and detector temperatures are maintained at 180°, 165°, and 270°, respectively; and a flame-ionization detector is used. The area of the $C_8H_{11}N$ peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: between 1.4970 and 1.4990, at 20°.

BRIEFING

***N*-(Trimethylsilyl)-imidazole,** *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43698-20

Change to read:

***N*-(Trimethylsilyl)-imidazole,** $C_6H_{12}N_2Si$—**140.26**

■[*18156-74-6*]■2S *(USP30)*
—A clear, colorless, to light yellow liquid.

Refractive index ⟨831⟩: between 1.4744 and 1.4764 at 20°.

BRIEFING

2,4,6-Trinitrobenzenesulfonic Acid, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-1

Change to read:

2,4,6-Trinitrobenzenesulfonic Acid, $C_6H_2(NO_2)_3SO_3H \cdot 3H_2O$—**347.21**

■[*2508-19-2*]■2S *(USP30)*
—Pale yellow to tan crystals. Use a suitable grade. Also available as a 5% (w/v) or a 1 M aqueous solution.

BRIEFING

Trioctylphosphine Oxide, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-2

Change to read:

Trioctylphosphine Oxide, $C_{24}H_{51}PO$—**386.63**

■[*78-50-2*]■2S (*USP30*)
—White, crystalline powder. Soluble in organic solvents; insoluble in water.

Melting range ⟨741⟩: between 54° and 56°.

BRIEFING

1,3,5-Triphenylbenzene, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-3

Change to read:

1,3,5-Triphenylbenzene, $(C_6H_5)_3C_6H_3$—**306.41**

■[*612-71-5*]■2S (*USP30*)
—White to off-white powder.

Melting range ⟨741⟩: between 172° and 175°.

BRIEFING

Triphenylmethane, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-4

Change to read:

Triphenylmethane, $C_{19}H_{16}$—**244.34**

■[*519-73-3*]■2S (*USP30*)
—Light brown powder.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°; and the column temperature is maintained at 200° and programmed to rise 10° per minute to 300°. The area of the $C_{19}H_{16}$ peak is not less than 99% of the total peak area.

Melting range ⟨791⟩: between 92° and 94°.

BRIEFING

Triphenylmethanol, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-5

Change to read:

Triphenylmethanol, $C_{19}H_{16}O$—**260.34**

■[*76-84-6*]■2S (*USP30*)
—White to off-white powder.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 280°; the detector temperature is maintained at 300°; and the column temperature is maintained at 180°. The area of the $C_{19}H_{16}O$ peak is not less than 96.5% of the total peak area.

BRIEFING

Triphenyltetrazolium Chloride, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-6

Change to read:

Triphenyltetrazolium Chloride, $C_{19}H_{15}ClN_4$—**334.80**

■[*298-96-4*]■2S (*USP30*)
—White to yellowish, crystalline powder. Soluble in about 10 parts of water and of alcohol; slightly soluble in acetone; insoluble in ether. Usually contains solvent of crystallization, and when dried at 105° it melts at about 240°, with decomposition.

Solubility—Separate 100-mg portions dissolve completely in 10 mL of water and in 10 mL of alcohol, respectively, to yield solutions that are clear, or practically so.

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 5.0% of its weight.

Residue on ignition (Reagent test): negligible, from 100 mg.

Sensitiveness—Dissolve 10 mg in 10 mL of dehydrated alcohol (*A*). Then dissolve 10 mg of dextrose in 20 mL of dehydrated alcohol (*B*). To 0.2 mL of *B* add 1 mL of dehydrated alcohol and 0.5 mL of dilute tetramethylammonium hydroxide TS (1 volume diluted with 9 volumes of dehydrated alcohol), then add 0.2 mL of *A:* a pronounced red color develops within about 10 minutes.

In-Process Revision

BRIEFING

Tris(2-aminoethyl)amine, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-7

Change to read:

Tris(2-aminoethyl)amine, $C_6H_{18}N_4$—**146.23**

■[*4097-89-6*]■2S (*USP30*)
—Yellow liquid. Soluble in methanol.

Assay—Dissolve about 80 mg in 30 mL of methanol. Add 40 mL of water, and titrate with 1 N hydrochloric acid, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 1 N hydrochloric acid is equivalent to 48.75 mg of $C_6H_{18}N_4$. Not less than 98.0% is found.

Refractive index ⟨831⟩: between 1.4956 and 1.4986 at 20°.

BRIEFING

Tris(hydroxymethyl)aminomethane, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-8

Change to read:

Tris(hydroxymethyl)aminomethane

■—[*77-86-1*]■2S (*USP30*)
—Use ACS reagent grade—See also *Tromethamine*.

BRIEFING

Tropaeolin OO, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-9

Change to read:

Tropaeolin OO *(Acid Orange 5),* $C_{18}H_{14}N_3NaO_3S$—**375.38**

■[*554-73-4*]■2S (*USP30*)
—Orange-yellow scales, or yellow powder. Soluble in water.

pH range: from 1.4 (red) to 2.6 (yellow).

BRIEFING

L-Tryptophane, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-10

Change to read:

L-Tryptophane, $C_{11}H_{12}N_2O_2$—**204.23**

■[*73-22-3*]■2S (*USP30*)
—White or not more than slightly yellow leaflets or powder. One g dissolves in about 100 mL of water; soluble in dilute acids and in solutions of the alkali hydroxides; slightly soluble in alcohol.

Assay—Accurately weigh about 300 mg, dissolve in a mixture of 3 mL of formic acid and 50 mL of glacial acetic acid, add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a green endpoint. Each mL of 0.1 N perchloric acid is equivalent to 20.42 mg of $C_{11}H_{12}N_2O_2$. Between 98.0% and 102.0%, calculated on the dried basis, is found.

Specific rotation ⟨781⟩: between –30.0° and –33.0°, determined in a solution containing 1.0 g of test specimen, previously dried at 105° for 3 hours, in 100 mL.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 0.3% of its weight.

Residue on ignition (Reagent test): not more than 0.1%.

Tyrosine—Dissolve 100 mg in 3 mL of diluted sulfuric acid, add 10 mL of mercuric sulfate TS, and heat on a steam bath for 10 minutes. Filter, wash with 5 mL of mercuric sulfate TS, and add to the combined filtrate 0.5 mL of sodium nitrite solution (1 in 20): no red color is produced within 15 minutes.

BRIEFING

Tubocurarine Chloride. It is proposed to add this new reagent used in the preparation of the *Running buffer* in the *Assay* in the monograph for *Pancuronium Bromide Injection,* presented elsewhere in this *PF.*

(HDQ: M. Marques) RTS—C44876

Add the following:

■**Tubocurarine Chloride** *(7′,12′-Dihydroxy-6,6′-dimethoxy-2,2′,2′-trimethyltubocuraranium Chloride),* $C_{37}H_{42}Cl_2N_2O_6$—**681.65**[*6989-98-6*]—Use a suitable grade with an assay result between 98.0% and 102.0%.

[NOTE—A suitable grade is available from Acros Organics, catalog number 24349 at www.acros.com.]■2S (*USP30*)

In-Process Revision

BRIEFING

Uracil, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-11

Change to read:

Uracil, $C_4H_4N_2O_2$—**112.09**

■[*66-22-8*]■2S (*USP30*)
—White to cream-colored, crystalline powder. Melts above 300°. One g dissolves in about 500 mL of water; less soluble in alcohol; soluble in ammonia TS and in sodium hydroxide TS. Its solutions yield no precipitate with the usual alkaloidal precipitants.

Residue on ignition⟨Reagent test⟩: negligible, from 100 mg.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 2% of its weight.

BRIEFING

Uranyl Acetate, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-12

Change to read:

Uranyl Acetate *(Uranium Acetate),* $UO_2(C_2H_3O_2)_2 \cdot 2H_2O$—**424.15**

■[*541-09-3*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Urea, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-13

Change to read:

Urea, NH_2CONH_2—**60.06**

■[*57-13-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Urethane, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-14

Change to read:

Urethane *(Ethyl carbamate),* $C_3H_7NO_2$—**89.09**

■[*51-79-6*]■2S (*USP30*)
—White powder with chunks. Freely soluble in water.

Melting range ⟨741⟩: between 48° and 50°.

BRIEFING

Uridine, *USP 29* page 3162—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-15

Change to read:

Uridine, $C_9H_{12}N_2O_6$—**244.20**

■[*58-96-8*]■2S (*USP30*)
—White powder.

Assay—

MOBILE PHASE—Prepare a mixture of methanol and 0.2 M ammonium acetate (90 : 10), and adjust with phosphoric acid to a pH of 7.0.

TEST SOLUTION: 0.5 mg per mL.

PROCEDURE—Inject about 20 µL of the *Test solution* into a liquid chromatograph (see *Chromatography* ⟨621⟩), equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 2.0 mL per minute. The area of the $C_9H_{12}N_2O_6$ peak is not less than 99% of the total peak area.

Melting range ⟨741⟩: between 166° and 171°.

BRIEFING

Valeric Acid, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-16

Change to read:

Valeric Acid, $C_5H_{10}O_2$—**102.13**

■[*109-52-4*]■2S (*USP30*)
—Clear, colorless liquid.

Assay—Accurately weigh about 500 mg, transfer to a suitable container, add 30 mL of water, and mix. Add 40 mL of water, and mix. Add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Each mL of 0.1 N sodium hydroxide is equivalent to 10.21 mg of $C_5H_{10}O_2$: not less than 99.0% of $C_5H_{10}O_2$ is found.

BRIEFING

Valerophenone, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-17

Change to read:

Valerophenone, $C_{11}H_{14}O$—**162.23**

■[*1009-14-9*]■2S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 150° and programmed to rise 10° per minute to 300°. The area of the $C_{11}H_{14}O$ peak is not less than 98% of the total peak area.

Refractive index ⟨831⟩: 1.5149 at 20°.

Boiling range: between 105° and 107°, at a pressure of 5 mm of mercury.

BRIEFING

Vanadium Pentoxide, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-18

Change to read:

Vanadium Pentoxide, V_2O_5—**181.88**

■[*1314-62-1*]■2S (*USP30*)
—Fine, yellow to orange-yellow powder. Soluble in concentrated acids and in alkalies; slightly soluble in water; insoluble in alcohol.

Assay—Transfer about 400 mg, accurately weighed, to a 500-mL conical flask, and add 150 mL of water and 30 mL of dilute sulfuric acid (1 in 2). Boil the solution on a hot plate for 5 minutes, add 50 mL of water, and continue boiling until a yellow solution is obtained. Transfer the hot plate and the flask to a well-ventilated hood, and bubble sulfur dioxide gas through the solution for 10 minutes, or until the solution is a clear, brilliant blue color. Rinse the gas delivery tube into the flask with a few mL of water, then bubble carbon dioxide gas through the solution for 30 minutes while continuing to boil the solution gently. Cool the solution to about 80°, and titrate with 0.1 N potassium permanganate VS to a yellow-orange endpoint. Perform a complete blank determination, and make any necessary correction. Each mL of 0.1 N potassium permanganate is equivalent to 9.095 mg of V_2O_5. Not less than 99.5% is found.

BRIEFING

Vanadyl Sulfate, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-19

Change to read:

Vanadyl Sulfate, $VOSO_4 \cdot xH_2O$ (anhydrous)—**163.00**

■[*27774-13-6*]■2S (*USP30*)
—Blue, hygroscopic crystals. Slowly and usually incompletely soluble in water.

Assay—Accurately weigh about 400 mg of the dried test specimen obtained in the test for *Water,* and transfer with 15 to 20 mL of water into a beaker. Add 3 mL of sulfuric acid, cover the beaker with a watch glass, and heat on a steam bath until all of the specimen is dissolved. Cool, dilute with 125 mL of water, and titrate with 0.1 N potassium permanganate VS to the production of a pinkish color that persists for 1 minute: each mL of 0.1 N potassium permanganate is equivalent to 16.30 mg of $VOSO_4$. Not less than 97% is found.

Water—Dry about 1 g, accurately weighed, at 220° to constant weight: it loses not more than 50.0% of its weight.

Pentavalent vanadium—Heat 1 g, accurately weighed, with 50 mL of water and 5 mL of hydrochloric acid in a flask until dissolved. Cool, add 2 g of potassium iodide, insert the stopper, and allow to stand for 30 minutes. Add 50 mL of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, adding 3 mL of starch TS as the indicator. Correct for the volume of thiosulfate consumed by a blank. Each mL of 0.1 N thiosulfate is equivalent to 5.095 mg of vanadium (V). Not more than 0.5% is found, calculated on the dried basis.

Substances not precipitated by ammonia—Dissolve 1.0 g by heating with 20 mL of water and 2 mL of hydrochloric acid. Dilute with water to about 75 mL, and neutralize to litmus paper with ammonia TS. Transfer the solution to a cylinder, slowly add 5 mL of ammonia TS and sufficient water to make 100 mL, and allow to stand overnight. Decant 50 mL of the supernatant through a filter, add 5 drops of sulfuric acid, evaporate to dryness, and ignite: the residue weighs not more than 10 mg (2.0%).

BRIEFING

Vinyl Acetate, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43703-20

Change to read:

Vinyl Acetate, $CH_3COOCH{=}CH_2$—**86.09**

■[*108-05-4*]■2S (*USP30*)
—Liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of G2; the column temperature is maintained at 100° and programmed to rise 10° per minute to 150°; the injection port is maintained at 100°; and the detector is maintained at 300°. The area of the $CH_3COOCH{=}CH_2$ peak is not less than 99% of the total peak area.

BRIEFING

1-Vinyl-2-pyrrolidone, *USP 29* page 3163 and page 1701 of *PF* 31(6) [Nov.–Dec. 2005]. See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-1

Change to read:

1-Vinyl-2-pyrrolidone, C_6H_9NO—**111.14**

■[*88-12-4*]■2S *(USP30)*
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of G2; the injection port temperature is maintained at 250°; the detector temperature is maintained at 300°; and the column temperature is maintained at 100° and programmed to rise 10° per minute to 250°. The area of the C_6H_9NO peak is not less than 99.0% of the total peak area.

Water, Method 1 ⟨921⟩: not more than 0.1%, determined on 2.5 g, using a mixture of 50 mL of methanol and 10 mL of butyrolactone as the solvent.

▲[NOTE—A suitable grade is available from Merck KGaA/ EMD chemicals, catalogue number 8.08518.0250, www.emd-chemicals.com.]▲*USP30*

BRIEFING

Wright's Stain, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-2

Change to read:

Wright's Stain

■[*68988-92-1*]■2S *(USP30)*
—A mixture of methylene blue, methylene azure, and the eosinates of both, available as a solid and as a solution in methanol. Use a suitable grade. [NOTE—If a solid is used, dissolve 6.0 g of Wright's stain powder (CAS# *68988-92-1,* dark green powder) and 0.6 g of Giemsa stain powder (CAS# *51811-82-6,* dark green to black powder or crystals) in 1000 mL of methanol. Stir overnight, and filter before use.]

BRIEFING

Xanthine, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-3

Change to read:

Xanthine, $C_5H_4N_4O_2$—**152.11**

■[*69-89-6*]■2S *(USP30)*
—White, crystalline powder. Decomposes on heating. Slightly soluble in water and in alcohol; soluble in sodium hydroxide TS; sparingly soluble in diluted hydrochloric acid. When subjected to the murexide reaction, a purple color is produced with the ammonia, but on the subsequent addition of fixed alkali hydroxides, the color is not discharged but is changed to violet.

Residue on ignition (Reagent test): negligible, from 100 mg.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 1% of its weight.

BRIEFING

Xanthydrol, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-4

Change to read:

Xanthydrol, $C_{13}H_{10}O_2$—**198.22**

■[*90-46-0*]■2S *(USP30)*
—Pale yellow, crystalline powder. Insoluble in water; soluble in alcohol, in chloroform, and in ether. Soluble in glacial acetic acid, forming a practically colorless solution; but when the powder is treated with diluted hydrochloric acid, a lemon-yellow color is produced.

Melting range ⟨741⟩: between 121° and 123°.

Residue on ignition—Ignite 500 mg with 0.5 mL of sulfuric acid: the residue weighs not more than 10 mg (2.0%).

BRIEFING

Xylene, *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-5

Change to read:

Xylene, C_8H_{10}—**106.17**

■[*1330-20-7*]■2S *(USP30)*
—Use ACS reagent grade.

BRIEFING

***o*-Xylene,** *USP 29* page 3163—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-6

Change to read:

***o*-Xylene,** C_8H_{10}—**106.17**

■[*95-47-6*]■2S (*USP30*)
—Clear, colorless, mobile, flammable liquid. Insoluble in water; miscible with alcohol and with ether.

Assay—When examined by gas-liquid chromatography, it shows a purity of not less than 95%. The following conditions have been found suitable: a 3-mm × 1.8-m stainless steel column packed with 1.75% hydrated aluminum silicate plus 5.0% diisodecyl phthalate on support S1; a flame-ionization detector; helium is the carrier gas, flowing at a rate of about 27.5 mL per minute; the column temperature is maintained at 80°; the injection port is maintained at about 180°; and the detector is maintained at about 280°.

Refractive index ⟨831⟩: between 1.5040 and 1.5060, at 20°.

BRIEFING

***p*-Xylene,** *USP 29* page 3164—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-7

Change to read:

***p*-Xylene,** C_8H_{10}—**106.17**

■[*106-42-3*]■2S (*USP30*)
—Colorless liquid.

Assay—Inject an appropriate volume into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame-ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 0.25-mm × 30-m capillary column coated with a 1-µm layer of phase G14; the column temperature is maintained at 50° and programmed to rise 10° per minute to 100°; the injection port is maintained at 130°; and the detector is maintained at 300°. The area of the C_8H_{10} peak is not less than 99% of the total peak area.

Refractive index ⟨831⟩: between 1.493 and 1.497 at 20°.

BRIEFING

Xylene Cyanole FF, *USP 29* page 3164—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-8

Change to read:

Xylene Cyanole FF, $C_{25}H_{27}N_2NaO_6S_2$—**538.61**

■[*2650-17-1*]■2S (*USP30*)
—Gray-blue to dark blue powder. Soluble in water.

Assay—Transfer about 50 mg, accurately weighed, to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Transfer 2.0 mL of the solution to a 50-mL volumetric flask, dilute with pH 7.0 phosphate buffer to volume (See *Solutions*, in this section), and mix. Using a suitable spectrophotometer, 1-cm cells, and water as the blank, record the absorbance of the solution at the wavelength of maximum absorbance at about 614 nm. From the observed absorbance, calculate the absorptivity (see *Spectrophotometry and Light-Scattering* ⟨851⟩): the absorptivity is not less than 55.9, corresponding to about 83% of $C_{25}H_{27}N_2NaO_6S_2$.

Loss on drying ⟨731⟩—Dry it at 110° to constant weight: it loses not more than 6.0% of its weight.

BRIEFING

Xylose, *USP 29* page 3164—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-9

Change to read:

Xylose, $C_5H_{10}O_5$—**150.13**

■[*58-86-6*]■2S (*USP30*)
—Use a suitable grade.

BRIEFING

Zinc, *USP 29* page 3164—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-10

Change to read:

Zinc, Zn—**At. Wt. 65.39**

■[*7440-66-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Zinc Acetate, *USP 29* page 3164—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-11

Change to read:

Zinc Acetate, $Zn(CH_3COO)_2 \cdot 2H_2O$—**219.51**

■[*557-34-6*]■2S (*USP30*)
—Use ACS reagent grade.

BRIEFING

Zirconyl Nitrate, *USP 29* page 3164—See briefing under *1-Nonyl Alcohol.*

(HDQ: M. Marques) RTS—43709-12

Change to read:

Zirconyl Nitrate, $ZrO(NO_3)_2$—**231.23**

■[*13826-66-9*]■2S (*USP30*)
—Use a suitable grade.

Volumetric Solutions

BRIEFING

Volumetric Solutions, *USP 29* page 3175 and page 939 of *PF* 32(3) [May–June 2006]. Two new volumetric solutions are being proposed: *Bismuth Nitrate,* which is being added to the Stage 6 proposal for *Edetate Calcium Disodium,* which also appears in this *PF;* and *Magnesium Chloride, 0.01 M.*

(HDQ: M. Marques) RTS—C44011; C46397

Add the following:

■**Bismuth Nitrate, 0.01 mol/L**
$Bi(NO_3)_3 \cdot 5H_2O$, **485.07**

1000 mL of this solution contains 4.851 g of bismuth nitrate pentahydrate

Dissolve 4.86 g of bismuth nitrate pentahydrate in 60 mL of dilute nitric acid, add water to make 1000 mL, and standardize the solution as follows:

Accurately measure 25 mL of the prepared bismuth nitrate solution, add 50 mL of water and 1 drop of xylenol orange TS, and titrate the solution with 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS until the red color changes to yellow. Calculate the molarity factor.■2S (*USP30*)

Add the following:

■**Magnesium Chloride, 0.01 M**
$MgCl_2 \cdot 6H_2O$, **203.30**

2.0330 g in 1000 mL

Dissolve about 2.04 g of magnesium chloride in 1000 mL of freshly boiled and cooled water, and standardize the solution as follows.

Accurately measure 25 mL of the prepared magnesium chloride solution. Add 50 mL of water, 3 mL of ammonia–ammonium chloride buffer TS and 0.04 g of eriochrome black T–sodium chloride reagent. Titrate with 0.05 M edetate disodium VS until the red-purple color of the solution changes to blue-purple.■2S (*USP30*)

$$M = \frac{(\text{mL edetate disodium VS}) \times (\text{M edetate disodium})}{\text{mL magnesium chloride}}$$

Change to read:

Potassium Hydroxide, Normal (1 N)
KOH, **56.11**

56.11 g in 1000 mL

Dissolve 68 g of potassium hydroxide in about 950 mL of water. Add a freshly prepared saturated solution of barium hydroxide until no more precipitate forms. Shake the mixture thoroughly, and allow it to stand overnight in a stoppered bottle. Decant the clear liquid, or filter the solution in a tight, polyolefin bottle, and standardize by the procedure set forth for *Sodium Hydroxide, Normal (1 N).*

~~$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH}}$~~

■$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL KOH}}$■1S (*USP30*)

Change to read:

Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)
NaOH, **40.00**

To 250 mL of alcohol add 2 mL of a 50% ~~(w/w)~~

■(w/v)■2S (*USP29*)
solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced.

$$N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL sodium hydroxide}}$$

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Change to read:

Sodium Hydroxide, Normal (1 N)
NaOH, **40.00**

40.00 g in 1000 mL

Dissolve 162 g of sodium hydroxide in 150 mL of carbon dioxide-free water, cool the solution to room temperature, and filter through hardened filter paper. Transfer 54.5 mL of the clear filtrate to a tight, polyolefin container, and dilute with carbon dioxide-free water to 1000 mL.

Accurately weigh about 5 g of potassium biphthalate, previously crushed lightly and dried at 120° for 2 hours, and dissolve in 75 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS, and titrate with the sodium hydroxide solution to the production of a permanent pink color. Each ~~204.2 mg~~ ■204.23 mg■1S (*USP30*) of potassium biphthalate is equivalent to 1 mL of 1 N sodium hydroxide.

$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH solution}}$$

NOTES—(1) Solutions of alkali hydroxides absorb carbon dioxide when exposed to air. They should be preserved in bottles having well-fitted, suitable stoppers, provided with a tube filled with a mixture of sodium hydroxide and lime (soda-lime tubes) so that air entering the container must pass through this tube, which will absorb the carbon dioxide. (2) Prepare solutions of lower concentration (e.g., 0.1 N, 0.01 N) by quantitatively diluting accurately measured volumes of the 1 N solution with sufficient carbon dioxide-free water to yield the desired concentration.

Restandardize the solution frequently.

Change to read:

Sodium Thiosulfate, Tenth-Normal (0.1 N)
$Na_2S_2O_3 \cdot 5H_2O$, **248.19**

24.82 g in 1000 mL

Dissolve about 26 g of sodium thiosulfate and 200 mg of sodium carbonate in 1000 mL of recently boiled and cooled water. Standardize the solution as follows.

Accurately weigh about 210 mg of primary standard potassium dichromate, previously pulverized and dried ~~at 120° for 4 hours,~~ ■according to the instructions on its label, if necessary,■1S (*USP30*) and dissolve in 100 mL of water in a glass-stoppered, 500-mL flask. Swirl to dissolve the solid, remove the stopper, and quickly add 3 g of potassium iodide, 2 g of sodium bicarbonate, and 5 mL of hydrochloric acid. Insert the stopper gently in the flask, swirl to mix, and allow to stand in the dark for exactly 10 minutes. Rinse the stopper and the inner walls of the flask with water, and titrate the liberated iodine with the sodium thiosulfate solution until the solution is yellowish green in color. Add 3 mL of starch TS, and continue the titration until the blue color is discharged. Perform a blank determination.

Restandardize the solution as frequently as supported by laboratory stability data. In the absence of such data, restandardize the solution weekly.

$$N = \frac{\text{mg } K_2Cr_2O_7}{49.04 \times \text{mL } Na_2S_2O_3}$$

BRIEFING

Chromatographic Reagents. It is proposed to add a new section *Chromatographic Reagents* under *Reagents, Indicators, and Solutions* based on the proposal of the General Chapters Expert Committee to move the list of *Packings, Phases,* and *Supports* under *Chromatographic Reagents* from the general chapter *Chromatography* ⟨621⟩. See also briefing under *Chromatography* ⟨621⟩.

(HDQ: M. Marques)

Add the following:

■CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE—Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

Packings

L1—Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, ~~3~~ ■1.5■1S (*USP30*) to 10 µm in diameter, ■or a monolithic silica rod.■1S (*USP29*)

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L2—Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to 50 µm in diameter.

L3—Porous silica particles, 5 to 10 µm in diameter.

L4—Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L5—Alumina of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L6—Strong cation-exchange packing–sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to 50 µm in diameter.

L7—Octylsilane chemically bonded to totally porous silica particles, ~~3~~ ■1.5■1S *(USP30)* to 10 µm in diameter.

L8—An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, 3 to 10 µm in diameter.

L9—■■1S *(USP29)* Irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating, ■3 to 10 µm in diameter.■1S *(USP29)*

L10—Nitrile groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L11—Phenyl groups chemically bonded to porous silica particles, ~~5~~■1.5■1S *(USP30)* to 10 µm in diameter.

L12—A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to 50 µm in diameter.

L13—Trimethylsilane chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L14—Silica gel having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating, 5 to 10 µm in diameter.

L15—Hexylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L16—Dimethylsilane chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L17—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to 11 µm in diameter.

L18—Amino and cyano groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L19—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about 9 µm in diameter.

L20—Dihydroxypropane groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L21—A rigid, spherical styrene-divinylbenzene copolymer, 5 to 10 µm in diameter.

L22—A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about 10 µm in size.

L23—An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about 10 µm in size.

L24—A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to 63 µm in diameter.

■[NOTE—Available as YMC-Pack PVA-SIL manufactured by YMC Co., Ltd. and distributed by Waters Corp. (www.waters.com).]■1S *(USP29)*

L25—Packing having the capacity to separate compounds with a molecular weight range from 100–5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26—Butyl silane chemically bonded to totally porous silica particles, ■3■1S *(USP29)* to 10 µm in diameter.

L27—Porous silica particles, 30 to 50 µm in diameter.

L28—A multifunctional support, which consists of a high purity, 100 Å, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.

L29—Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, 5 µm in diameter with a pore volume of 80 Å.

L30—Ethyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

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L31—A ■hydroxide-selective,■1S (*USP29*) strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of 8.5-µm macroporous particles having a pore size of 2000 Å and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene.

L32—A chiral ligand-exchange packing–L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to 10 µm in diameter.

L33—Packing having the capacity to separate dextrans by molecular size over a range of 4000 to 500,000 Da. It is spherical, silica-based, and processed to provide pH stability.

■[NOTE—Available as TSKgel G4000 SWXL from Tosoh Biosep (www.tosohbiosep.com).]■1S (*USP29*)

L34—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about 9 µm in diameter.

L35—A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of 150 Å.

L36—A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to 5-µm aminopropyl silica.

L37—Packing having the capacity to separate proteins by molecular size over a range of 2,000 to 40,000 Da. It is a polymethacrylate gel.

L38—A methacrylate-based size-exclusion packing for water-soluble samples.

L39—A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40—Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to 20 µm in diameter.

L41—Immobilized α_1-acid glycoprotein on spherical silica particles, 5 µm in diameter.

L42—Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, 5 µm in diameter.

L43—Pentafluorophenyl groups chemically bonded to silica particles by a propyl spacer, 5 to 10 µm in diameter.

L44—A multifunctional support, which consists of a high purity, 60 Å, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45—Beta cyclodextrin bonded to porous silica particles, 5 to 10 µm in diameter.

L46—Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, about 10 µm in diameter.

L47—High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.

■[NOTE—Available as CarboPac MA1 and distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

L48—Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, 15 µm in diameter.

L49—A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to 10 µm in diameter.

■[NOTE—Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.]■1S (*USP29*)

L50—Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm in diameter, and a surface area not less than 350 m^2 per g. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene.

■[NOTE—Available as OmniPac PAX-500 and distributed by Dionex Corp. (www.dionex.com).]■1S (*USP29*)

L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to 10 µm in diameter.

■[NOTE—Available as Chiralpak AD from Chiral Technologies, Inc., (www.chiraltech.com).]■1S (*USP29*)

L52—A strong cation-exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.

■[NOTE—Available as TSK IC SW Cation from Tosoh Biosep (www.tosohbiosep.com).]■1S *(USP29)*

L53—Weak cation-exchange resin consisting of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than 500 µEq/column.

■[NOTE—Available as IonPac CS14 distributed by Dionex Corp. (www.dionex.com).]■1S *(USP29)*

L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter.

■[NOTE—Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).]■1S *(USP29)*

L55—A strong cation-exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.

■[NOTE—Available as IC-Pak C M/D from Waters Corp. (www.waters.com).]■1S *(USP29)*

L56—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

■[NOTE—Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem).]■1S *(USP29)*

L57—A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about 5 µm in diameter, with a pore size of 120 Å.

■[NOTE—Available as Ultron ES-OVM from Agilent Technologies (www.agilent.com/chem).]■1S *(USP29)*

L58—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.

■[NOTE—Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143) www.bio-rad.com.]■1S *(USP29)*

L59—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa. It is spherical (10 µm), silica-based, and processed to provide hydrophilic characteristics and pH stability.

■[NOTE—Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05789 and 05371, respectively) (www.tosohbiosep.com).]■1S *(USP29)*

L60—Spherical, porous silica gel, ~~3 or 5 µm~~ ■10 µm or less■1S *(USP30)* in diameter, the surface of which has been covalently modified with ~~palmitamidopropyl~~ ■alkyl amide■1S *(USP30)* groups and endcapped.

■[NOTE—Available as Supelcosil ABZ from Supelco (www.sigma-aldrich.com/supelco).]■1S *(USP29)*

L61—A hydroxide selective strong anion-exchange resin consisting of a highly cross-linked core of 13 µm microporous particles having a pore size less than 10 Å units and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene with a latex coating composed of 85 nm diameter microbeads bonded with alkanol quaternary ammonium ions (6%).

■[NOTE—Available as Ion Pac AS-11 and AG-11 from Dionex (www.dionex.com).]■1S *(USP29)*

L62—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter.

~~L## (Enoxaparin Sodium, Dowex 1X8) [To come.]~~

~~L## (Enoxaparin Sodium, Dowex 50WX2) [To come.]~~

▲L## (Dalteparin Sodium, anion-exchange Dowex 1X8)—[To come.]

L## (Dalteparin Sodium, cation-exchange Dowex 50WX2)—[To come.]▲*USP30*

■L## (Glucosamine, Shodex NH2P-50)—Polyamine chemically bonded to cross-linked polyvinyl alcohol polymer, 5 µm in diameter.

[NOTE—Available as Shodex NH2P-50 from Shodex (www.shodex.com).]

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L## [Valganciclovir Hydrochloride, Crownpak CR(+)]—A crown ether coated on a 5-µm particle size silica gel substrate. The active site is *(S)*-18-crown-6-ether.

[NOTE—Available as Crownpak CR(+) from Daicel (www.daicel.com).]

L## (Trehalose, Sugar KS-801)—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, 6 to 17 µm in diameter.

[NOTE—Available as Sugar KS-801 from Shodex (www.shodex.com).]

L## (Levalbuterol, Chirobiotic T)—Glycopeptide teicoplanin linked through multiple covalent bonds to a 100-Å units spherical silica.

[NOTE—Available as Chirobiotic T from Astec (www.astecusa.com).]■1S (*USP30*)

Phases

G1—Dimethylpolysiloxane oil.

G2—Dimethylpolysiloxane gum.

G3—50% Phenyl-50% methylpolysiloxane.

G4—Diethylene glycol succinate polyester.

G5—3-Cyanopropylpolysiloxane.

G6—Trifluoropropylmethylpolysiloxane.

G7—50% 3-Cyanopropyl-50% phenylmethylsilicone.

G8—80% Bis(3-cyanopropyl)-20% 3-cyanopropylphenylpolysiloxane (percentages refer to molar substitution).

G9—Methylvinylpolysiloxane.

G10—Polyamide formed by reacting a C_{36} dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00 : 0.90 : 0.20.

G11—Bis(2-ethylhexyl) sebacate polyester.

G12—Phenyldiethanolamine succinate polyester.

G13—Sorbitol.

G14—Polyethylene glycol (av. mol. wt. of 950 to 1050).

G15—Polyethylene glycol (av. mol. wt. of 3000 to 3700).

G16—Polyethylene glycol compound (av. mol. wt. about 15,000). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.

G17—75% Phenyl-25% methylpolysiloxane.

G18—Polyalkylene glycol.

G19—25% Phenyl-25% cyanopropyl-50% methylsilicone.

G20—Polyethylene glycol (av. mol. wt. of 380 to 420).

G21—Neopentyl glycol succinate.

G22—Bis(2-ethylhexyl) phthalate.

G23—Polyethylene glycol adipate.

G24—Diisodecyl phthalate.

G25—Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. ■[NOTE—Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.]■1S (*USP29*)

G26—25% 2-Cyanoethyl-75% methylpolysiloxane.

G27—5% Phenyl-95% methylpolysiloxane.

G28—25% Phenyl-75% methylpolysiloxane.

G29—3,3′-Thiodipropionitrile.

G30—Tetraethylene glycol dimethyl ether.

G31—Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30.

G32—20% Phenylmethyl-80% dimethylpolysiloxane.

G33—20% Carborane-80% methylsilicone.

G34—Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35—A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.

G36—1% Vinyl-5% phenylmethylpolysiloxane.

G37—Polyimide.

G38—Phase G1 containing a small percentage of a tailing inhibitor.

■[NOTE—A suitable grade is available commercially as "SP2100/0.1% Carbowax 1500" from Supelco, Inc. (www.sigma-aldrich.com/supelco).]■1S (*USP29*)

G39—Polyethylene glycol (av. mol. wt. about 1500).

G40—Ethylene glycol adipate.

G41—Phenylmethyldimethylsilicone (10% phenyl-substituted).

G42—35% phenyl-65% dimethylpolysiloxane (percentages refer to molar substitution).

G43—6% cyanopropylphenyl-94% dimethylpolysiloxane (percentages refer to molar substitution).

G44—2% low molecular weight petrolatum hydrocarbon grease and 1% solution of potassium hydroxide.

G45—Divinylbenzene-ethylene glycol-dimethylacrylate.

G46—14% Cyanopropylphenyl-86% methylpolysiloxane.

G47—Polyethylene glycol (av. mol. wt. of about 8000).

G48—Highly polar, partially cross-linked cyanopolysiloxane.■■1S (*USP29*)

Supports

NOTE—Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.

S1A—Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with Na_2CO_3 flux and calcining above 900°. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane ■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*) to mask surface silanol groups.

S1AB—The siliceous earth as described above is both acid- and base-washed. ■[NOTE—Unless otherwise specified in the individual monograph, silanized support is intended.]■1S (*USP29*)

S1C—A support prepared from crushed firebrick and calcined or burned with a clay binder above 900° with subsequent acid-wash. It may be silanized.

S1NS—The siliceous earth is untreated.

S2—Styrene-divinylbenzene copolymer having a nominal surface area of less than 50 m^2 per g and an average pore diameter of 0.3 to 0.4 μm.

S3—Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to 600 m^2 per g and an average pore diameter of 0.0075 μm.

S4—Styrene-divinylbenzene copolymer with aromatic –O and –N groups, having a nominal surface area of 400 to 600 m^2 per g and an average pore diameter of 0.0076 μm.

S5—40- to 60-mesh, high-molecular weight tetrafluoroethylene polymer.

S6—Styrene-divinylbenzene copolymer having a nominal surface area of 250 to 350 m^2 per g and an average pore diameter of 0.0091 μm.

S7—Graphitized carbon having a nominal surface area of 12 m^2 per g.

S8—Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9—A porous polymer based on 2,6-diphenyl-*p*-phenylene oxide.

S10—A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11—Graphitized carbon having a nominal surface area of 100 m^2 per g modified with small amounts of petrolatum and polyethylene glycol compound. ■[NOTE—Commercially available as SP1500 on Carbopack B from Supelco (www.sigma-aldrich.com/supelco).]■1S (*USP29*)

S12—Graphitized carbon having a nominal surface area of 100 m^2 per g.■2S (*USP30*)

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REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 29* page 3184, page 3625 of the *First Supplement,* and page 941 of *PF* 32(3) [May–June 2006].

(HDQ) RTS—C42655; C43862; C44132; C45407; C45499; C45503

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Add the following:	
▲Benazepril Hydrochloride Tablets	W ▲*USP30*
Add the following:	
■Capecitabine Tablets	T ■2S *(USP30)*
Add the following:	
■Cat's Claw Capsules	T, LR ■2S *(USP30)*
Add the following:	
■Cat's Claw Tablets	T, LR ■2S *(USP30)*
Add the following:	
■Citalopram Tablets	W ■2S *(USP29)*
Add the following:	
■Black Cohosh Tablets	T, LR ■2S *(USP30)*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Dantrolene Sodium Capsules	T, LR ■2S *(USP30)*
Add the following:	
▲Desogestrel and Ethinyl Estradiol Tablets	W ▲*USP30*
Add the following:	
▲Diclofenac Potassium Tablets	T, LR ▲*USP30*
Add the following:	
▲Didanosine Tablets	T ▲*USP30*
Add the following:	
▲Estradiol Vaginal Tablets	T ▲*USP30*
Add the following:	
▲Estradiol and Norethindrone Acetate Tablets	W ▲*USP30*
Add the following:	
▲Fexofenadine Hydrochloride Tablets	W ▲*USP30*
Add the following:	
▲Fosinopril Sodium Tablets	T ▲*USP30*
Add the following:	
▲Fosinopril Sodium and Hydrochlorothiazide Tablets	T ▲*USP30*
Add the following:	
▲Ginkgo Capsules	T, LR ▲*USP30*
Add the following:	
▲Ginkgo Tablets	T, LR ▲*USP30*

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Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■American Ginseng Capsules	L, TR■2S *(USP29)*
Change to read:	
Asian Ginseng Capsules	T~~, LR~~ ▲▲*USP30*
Add the following:	
▲Glipizide and Metformin Hydrochloride Tablets	W▲*USP30*
Add the following:	
■Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets	T, LR■2S *(USP30)*
Add the following:	
■Glucosamine and Methylsulfonyl methane Tablets	T, LR■2S *(USP30)*
Add the following:	
▲Irbesartan Tablets	W▲*USP30*
Add the following:	
▲Irbesartan and Hydrochlorothiazide Tablets	W▲*USP30*
Add the following:	
▲Isosorbide Mononitrate Tablets	T▲*USP30*
Add the following:	
▲Isosorbide Mononitrate Tablets, Extended-Release	T▲*USP30*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
▲Ketoprofen Capsules, Extended-Release	T▲*USP30*
Add the following:	
▲Metformin Hydrochloride Tablets, Extended-Release	W, LR▲*USP30*
Add the following:	
■Methylsulfonylmethane Tablets	T, LR■1S *(USP30)*
Add the following:	
▲Modafinil Tablets	T▲*USP30*
Add the following:	
▲Nefazodone Hydrochloride Tablets	T▲*USP30*
Add the following:	
■Nevirapine Tablets	W■1S *(USP30)*
Add the following:	
▲Norgestimate and Ethinyl Estradiol Tablets	W▲*USP30*
Add the following:	
■Ondansetron Orally Disintegrating Tablets	LR■2S *(USP29)*
Add the following:	
▲Oxycodone Hydrochloride Tablets, Extended-Release	T, LR▲*USP30*
Add the following:	
■Pravastatin Sodium Tablets	T■1S *(USP30)*
Add the following:	
▲Quinapril Tablets	W▲*USP30*

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Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Risperidone Tablets	T, LR■2S (*USP30*)
Add the following:	
▲Tizanidine Tablets	T▲*USP30*
Add the following:	
▲Valerian Capsules	T, LR▲*USP30*
Add the following:	
■Valganciclovir Tablets	T■1S (*USP30*)
Add the following:	
▲Valsartan and Hydrochlorothiazide Tablets	~~W~~ T▲*USP30*

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 29* page 3191, page 3625 of the *First Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 812 of *PF* 29(3) [May–June 2003], page 1684 of *PF* 29(5) [Sept.–Oct. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 2183 of *PF* 30(6) [Nov.–Dec. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], page 1193 of *PF* 31(4) [July–Aug. 2005], page 1491 of *PF* 31(5) [Sept.–Oct. 2005], page 1703 of *PF* 31(6) [Nov.–Dec. 2005], page 188 of *PF* 32(1) [Jan.–Feb. 2006], page 662 of *PF* 32(2) [Mar.–Apr. 2006], and page 942 of *PF* 32(3) [May–June 2006].

(HDQ) RTS—C43499; C43750; C44166; C44223; C46125

Add the following:

■**Capecitabine:** White to off-white crystalline powder. Freely soluble in methanol; soluble in acetonitrile and in ethanol; sparingly soluble in water.■2S (*USP30*)

Add the following:

■**Carvedilol:** White or nearly white, crystalline powder. Slightly soluble in alcohol; practically insoluble in water and in dilute acids.■2S (*USP30*)

Change to read:

Doxorubicin Hydrochloride: Red-orange, hygroscopic, crystalline

■or amorphous■2S (*USP30*)
powder. Soluble in water, in isotonic sodium chloride solution, and in methanol; practically insoluble in chloroform, in ether, and in other organic solvents.

Add the following:

■**Levofloxacin** (hemihydrate)**:** Pale or bright yellow crystalline powder. Freely soluble in glacial acetic acid and in chloroform; sparingly soluble in methanol; slightly soluble in ethanol; practically insoluble in ether.■2S (*USP30*)

Add the following:

■**Polydextrose:** Off-white to light tan-colored solid. Very soluble in water; slightly soluble in glycerin and in propylene glycol; insoluble in alcohol. *NF category:* Bulking agent; humectant.■2S (*NF25*)

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 32(1) through 32(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF*.

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
General Notices—*Preservation, Packaging, Storage, and Labeling—Storage Temperature and Humidity; Guidelines for Packaging and Storage Statements in USP–NF Monographs (Controlled Cold Temperature)* (add)	31	3	718
<u>*USP Monographs*</u>			
Acetaminophen—*Packaging and storage*	31	4	1024
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetazolamide Oral Solution (new)	32	1	43
Acetazolamide Oral Suspension (new)	32	1	44
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Medical Air—*Definition, Packaging and storage*	31	4	1024
Albendazole Oral Suspension—*Labeling*	32	1	46
Alprazolam Oral Suspension (new)	32	1	46
Albumin Human—*Definition, Packaging and storage, Expiration date, Labeling, USP Reference standards* (add), *Identification A, B* (add), *Bacterial endotoxins* (add), *Safety* (add), *Sterility* (add), *pH* (add), *Molecular size distribution* (add), *Heat stability* (add), *Incubation* (add) *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add)	31	5	1338
Albuterol Tablets—*Assay*	31	3	726
Alendronate Sodium—*Packaging and storage*	31	5	1344
Allopurinol—*Definition, Packaging and storage, USP Reference standards, Chromatographic purity (delete), Related compounds,* (add), *Assay*	32	2	302
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Aluminum Sulfate and Calcium Acetate Powder for Topical Solution (new)	32	3	755
Amantadine Hydrochloride—*Chromatographic purity*	31	5	1344

In-Process Revision

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* Vol.	No.	Page(s)
Amifostine—*Related compounds*	32	3	756
Amifostine for Injection—*Related compounds*	32	3	757
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—*Dissolution*	31	4	1025
Amitriptyline Hydrochloride—*USP Reference standards, Identification, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	31	6	1606
Amlodipine Besylate (new)	32	3	757
Amoxicillin Tablets—*Dissolution*	32	2	305
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water* (delete)	31	4	1026
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Aspartic Acid—*Chloride*	31	5	1345
Aspirin Boluses—*Dissolution*	31	4	1026
Atenolol—*Assay*	31	5	1345
Atracurium Besylate—*Chromatographic purity, Assay*	32	2	305
Azathioprine Oral Suspension (new)	32	1	48
Azithromycin—*Labeling, USP Reference standards, Limit of related substances*	32	2	306
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Oral Solution (new)	32	1	49
Baclofen Oral Suspension (new)	32	1	51
Benazepril Hydrochloride (new)	31	4	1027
Benazepril Hydrochloride Tablets (new)	32	1	52
Benzonatate Capsules—*Dissolution* (add)	32	1	55
Betamethasone Oral Solution—*Thin-layer chromatographic identification test*	31	4	1032
Bethanechol Chloride Oral Solution (new)	32	1	55
Bethanechol Chloride Oral Suspension (new)	32	1	57
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	31	3	741
Bisoctrizole (new)	32	2	309
Bromocriptine Mesylate—*Chromatographic purity*	31	5	1346
Bromocriptine Mesylate Capsules—*Dissolution*	32	1	58
Budesonide (new)	30	6	1978
Bupropion Hydrochloride Extended-Release Tablets—*Drug release, Dissolution*	32	2	312
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butorphanol Tartrate Nasal Solution (new)	31	5	1346
Calcitonin Salmon (new)	32	3	760
Calcitonin Salmon Nasal Solution (new)	32	3	767
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	32	1	58
Calcitriol Injection (new)	32	1	61
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate—*USP Reference standards* (add), *Identification*	31	6	1608
Calcium Lactate Tablets—*Identification*	31	6	1609
Calcium Pantothenate—*USP Reference standards, Ordinary impurities*	32	1	62
Camphor—*Water*	31	3	742
Captopril Oral Solution (new)	32	1	63
Captopril Oral Suspension (new)	32	1	64
Carbamazepine—*USP Reference standards, Chromatographic purity (Related compounds), Assay*	32	1	65
Carbamazepine Tablets—*Dissolution*	31	4	1044
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium—*Heavy metals*	31	5	1349

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Carboxymethylcellulose Sodium Paste—*Heavy metals*	31	5	1349
Cefaclor Tablets (new)	32	2	314
Cefadroxil for Oral Suspension—*Dissolution* (add), *Water*	32	2	315
Cefepime Hydrochloride—*Limit of N-methylpyrrolidine, Related compounds*	32	2	316
Cefonicid for Injection—*Assay*	32	1	67
Ceftazidime—*USP Reference standards, Assay*	32	1	67
Ceftazidime Injection—*USP Reference standards*	32	1	68
Ceftazidime for Injection—*USP Reference standards*	32	1	68
Cetirizine Hydrochloride (new)	32	2	317
Chlorhexidine Gluconate Oral Rinse—*Assay*	32	3	768
Chlorhexidine Gluconate Solution—*Assay*	32	3	768
Chlorophyllin Copper Complex Sodium—*Content of total copper*	32	3	769
Chlorthalidone—*USP Reference standards, Limit of 4'-chloro-3'-sulfamoyl-2-benzophenone carboxylic acid (CCA) (Limit of chlorthalidone related compound A), Assay*	32	1	68
Cholestyramine Resin—*Dialyzable quaternary amines*	32	2	320
Cilostazol (new)	32	1	69
Cimetidine—*Identification, Chromatographic purity*	32	3	769
Cimetidine Tablets—*Dissolution*	32	1	72
Ciprofloxacin—*Chromatographic purity, Assay*	32	2	320
Ciprofloxacin and Dexamethasone Otic Suspension (new)	32	2	321
Ciprofloxacin Hydrochloride—*Chromatographic purity, Assay*	32	2	325
Ciprofloxacin Injection—*Limit of ciprofloxacin ethylenediamine analog, Assay*	32	2	326
Citalopram Tablets (new)	32	3	770
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid (delayed implementation to January 1, 2009)*	31	2	394
Cladribine—*Specific rotation, Water, Related compounds, Limit of residual solvents*	32	3	774
Clarithromycin Extended-Release Tablets—*Dissolution*	32	3	775
Clindamycin Hydrochloride Oral Solution—*pH*	31	5	1350
Clonazepam Oral Suspension (new)	32	1	73
Clopidogrel Bisulfate—*Related compounds, Assay*	32	1	74
Clopidogrel Tablets—*Related compounds, Assay*	32	1	76
Clotrimazole Lozenges—*Dissolution*	32	1	78
Cloxacillin Benzathine—*Assay*	31	4	1050
Cloxacillin Benzathine Intramammary Infusion—*Assay*	31	4	1051
Cyanocobalamin—*Pseudo cyanocobalamin*	31	5	1350
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dantrolene Sodium (new)	32	2	327
Dantrolene Sodium for Injection (new)	32	3	779
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Diazepam Extended-Release Capsules—*USP Reference standards, Assay*	32	2	330
Diclofenac Potassium (new)	31	5	1350
Diclofenac Potassium Tablets (new)	31	5	1352
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Didanosine (new)	32	3	781
Didanosine for Oral Solution (new)	31	5	1357
Didanosine Tablets (new)	32	3	784
Digoxin Oral Solution—*Assay*	31	5	1361
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873

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Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diltiazem Hydrochloride Oral Solution (new)	32	1	79
Diltiazem Hydrochloride Oral Suspension (new)	32	1	80
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1612
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1614
Diphtheria Toxin for Schick Test (delete)	31	6	1616
Dipyridamole Oral Suspension (new)	32	1	81
Divalproex Sodium (new)	31	5	1362
Docusate Calcium—*Limit of bis(2-ethylhexyl)maleate*	31	3	752
Docusate Potassium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Docusate Sodium—*Limit of bis(2-ethylhexyl)maleate*	31	3	753
Dolasetron Mesylate Oral Solution (new)	32	1	83
Dolasetron Mesylate Oral Suspension (new)	32	1	84
Doxazosin Mesylate (new)	29	5	1470
Doxazosin Tablets (new)	29	1	64
Doxepin Hydrochloride—*USP Reference standards, Identification, Melting range* (delete), *Chloride content* (delete), *Related compounds* (add)	32	2	330
Dronabinol—*USP Reference standards, Identification, Limit of* Δ^8*-tetrahydrocannabinol* (delete), *Related compounds* (add), *Assay*	32	1	86
Drospirenone (new)	32	3	787
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Ensulizole—*USP Reference standards, Assay*	31	6	1617
Estradiol and Norethindrone Acetate Tablets (new)	31	5	1364
Estradiol Transdermal System (new)	31	4	1063
Estradiol Vaginal Tablets (new)	31	6	1617
Conjugated Estrogens—*Definition*	30	3	840
Synthetic Conjugated Estrogens (new)	31	6	1620
Ethinyl Estradiol Tablets—*Disintegration* (delete), *Dissolution* (add), *Related compounds*	31	4	1067
Ethotoin Tablets—*USP Reference standards, Assay*	32	2	332
Ethyl Chloride—*Alcohol* (delete)	31	5	1368
Etidronate Disodium—*Limit of phosphite*	31	6	1625
Famotidine Injection (new)	32	2	333
Fenofibrate (new)	31	3	763
Fentanyl (new)	31	6	1626
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Fluconazole—*Melting range* (delete), *Related compounds*	32	2	335
Flucytozine Oral Suspension (new)	32	1	92
Flumazenil—*USP Reference standards, Related compounds, Assay*	32	1	94
Fluorometholone Acetate (new)	31	5	1371
Fluoxetine Delayed-Release Capsules—*Chromatographic purity*	32	2	337
Flurazepam Hydrochloride—*Identification*	31	3	766
Flurbiprofen—*Identification*	31	4	1069
Fluticasone Propionate—*Chemical information, Definition, Bromofluoromethane content* (delete), *Content of acetone, Assay*	32	2	337
Fluticasone Propionate Nasal Spray (new)	32	2	339
Fluvastatin Sodium—*Packaging and storage, USP Reference standards, Identification, Chromatographic purity*	32	1	103
Fluvastatin Capsules—*USP Reference standards, Identification, Chromatographic purity*	32	1	105
Fluvoxamine Maleate—*Maleic acid* (delete), *Assay*	32	2	344
Fluvoxamine Maleate Tablets (new)	30	5	1622
Formoterol Fumarate (new)	32	1	106
Fosinopril Sodium (new)	32	3	789

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Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Ganciclovir Oral Suspension (new)	32	1	113
Gemcitabine for Injection—*USP Reference standards, Chromatographic purity*	31	6	1630
Gemcitabine Hydrochloride—*USP Reference standards*	32	1	114
Glipizide and Metformin Hydrochloride Tablets (new)	31	6	1631
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Glycopyrrolate Tablets—*Identification*	31	4	1077
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	32	3	792
Helium—*Definition, Packaging and storage*	31	4	1077
Hepatitis B Virus Vaccine Inactivated (delete)	31	6	1641
Hydrocodone Bitartrate—*USP Reference standards* *Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hydroxyzine Hydrochloride—*USP Reference standards, Chromatographic purity*	32	1	114
Hyoscyamine Sulfate—*USP Reference standards, Identification, Melting temperature* (delete), *Loss on drying* (delete), *Water* (add), *Residue on ignition, Other alkaloids* (delete), *Readily carbonizable substances* (delete), *Chromatographic purity* (add), *Assay*	31	4	1078
Hyoscyamine Sulfate Elixir—*Identification*	31	5	1372
Hyoscyamine Sulfate Injection—*Identification*	31	5	1373
Hyoscyamine Sulfate Oral Solution—*Identification*	31	5	1373
Hyoscyamine Sulfate Tablets—*Identification*	31	5	1374
Hypromellose Ophthalmic Solution—*Identification*	31	3	771
Ibuprofen—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	796
Ibuprofen Oral Suspension—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	796
Ibuprofen Tablets—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	798
Indinavir Sulfate—*Heavy metals, Method I,* (delete), *Heavy metals* (add), *Chromatographic purity, Assay*	32	2	345
Insulin—*USP Reference standards*	31	5	1375
Insulin Human—*USP Reference standards*	31	5	1375
Sodium Iodide I 123 Capsules—*Definition*	31	6	1642
Sodium Iodide I 123 Solution—*Definition, Radionuclidic purity, Bacterial endotoxins, pH*	31	6	1642
Sodium Iodide I 131 Solution—*pH*	31	6	1643
Iodoform—*Molecular weight*	32	1	115
Irbesartan—*Limit of azide, Related compounds*	32	3	799
Irbesartan Tablets (new)	32	3	799
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isopropyl Alcohol—*USP Reference standards* (add), *Identification*	31	5	1375
Isosorbide Dinitrate Tablets—*Dissolution, Assay*	31	5	1375
Isosorbide Dinitrate Chewable Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Extended-Release Tablets—*Assay*	31	5	1376
Isosorbide Dinitrate Sublingual Tablets—*Assay*	31	5	1377
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082
Ivermectin—*Specific rotation, Limit of alcohol and formamide*	31	6	1645
Ketoprofen—*Assay*	31	3	772
Ketoprofen Extended-Release Capsules (new)	31	5	1378
Labetalol Hydrochloride Oral Solution (new)	32	1	116
Labetalol Hydrochloride Oral Suspension (new)	32	1	117
Lamivudine—*Assay*	32	2	346
Leflunomide (new)	31	5	1380
Leflunomide Tablets (new)	31	5	1383
Leuprolide Acetate (new)	30	3	882
Levocabastine Hydrochloride (new)	31	6	1647
Levofloxacin (new)	32	2	347
Lidocaine and Prilocaine Cream (new)	31	4	1087
Lindane—*Definition, Assay*	31	6	1648

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Lipid Injectable Emulsion (new)	32	2	350
Lisinopril Tablets—*Dissolution*	31	4	1090
Loperamide Hydrochloride Oral Solution—*Assay*	32	2	353
Lovastatin—*Assay*	32	1	118
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Milk of Magnesia—*Limit of calcium* (delete)	32	2	353
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	419
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution (new)	31	5	1386
Magnesium Chloride—*Identification*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	421
Magnesium Oxide—*Labeling, Bulk density* (add)	31	4	1091
Mangafodipir Trisodium—*Limit of residual solvents*	31	6	1650
Mannitol Injection—*Labeling*	32	2	263
Megestrol Acetate Oral Suspension—*Dissolution*	31	5	1387
Meloxicam (new)	31	1	57
Metformin Hydrochloride—*Related compounds*	31	4	1092
Metformin Hydrochloride Tablets—*Identification, Related compounds*	31	4	1093
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
Methoxyflurane—*Foreign odor* (delete)	31	5	1388
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Methyldopa Oral Suspension—*USP Reference standards, Limit of methyldopa-glucose reaction product* (delete)	32	2	354
Methylprednisolone—*Chromatographic purity*	32	2	354
Metolazone Oral Suspension (new)	32	1	119
Metoprolol Tartrate Oral Solution (new)	32	1	121
Metoprolol Tartrate Oral Suspension (new)	32	1	122
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Miconazole Nitrate Cream—*Identification*	32	1	123
Miconazole Nitrate Vaginal Suppositories—*Assay*	31	5	1389
Mirtazapine—*Heavy metals*	31	6	1650
Mitoxantrone Injection—*Packaging and storage*	32	2	355
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Morantel Tartrate—*pH*	32	2	355
Morphine Sulfate Extended-Release Capsules—*Packaging and storage* (add)	32	1	124
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage* (add)	32	1	124
Narasin Granular—*Molecular weight, Assay*	32	1	124
Narasin Premix—*Assay*	32	1	126
Nefazodone Hydrochloride (new)	32	3	802
Nefazodone Hydrochloride Tablets (new)	32	3	804
Nevirapine Tablets (new)	32	3	807
Nifedipine Extended-Release Tablets—*Drug release, Dissolution*	32	2	355
Nimodipine—*Identification, Related compounds*	32	2	360
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate—*USP Reference standards, Limit of residual solvents, Chromatographic purity, Assay*	31	5	1390
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Omeprazole—*Chromatographic purity*	31	4	1100

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Omeprazole Delayed-Release Capsules—*Identification, Chromatographic purity*	31	5	1392
Ondansetron Hydrochloride—*Limit of ondansetron related compound D, Assay*	32	1	126
Ondansetron Hydrochloride Oral Suspension (new)	32	1	127
Ondansetron Injection—*Chromatographic purity*	31	6	1651
Ondansetron Oral Solution—*Packaging and storage* (add), *Limit of ondansetron related compound D, Related compounds*	32	1	128
Ondansetron Orally Disintegrating Tablets (new)	31	4	1101
Orphenadrine Citrate Injection—*Assay*	31	6	1651
Oxandrolone—*Definition, USP Reference standards, Identification B, Ordinary impurities* (delete), *Related compounds* (add), *Assay*	31	1	64
Oxaprozin—*Packaging and storage* (add)	32	1	130
Oxaprozin Tablets—*Packaging and storage* (add)	32	1	130
Oxybutynin Chloride—*Related compounds*	32	3	810
Oxybutynin Chloride Extended-Release Tablets (new)	31	6	1652
Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxygen—*Definition, Packaging and storage*	31	4	1107
Oxygen 93 Percent—*Definition, Packaging and storage*	31	4	1107
Paclitaxel—*USP Reference standards, Related compounds*	32	2	361
Pamidronate Disodium (new)	31	4	1108
Pamidronate Disodium for Injection (new)	31	4	1111
Pancuronium Bromide (new)	32	1	130
Paricalcitol—*Identification, Chromatographic purity, Assay*	32	1	132
Paroxetine Hydrochloride—*USP Reference standards, Limit of 1-methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine, Chromatographic purity, Assay*	32	3	811
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital Sodium—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Pentobarbital Sodium Injection—*Identification, Assay*	32	2	364
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piroxicam Cream (new)	32	1	134
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay (delayed implementation to January 1, 2009)*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Perchlorate—*USP Reference standards* (delete), *Assay*	32	2	364
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Pravastatin Sodium (new)	32	3	813
Pravastatin Sodium Tablets (new)	32	3	817
Prednicarbate (new)	31	5	1398
Prednicarbate Cream (new)	32	3	819
Prednicarbate Ointment (new)	32	3	822
Prednisolone Sodium Phosphate—*USP Reference standards, Identification*	32	2	365
Promethazine Hydrochloride—*USP Reference standards, Related substances*	32	2	365
Promethazine Hydrochloride Tablets—*USP Reference standards, Related compounds, Assay*	32	2	367
Pseudoephedrine Sulfate—*Ordinary impurities*	32	1	135
Pyridoxine Hydrochloride Injection—*Assay*	32	2	369
Quazepam Tablets—*USP Reference standards, Assay*	32	2	370
Quinapril Tablets—*Packaging and storage*	29	4	1071

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Oral Rehydration Salts—*USP Reference standards* (add), *Identification F* (delete), *Assay for citrate (delayed implementation to January 1, 2009)*	31	5	1399
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
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Risperidone (new)	31	6	1659
Ritonavir (new)	32	2	370
Ropivacaine Hydrochloride Injection (new)	32	2	374
Rubella and Mumps Virus Vaccine Live (delete)	31	6	1662
Saccharin Calcium (new)—*Harmonization*	31	2	607
Saccharin Sodium (new)—*Harmonization*	31	4	1225
Saquinavir Capsules—*Dissolution*	32	3	824
Saquinavir Mesylate—*Identification*	31	5	1400
Schick Test Control (delete)	31	6	1662
Senna—*Title, Definition, Packaging and storage, Labeling* (add), *USP Reference standards* (add), *Botanic characteristics, Identification, Microbial enumeration* (add) *Loss on drying* (add), *Total ash* (add), *Assay* (add)	32	1	137
Senna Pods (new)	32	1	140
Sennosides—*Definition, Packaging and storage, Residue on ignition*	32	1	141
Sevoflurane (new)	30	1	178
Simvastatin—*Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	32	1	141
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	31	3	795
Sodium Bicarbonate Injection—*Packaging and storage*	31	5	1401
Sodium Chloride—*Limit of phosphates*	31	5	1401
Sodium Chloride—*Identification, Loss on drying, Limit of potassium (postponed indefinitely)*	32	2	264
Sodium Fluoride and Phosphoric Acid Topical Solution (delete)	32	3	824
Sodium Lactate Injection—*Identification B* (delete)	31	5	1402
Sodium Phosphates Rectal Solution—*Assay*	31	5	1403
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Sulfamethazine Granulated—*Assay*	31	3	797
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Technetium Tc 99m Fanolesomab Injection (new)—*Packaging and storage* (add)	31	5	1405
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Thiabendazole Chewable Tablets (new)	29	6	1991
Thimerosal—*Identification*	32	1	147
Thioridazine Hydrochloride—*Identification*	31	3	798
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
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Tolazamide—*Chromatographic purity*	31	4	1118
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Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
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Valproic Acid Injection (new)—*Title (delayed implementation to October 1, 2008)*	32	2	387
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add)	30	6	2055
Vasopressin—*Identification*	31	4	1127
Verapamil Hydrochloride—*USP Reference standards Identification, Chromatographic purity*	32	2	389
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Vinorelbine Injection—*Definition, Assay*	32	3	825
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Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add), *Oxidizable substances*	31	3	804
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⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms (new) *(Harmonization)—Title, Introduction, General Proce dures, Nutritive and Selective Properties of the Media and Suitability of the Test, Testing of Products, Buffer Solutions and Culture Media*	29	5	1722
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⟨401⟩ Fats and Fixed Oils—*Acid Value (Free Fatty Acids)*	31	4	1157
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⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	32	3	850
⟨797⟩ Pharmaceutical Compounding—Sterile Preparations—*Introduction; Organization of This Chapter, Definitions* (add); *Responsibility of Compounding Personnel; CSP Microbial Contamination Risk Levels; Immediate Use CSPs* (add); *Single-Dose and Multiple-Dose Containers* (add); *Hazardous Drugs as CSPs* (add); *Radiopharmaceuticals as CSPs* (add); *Verification of Compounding Accuracy and Sterility; Personnel Training and Evaluation in Aseptic Manipulation Skills; Environmental Quality and Control; Suggested Standard Operating Procedures; Environmental Monitoring* (add); *Processing; Finished Preparation Release Checks and Tests; Storage and Beyond-Use Dating; Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs; Acronyms* (add), *Appendix*	32	3	852
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *(Harmonization)*	31	1	228
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
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⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1092⟩ The Dissolution Procedure: Development and Validation (new)	31	5	1463
⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products—*Introduction (Tables 1 and 2)*	29	5	1733

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⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add),*Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1117⟩ Microbiological Best Laboratory Practices (new)	30	5	1713
⟨1118⟩ Monitoring Devices—Time, Temperature, and Humidity—*Electronic Time–Temperature History Recorders*	32	3	900
⟨1160⟩ Pharmaceutical Calculations in Prescription Compounding—*Basic Pharmaceutical Calculations*	31	3	847
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⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
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Cadmium Nitrate	32	2	633
Calcium Acetate	32	2	634
Calcium Carbonate	32	2	634
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Calcium Chloride	32	2	634
Calcium Chloride, Anhydrous	32	2	634
Calcium Citrate	32	2	634
Calcium Hydroxide	32	2	635

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Calcium Nitrate	32	2	635
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dl-10-Camphorsulfonic Acid	32	2	636
Capric Acid	32	2	636
Carbazole	32	2	636
Carbon Disulfide, CS	32	2	636
Carbon Tetrachloride	32	2	636
Carboxymethoxylamine Hemihydrochloride	32	2	637
Casein	32	2	637
Catechol	32	2	637
Cedar Oil	32	2	637
Ceric Sulfate	32	2	638
Chenodeoxycholic Acid	32	2	638
Chloramine T	32	2	638
Chlorine	32	2	638
1-Chloroadamantane	32	2	639
3-Chloroaniline	32	2	639
Chlorobenzene	32	2	639
m-Chlorobenzoic Acid	32	2	639
4-Chlorobenzoic Acid	32	2	639
4-Chlorobenzophenone	32	2	640
Chloroform	32	2	640
Chlorogenic Acid	32	2	640
1-Chloronaphthalene	32	2	640
2-Chloronicotinic Acid	32	2	640
2-Chloro-4-nitroaniline, 99%	32	2	641
Chloroplatinic Acid	32	2	641
5-Chlorosalicylic Acid	32	2	641
Chlorotrimethylsilane	32	2	641
Cholestane	32	2	641
Cholesteryl Benzoate	32	2	641
Choline Chloride	32	2	642
Chromium Trioxide	32	2	642
Chromotropic Acid	32	2	642
Chromotropic Acid Disodium Salt	32	2	642
Cinchonidine	32	2	642
Cinchonine	32	2	643
Citric Acid, Anhydrous	32	2	643
Cobalt Chloride	32	2	643
Cobalt Nitrate	32	2	643
Cobaltous Acetate	32	2	643
Congo Red	32	2	643
Coomassie Brilliant Blue R-250	32	2	644
Copper	32	2	644
Cortisone	32	2	644
m-Cresol Purple	32	2	644
Cupric Acetate	32	2	644
Cupric Chloride	32	2	645
Cupric Citrate	32	2	645
Cupric Sulfate, Anhydrous	32	2	645
Cyanoacetic Acid	32	2	645
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3,3′-Diaminobenzidine Hydrochloride	32	2	647
2,3-Diaminonaphthalene	32	2	647
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Diatomaceous Silica, Calcined	32	2	648
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2,6-Dichloroaniline	32	2	649
o-Dichlorobenzene	32	2	649
2,8-Dichlorodibenzo-*p*-dioxin (delete)	30	6	2168
2,8-Dichlorodibenzofuran (delete)	30	6	2168
Dichlorofluorescein	32	2	650
Dichlorofluoromethane	32	2	650
2,4-Dichloro-1-naphthol	32	2	650
2,4-Dichlorophenol (delete)	30	6	2168
2,6-Dichlorophenol-indophenol Sodium	32	2	650
2,6-Dichlorophenylacetic Acid	32	2	650
Dicyclohexyl	31	3	858
Dicyclohexylamine	32	2	651
Diethylamine	32	2	651
N,N-Diethylaniline	32	2	651
Diethylene Glycol	32	2	651
Diethylene Glycol Succinate Polyester	32	2	652
Diethylenetriamine	32	2	652
Di(2-ethylhexyl)phthalate	32	2	652
Digitonin	32	2	652
10,11-Dihydrocarbamazepine (delete)	32	2	652
Dihydroquinidine Hydrochloride	32	2	653
Dihydroquinine	32	2	653
2,5-Dihydroxybenzoic Acid	32	2	653
Diiodofluorescein	32	2	653
Diisodecyl Phthalate	32	2	654
Diisopropyl Ether	32	3	901
Diisopropylamine	32	2	654
Diisopropylethylamine	32	2	654
2,5-Dimethoxybenzaldehyde	32	2	654
1,2-Dimethoxyethane	32	2	655
(3,4-Dimethoxyphenyl)acetonitrile	32	2	655
Dimethyl Phthalate	32	2	655
Dimethyl Sulfone	32	2	655
Dimethyl Sulfoxide, Spectrophotometric Grade	32	2	655
N,N-Dimethylacetamide	32	2	656
p-Dimethylaminoazobenzene	32	2	656
p-Dimethylaminobenzaldehyde,	32	2	656
2-Dimethylaminoethyl Methacrylate (new)	31	4	1190
2,6-Dimethylaniline	32	2	656
N,N-Dimethylaniline	32	2	656
3,4-Dimethylbenzophenone	32	2	657
5,5-Dimethyl-1,3-cyclohexanedione	32	2	657
N,N-Dimethyldodecylamine-*N*-oxide (new)	27	4	2837
Dimethylformamide	32	2	657
N,N-Dimethylformamide Diethyl Acetal (delete)	32	2	657
N,N-Dimethyl-1-naphthylamine	32	2	657
N,N-Dimethyloctylamine	32	2	658
2,6-Dimethylphenol	32	2	658
N,N-Dimethyl-*p*-phenylenediamine Dihydrochloride	32	2	658
m-Dinitrobenzene	32	2	658
3,5-Dinitrobenzoyl Chloride	32	2	659
2,4-Dinitrochlorobenzene	32	2	659
2,4-Dinitrofluorobenzene	32	2	659
2,4-Dinitrophenylhydrazine	32	3	901
Dioxane	32	3	902
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Dodecyltrimethylammonium Bromide (new)	31	3	859
Diphenyl Ether	32	3	902
Diphenylamine	32	3	902
Diphenylcarbazide	32	3	902
Diphenylcarbazone	32	3	902
2,2-Diphenylglycine	32	3	902
Dipropyl Phthalate	32	3	903
4,4′-Dipyridyl Dihydrochloride	32	3	903
5,5′-Dithiobis(2-nitrobenzoic Acid)	32	3	903
Dithiothreitol	32	3	903
Dithizone	32	3	903
1-Dodecanol	32	3	903
n-Eicosane	32	3	904
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Eriochrome Cyanine R	32	3	904
Erythritol (delete)	31	5	1487
Ethanesulfonic Acid	32	3	905
2-Ethoxyethanol	32	3	905
Ethyl Acetate	32	3	905
Ethyl Acrylate	32	3	905
Ethyl Benzoate	32	3	905
Ethyl Cyanoacetate	32	3	906
Ethyl Ether	32	3	906
Ethyl Ether, Anhydrous	32	3	906
Ethyl Salicylate	32	3	906
2-Ethylaminopropiophenone Hydrochloride	32	3	906
4-Ethylbenzaldehyde	32	3	906
Ethylbenzene	32	3	907
Ethylene Dichloride	32	3	907
Ethylene Glycol	32	3	907
Ethylene Oxide in Methylene Chloride (50 mg/mL) (new)	31	3	859
1-Ethylquinaldinium Iodide	32	3	907
Fast Blue B Salt	32	3	907
Fast Blue BB Salt	32	3	908
Ferric Chloride	32	3	908
Ferric Nitrate	32	3	908
Ferric Sulfate	32	3	908
Ferrous Sulfate	32	3	909
Fluorene	32	3	909
9-Fluorenylmethyl Chloroformate	32	3	909
Fluorescamine	32	3	909
4′-Fluoroacetophenone	32	3	909
Formamide	32	3	909
Formic Acid	32	3	910
Formic Acid, 96 Percent	32	3	910
Fuchsin, Basic	32	3	910
Furfural	31	4	1190
Gadolinium (Gd III) Acetate Hydrate	32	3	910
Galactitol (delete)	31	5	1488
Geneticin (new)	31	6	1700
Gitoxin	32	3	910
D-Gluconic Acid, 50 Percent in Water	32	3	911
Glucose	32	3	911
D-Glucuronolactone	32	3	911
Glycerin	32	3	911
Glycolic Acid	32	3	911
Gold Chloride	32	3	911
Guaiacol	32	3	912
Guanidine Hydrochloride	32	3	912
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Hematein	32	3	912
Hematoxylin	32	3	912
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Hydrazine Dihydrochloride	32	3	914
Hydrazine Hydrate, 85% in Water	32	3	914
Hydriodic Acid	32	3	914
Hydrochloric Acid	32	3	915
Hydrochloric Acid, Diluted	32	3	915
Hydrofluoric Acid	32	3	915
Hydrogen Peroxide, 30 Percent	32	3	915
Hydrogen Sulfide	32	3	915
Hydroquinone	32	3	915
3′-Hydroxyacetophenone	32	3	916
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1-Hydroxybenzotriazole Hydrate	32	3	916
2-Hydroxybenzyl Alcohol	32	3	916
4-Hydroxyisophthalic Acid	32	3	917
Hydroxylamine Hydrochloride	32	3	917
Hydroxy Naphthol Blue	32	3	917
D-α-Hydroxyphenylglycine	32	3	917
4-(4-Hydroxyphenyl)-2-butanone	32	3	917
Hydroxypropyl-β-cyclodextrin (new)	31	6	1701
8-Hydroxyquinoline	32	3	918
Hypophosphorous Acid, 50 Percent	32	3	918
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Iminostilbene (delete)	32	2	659
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Inositol	32	3	918
Iodic Acid	32	3	919
Iodine	32	3	919
Iodine Monobromide	32	3	919
Iodine Monochloride	32	3	919
Isobutyl Acetate	32	3	919
Isobutyl Alcohol	32	3	919
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Isopropyl Alcohol	32	3	920
Isopropyl Alcohol, Dehydrated	32	3	920
Isopropyl Iodide	31	6	1701
Isopropyl Myristate	32	3	920
Isopropylamine	32	3	920
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Lactose	32	3	921
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Lead Acetate	32	3	921
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Lead Nitrate	32	3	922
Lead Standard Solution (new)	31	5	1488
Lithium Chloride	32	3	922
Lithium Hydroxide	32	3	922
Lithium Metaborate	32	3	922
Lithium Nitrate	32	3	922
Lithium Percholate	32	3	922
Lithium Sulfate	32	3	922
Lithocholic Acid	32	3	923
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Magnesium	32	3	923
Magnesium Acetate	32	3	923
Magnesium Chloride	32	3	923
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Magnesium Perchlorate, Anhydrous	32	3	924
Magnesium Sulfate	32	3	924
Magnesium Sulfate, Anhydrous	32	3	924
Maleic Acid	32	3	924
Manganese Dioxide, Activated	32	3	925
Mercuric Acetate	32	3	925
Mercuric Bromide	32	3	925
Mercuric Chloride	32	3	925
Mercuric Iodide, Red	32	3	925
Mercuric Nitrate	32	3	925
Mercuric Oxide, Yellow	32	3	926
Mercuric Sulfate	32	3	926
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Mercury	32	3	926
Mesityl Oxide	32	3	926
Metaphosphoric Acid	32	3	926
Methacrylic Acid	32	3	927
Methanesulfonic Acid	32	3	927
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5-Methoxy-2-methyl-3-indoleacetic Acid	32	3	927
Methyl Acetate	32	3	927
Methyl 4-Aminobenzoate	32	3	928
Methyl Arachidate	32	3	928
Methyl Behenate	32	3	928
Methyl Caprate	32	3	928
Methyl Caprylate	32	3	928
Methyl Carbamate	32	3	929
Methyl Chloroform	32	3	929
Methyl Erucate	32	3	929
Methyl Ethyl Ketone	32	3	929
Methyl Heptadecanoate	32	3	929
Methyl Iodide	32	3	929
Methyl Laurate	32	3	930
Methyl Lignocerate	32	3	930
Methyl Linoleate	32	3	930
Methyl Linolenate	32	3	930
Methyl Methacrylate	32	3	931
Methyl Myristate	32	3	931
Methyl Oleate	32	3	931
Methyl Palmitate	32	3	931
Methyl Stearate	32	3	931
Methyl Sulfoxide	32	3	932
Methylamine, 40 Percent in Water	32	3	932
p-Methylaminophenol Sulfate	32	3	932
Methylene Blue	32	3	932
Methylene Chloride	32	3	932
5-5′-Methylenedisalicylic Acid	32	3	932
4-Methyl-2-pentanone	32	3	933
2-Methyl-2-propyl-1,3-propanediol	32	3	933
N-Methylpyrrolidine	32	2	659
Molybdic Acid	32	3	933
Monochloroacetic Acid	32	3	933
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Naphthalene	32	3	933
1,3-Naphthalenediol	32	3	934
2,7-Naphthalenediol	32	3	934
2-Naphthalenesulfonic Acid	32	3	934
1-Naphthol	32	3	934
2-Naphthol	32	3	934
p-Naphtholbenzein	32	3	935
Naphthoresorcinol	32	3	935
1-Naphthylamine Hydrochloride	32	3	935
2-Napthyl Chloroformate	32	3	935
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Nitric Acid, Fuming	32	3	936
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p-Nitroaniline	32	3	937
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4-(*p*-Nitrobenzyl)pyridine	32	3	938
Nitromethane	32	3	938
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1-Nitroso-2-naphthol	32	3	938
Nitroso R Salt	32	3	939
Nitrous Oxide Certified Standard	32	3	939
Nonadecane	32	3	939
Nonanoic Acid	32	3	939
Palladium Matrix Modifier (new)	31	5	1488
Phenylhydrazine Hydrochloride	32	2	660
Anion-Exchange Resin, Styrene-Divinylbenzene	30	3	1043

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p-Toluenesulfonyl-L-arginine Methyl Ester Hydrochloride	32	1	186
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1,3,7-Trichlorodibenzo-*p*-dioxin (delete)	30	6	2169
Saccharin Calcium	31	2	607
Saccharin Calcium—*Harmonization*	31	2	609
Saccharin Sodium	31	2	612
Saccharin Sodium—*Harmonization*	31	2	613
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Phenol TS (new)	31	3	859
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	26	4	1135
	27	1	1908
	28	2	554
	28	6	1953
	29	1	266
	29	3	812
	29	5	1684
	30	4	1405
	30	5	1822
	30	6	2183
	31	1	122
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	31	5	1491
	31	6	1703
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NF Monographs			
Acetyltributyl Citrate—*Assay*	32	1	177
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Alfadex—*Definition, Packaging and storage* (add), *Loss on drying* (delete), *Water, Method I* (add), *Reducing sugars, Light-absorbing impurities, Organic volatile impurities, Method IV* (delete), *Residual solvents* (delete), *Assay*	32	2	395
Amino Methacrylate Copolymer (new)	31	4	1137
Calcium Silicate—*Definition, USP Reference standards* (add), *pH, Lead* (delete), *Limit of lead* (add), *Limit of fluoride, Assay for silicon dioxide, Assay for calcium oxide, Ratio of silicon dioxide to calcium oxide*	31	5	1417
Canola Oil (new)	31	6	1667
Carboxymethylcellulose Calcium—*Heavy metals*	31	5	1420
Carboxymethylcellulose Sodium 12—*Labeling, Viscosity, Heavy metals*	31	5	1420
Cellaburate—*Packaging and storage* (add)	31	5	1420
Cellacefate—*USP Reference standards*	32	1	179
Microcrystalline Cellulose—*Labeling, Identification, Particle size distribution estimation by analytical sieving*	31	5	1421

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Cyclomethicone—*Identification*	31	4	1140
Dibutyl Sebacate—*Saponification value*	31	4	1140
Diethanolamine—*USP Reference standards* (add), *Identification*	31	5	1422
Diisopropanolamine (new)	31	4	1140
Erythritol (new)	31	5	1422
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion (new)	31	4	1141
Ethylcellulose Aqueous Dispersion—*Labeling, Identification*	31	6	1668
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Hydroxypropyl Cellulose—*USP Reference standards* (add), *Identification*	31	5	1425
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Magnesium Stearate—*Harmonization*	30	1	340
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Maltol—*Packaging and storage*	31	5	1425
Monoethanolamine—*USP Reference standards* (add), *Identification* (add)	31	5	1425
Nitrogen—*Definition, Packaging and storage, Assay*	31	4	1145
Nitrogen 97 Percent—*Definition, Packaging and storage, Assay*	31	4	1146
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Paraffin—*Readily carbonizable substances*	31	5	1426
Polacrilin Potassium—*CAS number, Chemical name*	31	6	1671
Polyethylene Glycol—*Harmonization*	31	3	897
Polyethylene Oxide—*Packaging and storage, USP Reference standards, Identification, Heavy metals, Method II* (delete), *Heavy metals* (add), *Limit of free ethylene oxide, Organic volatile impurities, Method I* (delete), *Residual solvents* (delete)	32	2	398
Polyisobutylene—*Loss on drying*	32	3	828
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Potassium Alginate (new)	31	5	1426
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Tetrafluoroethane (new)	31	6	1672
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Triethyl Citrate—*Assay*	32	1	180
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Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
General Notices and Requirements			
†Tests and Assays (Foreign Substances and Impurities)	31	3	718
†Preservation, Packaging, Storage, and Labeling (Repackaging Instructions)	31	3	718
USP Monographs			
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
†Albumin Human (entire submission)	29	4	992
Albuterol Tablets—			
Dissolution	30	1	50
Dissolution	31	1	40
†Allopurinol—*USP Reference standards, Chromatographic purity, Related compounds, Assay*	28	5	1386
Alprazolam Tablets—*Dissolution*	30	5	1582
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Baclofen Tablets—*Dissolution*	30	1	61
Betamethasone Tablets—*Dissolution*	30	1	62
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Carboxymethylcellulose Sodium Suspension (entire submission)	30	3	812
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
†Citalopram Hydrobromide—*Related compounds*	31	3	742
†Citalopram Tablets (new)—*Dissolution, Related compounds*	31	3	745
Colchicine Tablets—*Dissolution*	30	1	91
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add)	29	6	1870
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Estradiol Transdermal System (new)—*Drug release*	30	4	1201
Ethinyl Estradiol Tablets—*Related compounds*	31	2	402
Ethosuximide Capsules—*Dissolution*	30	1	102

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
†Fluvastatin Sodium—*Loss on drying* (add), *Water* (delete)	32	1	103
Fluticasone Propionate—*Content of acetone (Procedure)*	31	4	1070
Gabapentin Capsules (new) (entire submission)	28	2	298
†Glyburide Tablets—*Dissolution*	29	2	418
Glycopyrrolate Tablets—			
Dissolution	30	1	105
†*Dissolution (Procedure, Tolerances)*	31	4	1077
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Indocyanine Green—*Definition, Assay*	29	6	1905
Irbesartan Tablets (new)—*Dissolution*	29	4	1035
Isosorbide Dinitrate Sublingual Tablets—			
Dissolution	30	1	113
†*Dissolution (Procedure, Tolerances)*	31	5	1377
†Diluted Isosorbide Mononitrate (entire submission)	31	4	1060
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Levothyroxine Sodium Oral Solution (new)—*Preview*	31	3	938
Lisinopril Tablets—*Dissolution*	30	1	121
Loperamide Hydrochloride Tablets—*Dissolution*	30	5	1633
Magnesium Oxide—*Bulk density* (add)	29	4	1047
†Mebendazole Oral Suspension—*Labeling*	32	1	119
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Meprobamate Tablets—*Dissolution*	30	1	129
Methenamine Tablets—*Dissolution*	30	1	130
Methocarbamol Tablets—*Dissolution*	30	1	130
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
†Morphine Sulfate Extended-Release Capsules—*Packaging and storage*	28	6	1822
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
†Nefazodone Hydrochloride (new)—*Related compounds*	31	4	1094
†Nefazodone Hydrochloride Tablets (new) (entire submission)	31	4	1096
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Ondansetron Orally Disintegrating Tablets (new)—*Disintegration, Dissolution*	30	6	2024
†Oxaprozin—*Packaging and storage*	29	4	1059
†Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new) (entire submission)	30	4	1276
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
†PEG 3350 and Electrolytes for Oral Solution (entire submission)	31	5	1393
Penicillamine Capsules—*Dissolution*	30	1	153
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036

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†Simvastatin—*Identification B, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	31	3	792
†Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate*	31	3	797
†Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Spironolactone Oral Suspension (new) (entire submission)	30	3	929
Spironolactone and Hydrochlorothiazide Oral Suspension (new) (entire submission)	30	3	930
†Sumatriptan Succinate (new)—*Preview*	27	5	3157
Terbutaline Sulfate Tablets—*Dissolution*	31	1	76
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Timolol Maleate Tablets—*Dissolution*	30	1	191
†Titanium Dioxide (new) (entire submission)	30	4	1301
Titanium Dioxide (new) (entire submission)	30	4	1304
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
†Valproic Acid Injection (new) (entire submission)	31	3	801
	31	5	1412
Vecuronium Bromide for Injection (new)—*Preview*	25	4	8449
Dietary Supplements Monographs			
†Ginkgo Capsules (new) (entire submission)	27	2	2238
†Ginkgo Tablets (new) (entire submission)	27	2	2240
†Powdered Ginkgo Extract (new) (entire submission)	27	2	2233
Asian Ginseng Capsules (new)—*Dissolution*	30	2	571
American Ginseng Capsules (new)—*Dissolution*	30	2	565
American Ginseng Tablets—*Dissolution*	30	2	567
†Lutein—*Identification A, Zeaxanthin and other related compounds, Content of lutein*	31	4	1133
†Lutein Preparation—*Identification A, Zeaxanthin and other related compounds, Content of lutein*	31	4	1134
Valerian Capsules (new)—*Disintegration and dissolution*	27	1	1825
USP General Test Chapters			
†⟨1⟩ Injections—*Packaging*	31	1	192
⟨11⟩ USP Reference Standards			
†USP 23-epi-26-Deoxyacetin RS	28	5	1468
USP Fluvastatin for System Suitability RS (add)	31	1	99
†*USP Human Albumin RS*	29	6	2022
USP Polyoxyl 35 Castor Oil RS	30	5	1674
⟨41⟩ Weights and Balances (entire submission)	31	2	508
†⟨267⟩ Porosimetry by Mercury Intrusion (new) (entire submission)	28	3	893
⟨386⟩ Environmentally Sensitive Preparations (new) (entire submission)	30	5	1680
⟨429⟩ Light Diffraction Measure of Particle Size (new) (entire submission)	28	3	895
†⟨616⟩ Bulk Density and Tapped Density (entire submission)	28	3	901
⟨621⟩ Chromatography—*System Suitability (All revisions after the first two paragraphs, through the end up to Glossary)*	30	6	2094
†⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
†⟨699⟩ Density of Solids—*Preview*	28	2	603
⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets* (delete), *Interpretation*	30	1	234
USP General Information Chapters			
†⟨1058⟩ Analytical Instrument Qualification (new) (entire submission)	31	1	233
†⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients (entire submission)	28	5	1504
†⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)—*Preview*	28	5	1650

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Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
⟨1089⟩ In Vitro, Absorption-Indicating Cell Culture System (new)—*Preview*	25	5	8733
†⟨1092⟩ The Dissolution Procedure: Development and Validation (new)—*Preview*	30	1	351
†⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)—*Preview*	28	5	1662
Dietary Supplements Chapters			
†⟨2040⟩ Disintegration and Dissolution of Nutritional Supplements—*Preview*	28	5	1673
Reagents, Indicators, and Solutions			
1,4-Butanediol (add)—*Preview*	25	5	8747
†Isoferulic Acid (add)	27	4	2837
1-Vinyl-2-pyrrolidone	31	1	108
Reference Tables			
Container Specifications			
†Black Cohosh Tablets	27	4	2874
Citalopram Hydrobromide Tablets (add)	31	3	859
Description and Relative Solubility			
Magnesium Oxide	29	4	1262
Titanium Dioxide (add)	30	4	1405
NF Monographs			
Alfadex—*Packaging and storage*	30	1	202
†Black Cohosh (entire submission)	28	5	1455
†Powdered Black Cohosh (entire submission)	28	5	1460
†Powdered Black Cohosh Extract (entire submission)	28	5	1461
†Black Cohosh Tablets (entire submission)	28	5	1462
†Corn Syrup (new) (entire submission)	28	2	403
†High Fructose Corn Syrup (new) (entire submission)	28	2	408
†Magnesium Stearate—*Microbial limits*	29	6	2018
Sodium Caprylate—*Packaging and storage*	30	3	990
†Stearic Acid—*Microbial limits* (add)	29	2	480
†Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706

†New cancellations in *PF* 32(4).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

MONOGRAPHS (USP)

BRIEFING

Dibasic Calcium Phosphate Dihydrate, *USP 29* page 359. The Japanese Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Dibasic Calcium Phosphate Dihydrate* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, is based on the corresponding monograph for Dibasic Calcium Phosphate Dihydrate that was prepared by the Japanese Pharmacopoeia. The Japanese Pharmacopoeia draft was based in part on comments from the European Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the Japanese Pharmacopoeia.

Differences between the Japanese Pharmacopoeia Adoption Stage 6 document and the current *USP* monograph for Dibasic Calcium Phosphate include the following:

1. *Definition*—The current Dibasic Calcium Phosphate monograph is proposed to be split into two separate monographs: Anhydrous Dibasic Calcium Phosphate and Dibasic Calcium Phosphate Dihydrate.
2. *Packaging and storage*—Retained as a nonharmonized attribute.
3. *Labeling*—Statement removed as it is no longer necessary with two monographs for the anhydrous and the dihydrate forms of Dibasic Calcium Phosphate.
4. *USP Reference standards*—No change.
5. *Identification*—Changed test *A* by increasing the volume of hydrochloric acid to assist in sample dissolution. Changed test *B* by decreasing the sample size and volume of nitric acid, and providing temperature and time for warming of sample.
6. *Loss on ignition*—Removed specification pertaining to anhydrous material.
7. *Carbonate*—Added statement to require carbon dioxide-free water in sample preparation.
8. *Chloride*—Changed sample size and volume of diluent to allow for complete dissolution of the sample.
9. *Sulfate*—Decreased sample size.
10. *Arsenic*—Retained as a nonharmonized attribute.
11. *Barium*—Added statement "heat to boiling".
12. *Heavy metals*—Retained as a nonharmonized attribute.
13. *Limit of acid-insoluble substances*—Added statement to indicate "heat to boiling" in preparation step. Added step to incinerate residue at 600°.
14. *Limit of fluoride*—Retained as a nonharmonized attribute.
15. *Organic volatile impurities*—Test removed from harmonization draft.
16. *Residual solvents*—Test removed from harmonization draft.
17. *Assay*—Replaced existing method with new titration assay to be consistent with JP standards.

(DSN: K. Moore) RTS—C44231

Change to read:

~~Dibasic Calcium Phosphate~~

■Dibasic Calcium Phosphate Dihydrate■2S (*USP30*)

Add the following:

■**Pharmacopeial Discussion Group Sign-Off Document**

Attribute	JP	EP	USP
Definition	+	+	+
Identification A	+	+	+
Identification B	+	+	+
Acid-insoluble substances	+	+	+
Chloride	+	+	+
Sulfate	+	+	+
Carbonate	+	+	+
Barium	+	+	+
Loss on ignition	+	+	+
Assay	+	+	+

Legend: + will adopt and implement; - will not stipulate.

Nonharmonized attributes: Packaging and storage, Heavy metals, Limit of fluoride, Iron.

Specific local attributes: Identification C (EP), Lead (USP), Description (JP)■2S (*USP30*)

Delete the following:

~~■$CaHPO_4$ 136.06~~
~~Phosphoric acid, calcium salt (1 : 1).~~
~~Calcium phosphate (1 : 1) [7757-93-9].~~
~~Dihydrate 172.09 [7789-77-7].~~■2S (*USP30*)

Add the following:

■$CaHPO_4 \cdot 2H_2O$

Phosphoric acid, calcium salt (1 : 1).

Calcium phosphate, Dihydrate (1 : 1)

[*7789-77-7*].■2S (*USP30*)

Delete the following:

~~■» Dibasic Calcium Phosphate is anhydrous or contains two molecules of water of hydration. It contains not less than 98.0 percent and not more than 105.0 percent of~~

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~~anhydrous dibasic calcium phosphate ($CaHPO_4$) or of dibasic calcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$).~~ ■2S (*USP30*)

Add the following:

■» Dibasic Calcium Phosphate Dihydrate contains two molecules of water of hydration. It contains not less than 98.0 percent and not more than 105.0 percent of dibasic calcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$). ■2S (*USP30*)

Delete the following:

■~~**Packaging and storage** Preserve in well-closed containers.~~ ■2S (*USP30*)

Add the following:

■**Packaging and storage**—Preserve in well-closed containers. No storage requirements specified. ■2S (*USP30*)

Delete the following:

■~~**Labeling** Label it to indicate whether it is anhydrous or the dihydrate.~~ ■2S (*USP30*)

USP Reference standards ⟨11⟩—*USP Sodium Fluoride RS.*

Delete the following:

■~~**Identification**~~

~~**A:** Dissolve about 100 mg by warming with a mixture of 5 mL of 3 N hydrochloric acid and 5 mL of water, add 2.5 mL of 6 N ammonium hydroxide dropwise, with shaking, and then add 5 mL of ammonium oxalate TS: a white precipitate is formed.~~

~~**B:** To 10 mL of a warm solution (1 in 100) in a slight excess of nitric acid add 10 mL of ammonium molybdate TS: a yellow precipitate of ammonium phosphomolybdate is formed.~~ ■2S (*USP30*)

Add the following:

■**Identification—**

A: Dissolve about 100 mg by warming in 10 mL of 2 N hydrochloric acid, add 2.5 mL of ammonia TS dropwise, with shaking, and then add 5 mL of ammonium oxalate TS: a white precipitate is formed.

B:

Ammonium molybdate solution—Dissolve 21.2 g of ammonium molybdate in water to make 200 mL of solution (10%). Prepare before use.

Dissolve about 100 mg of sample in 5 mL of diluted nitric acid. Warm the solution to 70°, and add 2 mL of *Ammonium molybdate solution:* a yellow precipitate of ammonium phosphomolybdate is formed. ■2S (*USP30*)

Delete the following:

■~~**Loss on ignition** ⟨733⟩ Ignite it at 800° to 825° to constant weight: anhydrous Dibasic Calcium Phosphate loses between 6.6% and 8.5% of its weight, and the dihydrate form of Dibasic Calcium Phosphate loses between 24.5% and 26.5% of its weight.~~ ■2S (*USP30*)

Add the following:

■**Loss on ignition** ⟨733⟩—Ignite about 1 g at 800° to 825° to constant weight: the material loses between 24.5% and 26.5% of its weight. ■2S (*USP30*)

Delete the following:

■~~**Carbonate** Mix 1.0 g with 5 mL of water, and add 2 mL of hydrochloric acid: no effervescence occurs.~~ ■2S (*USP30*)

Add the following:

■**Carbonate**—Mix 1.0 g with 5 mL of carbon dioxide-free water, and immediately add 2 mL of hydrochloric acid: no effervescence occurs. ■2S (*USP30*)

Delete the following:

■~~**Chloride** ⟨221⟩ To 0.30 g add 10 mL of water and 2 mL of nitric acid, and warm gently, if necessary, until no more dissolves. Dilute to 25 mL, filter, if necessary, and add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 1.0 mL of 0.020 N hydrochloric acid (0.25%).~~ ■2S (*USP30*)

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Add the following:

■**Chloride** ⟨221⟩—To 0.20 g add 20 mL of water and 13 mL of diluted nitric acid, and warm gently, if necessary, until no more dissolves. Dilute to 100 mL, and filter, if necessary. To 50 mL of this solution add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 0.70 mL of 0.010 N hydrochloric acid (0.25%).■2S (*USP30*)

Delete the following:

■~~**Sulfate** ⟨221⟩—Dissolve 1.0 g in the smallest possible amount of 3 N hydrochloric acid, dilute with water to 100 mL, and filter, if necessary. To 20 mL of the filtrate add 1 mL of barium chloride TS: the turbidity does not exceed that produced by 1.0 mL of 0.020 N sulfuric acid (0.5%).~■2S (*USP30*)

Add the following:

■**Sulfate** ⟨221⟩—Dissolve 0.5 g in 5 mL of water and 5 mL of diluted hydrochloric acid, dilute with water to 100 mL, and filter, if necessary. To 20 mL of the filtrate add 1 mL of diluted hydrochloric acid, and dilute with water to 50 mL. Add 1 mL of barium chloride TS: the turbidity does not exceed that produced by 1.0 mL of 0.010 N sulfuric acid (0.5%).■2S (*USP30*)

Arsenic, *Method I* ⟨211⟩—Prepare the *Test Preparation* by dissolving 1.0 g in 25 mL of 3 N hydrochloric acid, and diluting with water to 55 mL: the resulting solution meets the requirements of the test, the addition of 20 mL of 7 N sulfuric acid specified under *Procedure* being omitted. The limit is 3 µg per g.

Delete the following:

■~~**Barium**—Heat 0.50 g with 10 mL of water, and add hydrochloric acid dropwise, stirring after each addition, until no more dissolves. Filter, and to the filtrate add 2 mL of potassium sulfate TS: no turbidity is produced within 10 minutes.~■2S (*USP30*)

Add the following:

■**Barium**—Heat to boiling 0.50 g with 10 mL of water, and add 1 mL of hydrochloric acid dropwise, stirring after each addition. Allow to cool, and filter, if necessary, and to the filtrate add 2 mL of potassium sulfate TS: no turbidity is produced within 10 minutes.■2S (*USP30*)

Heavy metals, *Method I* ⟨231⟩—Warm 1.3 g with 3 mL of 3 N hydrochloric acid until no more dissolves, dilute with water to 50 mL, and filter: the limit is 0.003%.

Delete the following:

■~~**Limit of acid-insoluble substances**—Heat 5.0 g with a mixture of 40 mL of water and 10 mL of hydrochloric acid until no more dissolves, and dilute with water to 100 mL. If an insoluble residue remains, filter, wash with hot water until the last washing does not give a reaction for chloride, and dry the residue at 105° for 1 hour. The weight of the residue does not exceed 10 mg: not more than 0.2% of acid-insoluble substances is found.~■2S (*USP30*)

Add the following:

■**Limit of acid-insoluble substances**—Dissolve 5.0 g with a mixture of 40 mL of water and 10 mL of hydrochloric acid by boiling gently for 5 minutes. After cooling, collect the insoluble substance on ashless filter paper, and wash with water until the last washing does not give a reaction for chloride (no turbidity results from the addition of silver nitrate TS.) Ignite to incinerate completely the residue and ashless filter paper for assay at 600 ± 50°. The weight of the residue does not exceed 10 mg: not more than 0.2% of acid-insoluble substances is found.■2S (*USP30*)

Limit of fluoride—[NOTE—Prepare and store all solutions in plastic containers.]

Buffer solution—Dissolve 73.5 g of sodium citrate dihydrate in water to make 250 mL of solution.

Standard solution—Dissolve an accurately weighed quantity of USP Sodium Fluoride RS quantitatively in water to obtain a solution containing 1.1052 mg per mL. Transfer 20.0 mL of the resulting solution to a 100-mL volumetric flask containing 50 mL of *Buffer solution,* dilute with water to volume, and mix. Each mL of this solution contains 100 µg of fluoride ion.

Electrode system—Use a fluoride-specific, ion-indicating electrode and a silver–silver chloride reference electrode connected to a pH meter capable of measuring potentials with a minimum reproducibility of ±0.2 mV (see *pH* ⟨791⟩).

Standard response line—Transfer 50.0 mL of *Buffer solution* and 2.0 mL of hydrochloric acid to a beaker, and add water to make 100 mL. Add a plastic-coated stirring bar, insert the electrodes into the solution, stir for 15 minutes, and read the potential, in mV. Continue stirring, and at 5-minute intervals add 100 µL, 100 µL, 300 µL, and 500 µL of *Standard solution,* reading the potential 5 minutes after each addition. Plot the logarithms of the cumulative fluoride ion concentrations (0.1 µg per mL, 0.2 µg per mL, 0.5 µg per mL, and 1.0 µg per mL) versus potential, in mV.

Procedure—Transfer 2.0 g of the specimen under test to a beaker containing a plastic-coated stirring bar, add 20 mL of water and 2.0 mL of hydrochloric acid, and stir until dissolved. Add 50.0 mL of *Buffer solution* and sufficient water to make 100 mL of test solution. Rinse and dry the electrodes, insert them into the test solution, stir for 5 minutes, and read the potential, in mV. From the measured potential and the *Standard response line* determine the concentration, *C,* in µg per mL, of fluoride ion in the test solution. Calculate the percentage of fluoride in the specimen taken by multiplying *C* by 0.005: the limit is 0.005%.

Delete the following:

■~~**Organic volatile impurities,** *Method IV* ⟨467⟩**:** meets the requirements.~~■2S (*USP30*)

Delete the following:

■~~**Residual solvents** ⟨467⟩**:** meets the requirements.~~
~~(Official January 1, 2007)~~■2S (*USP30*)

Delete the following:

■~~**Assay**—Dissolve about 250 mg of Dibasic Calcium Phosphate, accurately weighed, with the aid of gentle heat if necessary, in a mixture of hydrochloric acid and water (5 : 3) contained in a 250-mL beaker equipped with a magnetic stirrer, and cautiously add 125 mL of water. With constant stirring, add, in the order named, 0.5 mL of triethanolamine, 300 mg of hydroxy naphthol blue, and, from a 50-mL buret, about 23 mL of 0.05 M edetate disodium VS. Add sodium hydroxide solution (45 in 100) until the initial red color changes to clear blue. Continue to add it dropwise until the color changes to violet, and add an additional 0.5 mL. The pH is between 12.3 and 12.5. Continue the titration dropwise with the 0.05 M edetate disodium VS to the appearance of a clear blue endpoint that persists for not less than 60 seconds. Each mL of 0.05 M edetate disodium is equivalent to 6.803 mg of $CaHPO_4$, or to 8.604 mg of $CaHPO_4 \cdot 2H_2O$.~~■2S (*USP30*)

Add the following:

■**Assay—**

Ammonia–ammonium chloride buffer, pH 10.7—Dissolve 53.5 g of ammonium chloride in water. Add 570 mL of ammonia water, stronger. Dilute with water to make 1000 mL.

Transfer about 400 mg of Dibasic Calcium Phosphate Dihydrate, accurately weighed, into a 200-mL volumetric flask. Dissolve in 12 mL of diluted hydrochloric acid with the aid of gentle heat, if necessary, and dilute with water to volume. Transfer 20.0 mL of this solution to a solution containing 25.0 mL of 0.02 M edetate disodium VS, 50 mL of water, and 5 mL of *Ammonia–ammonium chloride buffer, pH 10.7*. Add 25 mg of eriochrome black T–sodium chloride, and titrate the excess edetate disodium with 0.02 M zinc sulfate VS. Perform a blank determination in the same manner. Each mL of 0.02 M edetate disodium is equivalent to 3.442 mg of $CaHPO_4 \cdot 2H_2O$.■2S (*USP30*)

BRIEFING

Anhydrous Dibasic Calcium Phosphate, *USP 29* page 359. The Japanese Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Anhydrous Dibasic Calcium Phosphate* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, is based on the corresponding monograph for Anhydrous Dibasic Calcium Phosphate that was prepared by the Japanese Pharmacopoeia. The Japanese Pharmacopoeia draft was based in part on comments from the European Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the Japanese Pharmacopoeia.

Differences between the Japanese Pharmacopoeia Adoption Stage 6 document and the current *USP* monograph for Dibasic Calcium Phosphate include the following:

1. *Definition*—The current Dibasic Calcium Phosphate monograph is proposed to be split into two separate monographs: Anhydrous Dibasic Calcium Phosphate and Dibasic Calcium Phosphate Dihydrate.
2. *Packaging and storage*—Retained as a nonharmonized attribute.
3. *Labeling*—Statement removed as it is no longer necessary with two monographs for the anhydrous and the dihydrate forms of Dibasic Calcium Phosphate.
4. *USP Reference standards*—No change.
5. *Identification*—Changed test *A* by increasing the volume of hydrochloric acid to assist in sample dissolution. Changed test *B* by decreasing sample size and volume of nitric acid, and providing temperature and time for warming of sample.
6. *Loss on ignition*—Removed specification pertaining to dihydrate material.
7. *Carbonate*—Added statement to require carbon dioxide-free water in sample preparation.
8. *Chloride*—Changed sample size and volume of diluent to allow for complete dissolution of the sample.
9. *Sulfate*—Decreased sample size.
10. *Arsenic*—Retained as a nonharmonized attribute.
11. *Barium*—Added statement "heat to boiling".
12. *Heavy metals*—Retained as a nonharmonized attribute.
13. *Limit of acid-insoluble substances*—Added statement to indicate "heat to boiling" in preparation step. Added step to incinerate residue at 600°.
14. *Limit of fluoride*—Retained as a nonharmonized attribute.
15. *Organic volatile impurities*—Test removed from harmonization draft.
16. *Residual solvents*—Test removed from harmonization draft.
17. *Assay*—Replaced existing method with new titration assay to be consistent with JP standards.

(DSN: K. Moore) RTS—C44232

Change to read:

~~**Dibasic Calcium Phosphate**~~

■Anhydrous Dibasic Calcium Phosphate■2S (*USP30*)

Add the following:

■Pharmacopeial Discussion Group Sign-Off Document

Attribute	JP	EP	USP
Definition	+	+	+
Identification A	+	+	+
Identification B	+	+	+
Acid-insoluble substances	+	+	+
Chloride	+	+	+
Sulfate	+	+	+
Carbonate	+	+	+
Barium	+	+	+
Loss on ignition	+	+	+
Assay	+	+	+

Legend: + will adopt and implement; - will not stipulate.

Nonharmonized attributes: Packaging and storage, Heavy metals, Limit of fluoride, Iron

Specific local attributes: Identification C (EP), Lead (USP), Description (JP)■2S (*USP30*)

Delete the following:

■~~$CaHPO_4$ 136.06
Phosphoric acid, calcium salt (1 : 1).
Calcium phosphate (1 : 1) [*7757-93-9*].
Dihydrate 172.09 [*7789-77-7*].~~■2S (*USP30*)

Add the following:

■$CaHPO_4$ 136.06

Phosphoric acid, calcium salt (1 : 1).

Calcium phosphate (1 : 1) [*7757-93-9*].■2S (*USP30*)

Delete the following:

■~~» Dibasic Calcium Phosphate is anhydrous or contains two molecules of water of hydration. It contains not less than 98.0 percent and not more than 105.0 percent of anhydrous dibasic calcium phosphate ($CaHPO_4$) or of dibasic calcium phosphate dihydrate ($CaHPO_4 \cdot 2H_2O$).~~■2S (*USP30*)

Add the following:

■» Anhydrous Dibasic Calcium Phosphate contains not less than 98.0 percent and not more than 103.0 percent of anhydrous dibasic calcium phosphate ($CaHPO_4$).■2S (*USP30*)

Delete the following:

■~~**Packaging and storage** Preserve in well-closed containers.~~■2S (*USP30*)

Add the following:

■**Packaging and storage**—Preserve in well-closed containers. No storage requirements specified.■2S (*USP30*)

Delete the following:

■~~**Labeling** Label it to indicate whether it is anhydrous or the dihydrate.~~■2S (*USP30*)
USP Reference standards ⟨11⟩—*USP Sodium Fluoride RS.*

Delete the following:

■~~**Identification—**
A: Dissolve about 100 mg by warming with a mixture of 5 mL of 3 N hydrochloric acid and 5 mL of water, add 2.5 mL of 6 N ammonium hydroxide dropwise, with shaking, and then add 5 mL of ammonium oxalate TS: a white precipitate is formed.
B: To 10 mL of a warm solution (1 in 100) in a slight excess of nitric acid add 10 mL of ammonium molybdate TS: a yellow precipitate of ammonium phosphomolybdate is formed.~~■2S (*USP30*)

Add the following:

■**Identification—**

A: Dissolve about 100 mg by warming in 10 mL of 2 N hydrochloric acid, add 2.5 mL of ammonia TS dropwise, with shaking, and then add 5 mL of ammonium oxalate TS: a white precipitate is formed.

B:

Ammonium molybdate solution—Dissolve 21.2 g of ammonium molybdate in water to make 200 mL of solution (10%). Prepare before use.

Dissolve about 100 mg of sample in 5 mL of diluted nitric acid. Warm the solution to 70°, and add 2 mL of *Ammonium molybdate solution:* a yellow precipitate of ammonium phosphomolybdate is formed.■2S (*USP30*)

Delete the following:

■~~**Loss on ignition** ⟨733⟩—Ignite it at 800° to 825° to constant weight: anhydrous Dibasic Calcium Phosphate loses between 6.6% and 8.5% of its weight, and the dihydrate form of Dibasic Calcium Phosphate loses between 24.5% and 26.5% of its weight.~~■2S (*USP30*)

Add the following:

■**Loss on ignition** ⟨733⟩—Ignite about 1 g at 800° to 825° to constant weight: the material loses between 6.6% and 8.5% of its weight.■2S (*USP30*)

Delete the following:

■~~**Carbonate**—Mix 1.0 g with 5 mL of water, and add 2 mL of hydrochloric acid: no effervescence occurs.~~■2S (*USP30*)

Add the following:

■**Carbonate**—Mix 1.0 g with 5 mL of carbon dioxide-free water, and immediately add 2 mL of hydrochloric acid: no effervescence occurs.■2S (*USP30*)

Delete the following:

■~~**Chloride** ⟨221⟩—To 0.30 g add 10 mL of water and 2 mL of nitric acid, and warm gently, if necessary, until no more dissolves. Dilute to 25 mL, filter, if necessary, and add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 1.0 mL of 0.020 N hydrochloric acid (0.25%).~~■2S (*USP30*)

Add the following:

■**Chloride** ⟨221⟩—To 0.20 g add 20 mL of water and 13 mL of diluted nitric acid, and warm gently, if necessary, until no more dissolves. Dilute to 100 mL, and filter, if necessary. To 50 mL of this solution add 1 mL of silver nitrate TS: the turbidity does not exceed that produced by 0.70 mL of 0.010 N hydrochloric acid (0.25%).■2S (*USP30*)

Delete the following:

■~~**Sulfate** ⟨221⟩—Dissolve 1.0 g in the smallest possible amount of 3 N hydrochloric acid, dilute with water to 100 mL, and filter, if necessary. To 20 mL of the filtrate add 1 mL of barium chloride TS: the turbidity does not exceed that produced by 1.0 mL of 0.020 N sulfuric acid (0.5%).~~■2S (*USP30*)

Add the following:

■**Sulfate** ⟨221⟩—Dissolve 0.5 g in 5 mL of water and 5 mL of diluted hydrochloric acid, dilute with water to 100 mL, and filter, if necessary. To 20 mL of the filtrate add 1 mL of diluted hydrochloric acid, and dilute with water to 50 mL. Add 1 mL of barium chloride TS: the turbidity does not exceed that produced by 1.0 mL of 0.010 N sulfuric acid (0.5%).■2S (*USP30*)

Arsenic, *Method I* ⟨211⟩—Prepare the *Test Preparation* by dissolving 1.0 g in 25 mL of 3 N hydrochloric acid, and diluting with water to 55 mL: the resulting solution meets the requirements of the test, the addition of 20 mL of 7 N sulfuric acid specified under *Procedure* being omitted. The limit is 3 µg per g.

Delete the following:

■~~**Barium**—Heat 0.50 g with 10 mL of water, and add hydrochloric acid dropwise, stirring after each addition, until no more dissolves. Filter, and to the filtrate add 2 mL of potassium sulfate TS: no turbidity is produced within 10 minutes.~~■2S (*USP30*)

Add the following:

■**Barium**—Heat to boiling 0.50 g with 10 mL of water, and add 1 mL of hydrochloric acid dropwise, stirring after each addition. Allow to cool, and filter, if necessary, and to the filtrate add 2 mL of potassium sulfate TS: no turbidity is produced within 10 minutes.■2S (*USP30*)

Heavy metals, *Method I* ⟨231⟩—Warm 1.3 g with 3 mL of 3 N hydrochloric acid until no more dissolves, dilute with water to 50 mL, and filter: the limit is 0.003%.

Delete the following:

■~~**Limit of acid-insoluble substances**—Heat 5.0 g with a mixture of 40 mL of water and 10 mL of hydrochloric acid until no more dissolves, and dilute with water to 100 mL. If an insoluble residue remains, filter, wash with hot water until the last washing does not give a reaction for chloride, and dry the residue at 105° for 1 hour. The weight of the residue does not exceed 10 mg: not more than 0.2% of acid-insoluble substances is found.~~■2S (*USP30*)

Add the following:

■**Limit of acid-insoluble substances**—Dissolve 5.0 g with a mixture of 40 mL of water and 10 mL of hydrochloric acid by boiling gently for 5 minutes. After cooling, collect the insoluble substance on ashless filter paper, and wash with water until the last washing does not give a reaction for chloride (no turbidity results from the addition of silver nitrate TS.) Ignite to incinerate completely the residue and ashless

filter paper for assay at 600 ± 50°. The weight of the residue does not exceed 10 mg: not more than 0.2% of acid-insoluble substances is found.■2S (*USP30*)

Limit of fluoride—[NOTE—Prepare and store all solutions in plastic containers.]

Buffer solution—Dissolve 73.5 g of sodium citrate dihydrate in water to make 250 mL of solution.

Standard solution—Dissolve an accurately weighed quantity of USP Sodium Fluoride RS quantitatively in water to obtain a solution containing 1.1052 mg per mL. Transfer 20.0 mL of the resulting solution to a 100-mL volumetric flask containing 50 mL of *Buffer solution,* dilute with water to volume, and mix. Each mL of this solution contains 100 µg of fluoride ion.

Electrode system—Use a fluoride-specific, ion-indicating electrode and a silver–silver chloride reference electrode connected to a pH meter capable of measuring potentials with a minimum reproducibility of ±0.2 mV (see *pH* ⟨791⟩).

Standard response line—Transfer 50.0 mL of *Buffer solution* and 2.0 mL of hydrochloric acid to a beaker, and add water to make 100 mL. Add a plastic-coated stirring bar, insert the electrodes into the solution, stir for 15 minutes, and read the potential, in mV. Continue stirring, and at 5-minute intervals add 100 µL, 100 µL, 300 µL, and 500 µL of *Standard solution,* reading the potential 5 minutes after each addition. Plot the logarithms of the cumulative fluoride ion concentrations (0.1 µg per mL, 0.2 µg per mL, 0.5 µg per mL, and 1.0 µg per mL) versus potential, in mV.

Procedure—Transfer 2.0 g of the specimen under test to a beaker containing a plastic-coated stirring bar, add 20 mL of water and 2.0 mL of hydrochloric acid, and stir until dissolved. Add 50.0 mL of *Buffer solution* and sufficient water to make 100 mL of test solution. Rinse and dry the electrodes, insert them into the test solution, stir for 5 minutes, and read the potential, in mV. From the measured potential and the *Standard response line* determine the concentration, *C,* in µg per mL, of fluoride ion in the test solution. Calculate the percentage of fluoride in the specimen taken by multiplying *C* by 0.005: the limit is 0.005%.

Delete the following:

■~~**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements.~~■2S (*USP30*)

Delete the following:

■~~**Residual solvents** ⟨467⟩**:** meets the requirements.~~

~~(Official January 1, 2007)~~■2S (*USP30*)

Delete the following:

■~~**Assay**—Dissolve about 250 mg of Dibasic Calcium Phosphate, accurately weighed, with the aid of gentle heat if necessary, in a mixture of hydrochloric acid and water (5 : 3) contained in a 250-mL beaker equipped with a magnetic stirrer, and cautiously add 125 mL of water. With constant stirring, add, in the order named, 0.5 mL of triethanolamine, 300 mg of hydroxy naphthol blue, and, from a 50-mL buret, about 23 mL of 0.05 M edetate disodium VS. Add sodium hydroxide solution (45 in 100) until the initial red color changes to clear blue. Continue to add it dropwise until the color changes to violet, and add an additional 0.5 mL. The pH is between 12.3 and 12.5. Continue the titration dropwise with the 0.05 M edetate disodium VS to the appearance of a clear blue endpoint that persists for not less than 60 seconds. Each mL of 0.05 M edetate disodium is equivalent to 6.803 mg of $CaHPO_4$ or to 8.604 mg of $CaHPO_4 \cdot 2H_2O$.~~■2S (*USP30*)

Add the following:

■**Assay—**

Ammonia–ammonium chloride buffer, pH 10.7—Dissolve 53.5 g of ammonium chloride in water. Add 570 mL of ammonia water, stronger. Dilute with water to make 1000 mL.

Transfer about 400 mg of Anhydrous Dibasic Calcium Phosphate, accurately weighed, into a 200-mL volumetric flask. Dissolve in 12 mL of diluted hydrochloric acid with the aid of gentle heat, if necessary, and dilute with water to volume. Transfer 20.0 mL of this solution to a solution containing 25.0 mL of 0.02 M edetate disodium VS, 50 mL of water, and 5 mL of *Ammonia–ammonium chloride buffer, pH 10.7*. Add 25 mg of eriochrome black T–sodium chloride, and titrate the excess edetate disodium with 0.02 M zinc sulfate VS. Perform a blank determination in the same manner. Each mL of 0.02 M edetate disodium is equivalent to 2.721 mg of $CaHPO_4$.■2S (*USP30*)

BRIEFING

Edetate Calcium Disodium, *USP 29* page 779. The Japanese Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Edetate Calcium Disodium* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, is based on the corresponding monograph for Edetate Calcium Disodium that was prepared by the Japanese Pharmacopoeia. The Japanese Pharmacopoeia draft was based in part on comments from the European Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the Japanese Pharmacopoeia.

Differences between the Japanese Pharmacopoeia **Adoption Stage 6** document and the current *USP* monograph for Edetate Calcium Disodium include the following:

(1) *Definition*—Changed to reflect new purity specifications (not less than 98.0%).
(2) *Storage*—Retained as a nonharmonized attribute.
(3) *Identification—Identification* test *A* (IR absorption) is retained as a nonharmonized attribute. Tests *B* and *C* are replaced by more definitive tests for calcium and sodium, respectively. Test *B* was updated to include experimental detail consistent with JP standards. *Identification* test *C* replaced the existing procedure with a pyroantimonate test to be consistent with JP standards.
(4) *pH*—No change.
(5) *Chloride*—New test added to reflect sign-off draft.

(6) *Magnesium-chelating substances*—Renamed as *Disodium edetate.* Changed to reflect decrease in sample concentration, and titrant changed to magnesium chloride to be consistent with JP.
(7) *Water*—Updated specification to include lower limit of 5.0% to be consistent with JP.
(8) *Heavy metals*—Retained as a nonharmonized attribute.
(9) *Limit of nitrilotriacetic acid*—Retained as a nonharmonized attribute.
(10) *Assay*—Procedure changed to harmonize with JP and EP standards. Decreased sample size to 0.5 g and increased volume of water in test solution to 200 mL. Changed titrant to bismuth nitrate and indicator to xylenol orange to eliminate use of mercuric nitrate.

(MD-GRE: K. Moore) RTS—C44011

Edetate Calcium Disodium

Add the following:

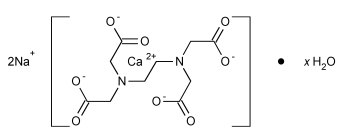
■**Pharmacopeial Discussion Group Sign-Off Document**

Attributes	EP	JP	USP
Definition	+	+	+
Identification B	+	+	+
Identification C	+	+	+
pH	+	+	+
Purity (1) Chloride	+	+	+
Purity (2) Disodium edetate	+	+	+
Water	+	+	+
Assay	+	+	+

Legend: + will adopt and implement; - will not stipulate.

Nonharmonized attributes: Clarity and/or color of solution, Heavy metals, Identification by IR absorption, Limit of nitrilotriacetic acid, Storage.

Specific local attributes: Description (JP), Iron (EP).■2S (*USP30*)



$C_{10}H_{12}CaN_2Na_2O_8 \cdot xH_2O$ 374.27
Calciate (2-), [[*N,N*′-1,2-ethanediylbis[*N*-(carboxymethyl)glycinato]](4-)-*N,N*′,*O,O*′,O^N,$O^{N'}$]-, disodium, hydrate, (*OC*-6-21)-.
Disodium[(ethylenedinitrilo)tetraacetato]calciate(2-) hydrate [*23411-34-9*].
Anhydrous [*62-33-9*].

Delete the following:

■~~» Edetate Calcium Disodium is a mixture of the dihydrate and trihydrate of calcium disodium ethylenediaminetetraacetate (predominantly the dihydrate). It contains not less than 97.0 percent and not more than 102.0 percent of $C_{10}H_{12}CaN_2Na_2O_8$, calculated on the anhydrous basis.~~■2S (*USP30*)

Add the following:

■» Edetate Calcium Disodium contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}CaN_2Na_2O_8$ (374.27), calculated on the anhydrous basis.■2S (*USP30*)

Delete the following:

■~~**Packaging and storage**—Preserve in tight containers.~~■2S (*USP30*)

Add the following:

■**Packaging and storage**—Preserve in tight containers. No storage requirements specified.■2S (*USP30*)
USP Reference standards ⟨11⟩—*USP Edetate Calcium Disodium RS.*

Delete the following:

■~~**Identification—**~~
~~**A:** *Infrared Absorption* ⟨197M⟩.~~
~~**B:** A solution (1 in 20) responds to the oxalate test for *Calcium* ⟨191⟩ and to the flame test for *Sodium* ⟨191⟩.~~
~~**C:** To 5 mL of water add 2 drops of ammonium thiocyanate TS and 2 drops of ferric chloride TS. To the deep red solution add about 50 mg of Edetate Calcium Disodium, and mix: the deep red color disappears.~~■2S (*USP30*)

Add the following:

■**Identification—**

A: *Infrared Absorption* ⟨197M⟩.

B: Dissolve 2 g in 10 mL of water, add 6 mL of lead (II) nitrate solution (33 in 1000), shake, and add 3 mL of potassium iodide TS: no yellow precipitate is formed. Make this solution alkaline by the addition of diluted ammonia solution (7 in 50), and add 3 mL of ammonium oxalate TS: a white precipitate is formed.

Harmonization

C: Dissolve 0.5 g in 10 mL of water, and add 10 mL of potassium pyroantimonate TS: a white, crystalline precipitate is formed. The formation of the precipitate is accelerated by rubbing the inside wall of the test tube with a glass rod.■2S (*USP30*)
pH ⟨791⟩: between 6.5 and 8.0, in a solution (1 in 5).

Add the following:

■**Chloride** ⟨221⟩—To 0.70 g add 20 mL of water and 30 mL of diluted nitric acid, allow to stand for 30 minutes, and filter. To 10 mL of the filtrate add water to make 50 mL, and perform the test using this solution as the test solution. Prepare the control solution with 0.40 mL of 0.01 M hydrochloric acid VS (not more than 0.10%).■2S (*USP30*)

Delete the following:

■~~**Magnesium-chelating substances**—Weigh accurately 1.0 g, transfer to a small beaker, and dissolve in 5 mL of water. Add 5 mL of ammonia-ammonium chloride buffer TS. Then to the buffered solution add 5 drops of eriochrome black TS, and titrate with 0.10 M magnesium acetate to the appearance of a deep wine-red color: not more than 2.0 mL is required.~~■2S (*USP30*)

Add the following:

■**Disodium edetate**—Dissolve 1.00 g of Edetate Calcium Disodium in 50 mL of water, add 5 mL of ammonia–ammonium chloride buffer TS, and 40 mg of eriochrome black T–sodium chloride indicator. Titrate with 0.01 M magnesium chloride VS until the color of the solution changes from blue to red-violet: not more than 3.0 mL of 0.01 M magnesium chloride VS is consumed (not more than 1.0%).■2S (*USP30*)

Delete the following:

■~~**Water,** *Method I* ⟨921⟩: not more than 13.0%.~~■2S (*USP30*)

Add the following:

■**Water,** *Method I* ⟨921⟩: between 5.0% and 13.0%, determined on 0.2 g.■2S (*USP30*)
Heavy metals, *Method II* ⟨231⟩: 0.002%.
Limit of nitrilotriacetic acid—
Mobile phase, Cupric nitrate solution, Stock standard solution, and *Chromatographic system*—Prepare as directed in the test for *Limit of nitrilotriacetic acid* under *Edetate Disodium*.
Resolution solution—Using Edetate Calcium Disodium instead of *Edetate Disodium,* prepare as directed for *Resolution solution* in the test for *Limit of nitrilotriacetic acid* under *Edetate Disodium*.
Standard solution—Transfer 1.0 g of Edetate Calcium Disodium to a 100-mL volumetric flask, add 100 µL of *Stock standard solution,* dilute with *Cupric nitrate solution* to volume, and mix. Sonicate, if necessary, to achieve complete solution.
Test solution—Transfer 1.0 g of Edetate Calcium Disodium to a 100-mL volumetric flask, dilute with *Cupric nitrate solution* to volume, and mix. Sonicate, if necessary, to achieve complete solution.
Procedure—Proceed as directed for *Procedure* in the test for *Limit of nitrilotriacetic acid* under *Edetate Disodium:* the response of the nitrilotriacetic acid peak of the *Test solution* does not exceed the difference between the nitrilotriacetic acid peak responses obtained from the *Standard solution* and the *Test solution* (0.1%).

Delete the following:

■~~**Residual solvents** ⟨467⟩: meets the requirements.
(Official January 1, 2007)~~■2S (*USP30*)

Delete the following:

■~~**Assay**—Weigh accurately about 1.2 g of Edetate Calcium Disodium, transfer to a 250-mL beaker, and dissolve in 75 mL of water. Add 25 mL of 1 N acetic acid and 1 mL of diphenylcarbazone TS, and titrate slowly with 0.1 M mercuric nitrate VS to the appearance of the first purplish color. Perform a blank determination, and make any necessary correction. Each mL of 0.1 M mercuric nitrate is equivalent to 37.43 mg of $C_{10}H_{12}CaN_2Na_2O_8$.~~■2S (*USP30*)

Add the following:

■**Assay**—Transfer about 500 mg of Edetate Calcium Disodium, accurately weighed, into a 200-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. Transfer exactly 20 mL of this solution to 80 mL of water, and adjust with dilute nitric acid to a pH of 2 to 3. Add two drops of xylenol orange TS, and titrate with 0.01 M bismuth nitrate VS until the color of the solution changes from yellow to red. Each mL of 0.01 M bismuth nitrate VS is equivalent to 3.743 mg of $C_{10}H_{12}CaN_2Na_2O_8$.■2S (*USP30*)

PHARMACOPEIAL PREVIEWS

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Proposed Monograph for Piroxicam Topical Cream 3%

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ABSTRACT The purpose of this *Stimuli* article is to provide background information, the proposed monograph, and stability data for Piroxicam Topical Cream 3%. This monograph has been prepared under the guidance of the USP Expert Committee for Pharmaceutical Compounding.

RATIONALE

This *Stimuli* article describes a proposed pharmacopeial monograph for a topical dosage form in a gel base (*1*). A topical gel base is available at 0.5% and also as a cream base at 1% in some countries (*2*). It was deemed appropriate for compounding pharmacists to formulate this drug in a cream base in order to provide a preparation with a concentration of 3% piroxicam. This preparation would have the advantages of a cream, such as emollient and moisturizing properties, and at the same time provide a preparation with a higher concentration of the drug for therapeutic use.

INDICATIONS AND USE

Piroxicam is classified as a nonsteroidal, anti-inflammatory systemic agent (*3*). Oral administration of piroxicam is indicated mainly for its analgesic, anti-inflammatory, antipyretic properties, and the dose range is 10–30 mg/day. As a topical gel, the drug is also useful for the local treatment of a number of painful or inflammatory conditions. (*2*).

TOPICAL PREPARATIONS

Larson and Lombardino prepared piroxicam at concentrations up to 1.0% in an ointment base, and the product was shown to be a potent inhibitor of inflammation in rats (*4*). Schiantarelli et al. indicated that piroxicam 5% in an oil-in-water (o/w) emulsion base exerted anti-inflammatory action against superficial and deep-seated inflammation in laboratory animals. The anti-inflammatory effect was attributed to a fraction of the drug diffusing through the underlying nonvascular tissues or via the lymphatic system (*5*). Tsai et al. investigated the percutaneous absorption of piroxicam 3.3% from four major classes of ointment bases in rabbits. The greatest area under the curve (AUC) was obtained with an o/w base that could be enhanced by replacing the water pH 7.2 with a $NaHCO_3$ solution of pH 9.2. The enhancement was attributed to an increase in the solubility of the drug and the destructive effect on the skin. Of those bases containing water at pH 7.2, the o/w emulsion containing 5% urea gave the best results (*6*). A 1% cream was effective in a human test, but the formula was not given (*7*).

Several papers investigate or describe gel preparations (*8–17*). Beetge et al. showed that the AUC for piroxicam was higher than that for four other gel formulations of NSAIDS after transdermal application in vivo to rats, an effect that was attributed to the lipophilic character of the drug (*18*).

Additional research of topical piroxicam preparations involved a fatty alcohol propylene glycol base (*19*). The effects of a number of additives on the biological activities of piroxicam have been studied, for example lecithin in gel ointments by Natuski and Takabatake (*20*), oleic acid and dimethylsulfoxide by Hsu et al. (*21*), and pyroglutamates in ointments by Makino et al. (*22*). In vitro studies by Rafiee-Tehrani and Mehramizi showed that the release from cream formulations can be described by a diffusion mechanism and that in general a hydroalcoholic gel formulation with hydroxypropyl cellulose is a more suitable preparation of piroxicam compared with an o/w cream preparation (*23*).

Francoeur et al. showed that the penetration of piroxicam does not depend on primary absorption into the systemic circulation but instead on the arrangement of the vasculature at the site of application (*24*). Li et al. showed that most piroxicam penetrating to local deep tissues in rats can be attributed to direct penetration, and they felt that topical delivery is superior to the oral route when the target is local tissue under the skin (*25*). In pigs the local delivery of topical piroxicam is independent of systemic absorption, and the nature of cutaneous vasculature at different sites should be considered (*26*). Moore et al. (*27*) by a large meta analysis involving 86 randomized controlled trials concluded that topical nonsteroidal anti-inflammatory drugs are effective for the treatment of acute pain and chronic conditions.

Stability in Solution

Several reports discuss the stability of piroxicam in solution. Backensfeld et al. (*28*) showed that the drug was stable in a buffered solution at pH 7.4, with 101.1% remaining after 475 days at 21 °C. Chen et al. (*29*) found that piroxicam was photosensitive to sunlight but rather stable to temperature stress; unfortunately the solvent was not stated. In gel form, composition not stated, piroxicam had a shelf life of 3.39 years at 25 °C (*30*). In acid and basic solutions, a yellow color appears, and Fini et al. (*31*) indicated that this was due possibly to a change in tautomeric equilibrium with pH rather than because of the decomposition of the drug. Mito and Sekiguchi (*32*) indicated that solutions of piroxicam containing water-soluble polymers or surfactants in buffers at a pH range between

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6.0 and 8.0 were very stable. For example, the drug in a Tween solution at pH 8.0 at 40 °C for 6 months did not show any change in absorbance. Arrhenius parameters have been calculated by Shin et al. (*33*) for the drug in mixed aqueous propylene glycol or polyethylene glycol. Singhai et al. (*34*) found that most formulations were unaffected with respect to color stability at room temperature for 45 days. They also investigated stress conditions involving light, temperature, humidity, and shaking.

The drug in the solid state has been reported to be thermally stable in brown powder glass jars stored in the dark at 20 °C and 40 °C and did not show any decomposition after two years (*35*). The photostability of piroxicam was investigated by subjecting the drug, stored in colorless bottles, to 300–830 nm at 30 °C for 72 hours. The concentration of the drug decreased from 99.8% to 99.6% as determined by HPLC (*35*).

Formulation

The physicochemical properties of the drug relevant to formulation are the ionization constants, partition coefficient, solubility, polymorphism, and hydration. The pKa values are 1.8 and 5.1 (*36*). In addition, a pKa of 6.3 effected by the enolic hydroxyl group at C-4 in dioxane and water has been reported (*37*). The partition coefficient between *n*-octanol and an aqueous buffer pH 7.4 is 1.8. Piroxicam is insoluble in water, sparingly soluble in diisopropyl ether, and only slightly more soluble in the lower aliphatic alcohols, namely methanol, ethanol, and isopropylalcohol, and soluble in acetone 1:50 and chloroform 1:20 (*35*). It has been noted that polyethylene glycol and propylene glycol increase the solubility in water (*33*).

The 3% topical piroxicam cream formulation was selected on the basis of the research of Dallas et al. (*38*). They showed that in rabbits a 3% concentration provided considerably greater serum levels and total serum concentration compared to a 1% concentration. Although many factors must be considered when a practitioner prepares an effective topical formulation, one guide is to ensure that nearly all the drug is dissolved and at saturation. This drug, which is insoluble in water, has a pKa of 6.3 (or 5.1), and thus a number of articles have indicated the use of water at neutral or alkaline pH values to increase the solubility. If the pH of the aqueous phase is 7.2 and pH = pKa + log(salt concentration/acid concentration), then a ratio of 7.9 to 1 of salt to acid form of the drug, providing all the drug is in solution, would allow both forms to be available to penetrate the skin.

The formula discussed by Dallas et al. (*38*) is a modified *USP* hydrophilic ointment. The Dallas formula includes sodium hydroxide and contains less stearyl alcohol and parabens and more water than the *USP* formula. The 100-g preparation contains 0.0025 eq. of sodium hydroxide, which will convert most of the drug, 1 g (0.003018 eq.), to the salt form. Although the solubility of the drug in propylene glycol is not provided, it will likely increase the solubility of the piroxicam in the preparation. In a subsequent publication, Babar et al. (*39*) decreased the concentration of white petrolatum, altered the concentration of the parabens, and increased the concentration of the sodium lauryl sulfate. In a preparation containing 3% of the drug, it is likely that the drug will be beyond the solubility limit of the aqueous phase and perhaps the oil phase, thus providing a saturated product resulting in a reservoir and perhaps providing a sustained or constant release. The formulation described below is similar to Formula B investigated by Dallas et al. (*38*).

Experimental Stability Studies

The stability of piroxicam was investigated by the USP Research and Development Laboratory (RDL). Four batches of the Piroxican Topical Cream 3% of 100 g each were prepared according to the method and formula described below. A placebo was also prepared containing all the ingredients except piroxicam, in which water replaced the weight of the piroxicam. The creams were stored in plastic, resealable containers and stored in an environmental chamber maintained at 25 °C and 25% relative humidity. The creams were bright yellow, and the placebo was white.

The development of a suitable stability-indicating method for the cream was accomplished by RDL as described in Project #97-053A. Briefly, the HPLC assay involved a Hewlett Packard liquid chromatograph with a UV detector set at 254 nm and a μBondaPak C18 4.6 mm × 30 cm 10-μm analytical column. The mobile phase was a buffer consisting of 0.04 M citric acid and 0.38 M dibasic sodium phosphate solution and methanol, approximately 50:50 (v/v). The diluent was 4.5 mL hydrochloric acid diluted to 5 L with methanol. The standard preparation consisted of 5 mg of USP Piroxicam Reference Standard (RS) and 2 mL of chloroform mixed and diluted to 100 mL with diluent. The sample preparation was made by adding approximately 340 mg of cream to 4 mL of chloroform and 150 mL of diluent, and after the mixture was shaken it was diluted to 200 mL with diluent.

The creams were assayed against USP Piroxicam RS five different times during a four-month period as indicated in *Table 1,* which shows the number of days after the preparation of the cream. Each cream was assayed four times at each time period (*Table 1*). The assay of the placebo did not show peaks for piroxicam at any of the times of measurement. The average results for the first day of analysis showed an excess of piroxicam in the cream when compared with the frequently stated rubric for creams and ointments in *USP:* "It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of" active drug. One explanation for this anomaly is that the products may have been compounded with a slight overage. One might note, however, that the average range of 100.2 to 117.8 is well within the usual *USP* required range of 20%. This excursion suggests that an overage is not necessary because the active drug is quite stable. A comparison of the piroxicam concentration at day 1 with that on day 121 shows a tendency toward a small increase in the piroxicam concentration. Nevertheless there was variability in the average values as time progressed, which may have been due to the possibility that some of the piroxicam was suspended in the vehicle. In conclusion, although the analytical results were somewhat variable, the Piroxicam Topical Cream preparation appeared to be stable during four months.

Table I. Piroxicam Topical Cream Assay Results

		Samples			
	Days	A	B	C	D
	1	111.5	102.7	113.9	105.4
	1	113.2	107.0	114.4	99.1
	1	110.8	103.3	114.0	103.4
	1	110.5	110.9	114.5	109.7
Average		111.5	106.0	114.2	104.4
	15	100.4	101.6	106.0	108.4
	15	112.7	97.0	116.8	108.5
	15	104.7	107.5	107.7	109.8
	15	111.1	106.3	114.1	108.7
Average		107.2	103.1	111.2	108.8
	32	99.5	102.5	108.2	102.8
	32	107.9	106.3	75.4	105.3
	32	113.3	98.6	103.7	108.1
	32	110.8	96.3	113.4	97.3
Average		107.9	100.9	100.2	103.3
	61	116.2	107.7	115.4	109.3
	61	108.7	108.8	116.1	107.2
	61	105.7	87.0	97.4	102.1
	61	107.5	106.6	111.4	79.6
Average		109.5	102.5	110.1	99.6
	121	125.1	112.9	125.0	99.3
	121	116.2	104.1	133.6	102.0
	121	128.6	111.4	123.4	106.7
	121	114.6	113.8	89.3	117.1
Average		121.1	110.5	117.8	106.3

PROPOSED NEW MONOGRAPH
Title: Piroxicam Topical Cream 3%

Formula

White petrolatum	25.0 g
Stearyl alcohol	15.0 g
Propylparaben	0.06 g
Methylparaben	0.15 g
Propylene glycol	12.0 g
Sodium lauryl sulfate	1.0 g
Sodium hydroxide 1 M	2.5 mL
Piroxicam	3.0 g
Purified water, a sufficient quantity to make	100.0 g

Method of Preparation

1. All the ingredients are accurately weighed.
2. All the oil-phase ingredients are placed in a separate stainless steel container and are heated to 80 ± 5 °C.
3. All the aqueous phase ingredients are placed in a separate stainless steel container and are heated to 80 ± 5 °C.
4. The aqueous phase is added to the oil phase with continuous stirring.
5. The emulsion is then cooled to about 50 °C.
6. The piroxicam is added to the sodium hydroxide solution with titration to form a suspension.
7. The warm emulsion is added to the piroxicam suspension geometrically with titration.

Packaging

Store in plastic resealable containers.

Storage

At room temperature.

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Preparations for Nebulization: Characterization*

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ABSTRACT Currently, neither the *United States Pharmacopeia* nor the *European Pharmacopoeia* contains procedures to aerodynamically assess nebulization preparations. The USP Aerosols Expert Committee supports the development of tests to assess the quality of such products. This *Stimuli* article provides two tests with associated procedures. Depending on the feedback received on this *Stimuli* article, the Committee will consider including the two tests in *USP* General Chapter *Aerosols* ⟨601⟩.

INTRODUCTION

USP General Chapter *Aerosols* ⟨601⟩ does not include any information about aerodynamically assessing nebulization preparations. The *European Pharmacopoeia* monograph titled *Preparations for inhalation,* subsection on *Liquid preparations for nebulisation,* states that ''continuously operating nebulisers... allow the dose to be inhaled at an appropriate rate and particle size that ensures deposition of the preparation in the lungs.'' However, associated procedures are not provided. The European Committee for Standardisation (CEN) has worked on the assessment of the capabilities of the nebulizers themselves but has not addressed nebulization preparations.

An international group was formed in order to develop standardized procedures for testing preparations for nebulization. The proposed procedures have been tested in a number of laboratories, and a collaborative study involving the European Pharmaceutical Aerosol Group (EPAG) will take place in 2006. This study will be led by Steve Nichols at Sanofi-Aventis.

Readers are invited to comment on the applicability of the two tests described, as well as on the procedures themselves. The proposed procedures have also been presented for comment in *PharmEuropa* volume 18.2 (April 2006).

TESTS

Products used for nebulization and intended for pulmonary delivery are characterized using the following tests:

- Drug Delivery Rate and Total Drug Delivered and
- Aerodynamic Assessment of Nebulized Aerosols.

These tests standardize the approach for assessing the dose that would be delivered to a patient but are not intended to assess the nebulizer device itself. A procedure for the latter is described in a CEN Standard (*1*). The size distribution of the mass—rather than the number of droplets—is a more appropriate means to evaluate product performance because drug mass as a function of aerodynamic diameter is more indicative of therapeutic effect within the respiratory tract.

1. Drug Delivery Rate and Total Drug Delivered

These tests are performed to assess the total drug delivered to a patient and the rate of delivery to the patient using standardized conditions of volumetric flow rate. It is essential that breath-enhanced and breath-actuated nebulizers be evaluated by a breathing simulator because the output of these types of devices depends to a great extent on the inhalation flow rate. The methodology below describes the use of a standard breathing pattern defined for adults. Should a particular product for nebulization be indicated *only* for pediatric use, then pediatric breathing pattern(s) should be utilized (*2*). Breathing patterns, rather than continuous flow rates, are used in order to provide a more appropriate measure of the mass of drug that would be delivered to patients.

Drug Delivery Rate and Total Drug Delivered are appropriate characteristics because they allow the delivered mass to be characterized in a standard way regardless of the nebulizer used. Accordingly, the test methodology described below permits the mass of drug delivered in the first period (typically 1 min) to be measured (consequently giving an assessment of drug delivery *rate*) as well as capturing the total drug mass delivered.

1a. Procedure for Drug Delivery Rate and Total Drug Delivered

Breath simulator

A commercially available breath simulator (*3*) that is able to generate the breathing profile specified in *Table 1* is used for the test. The pattern is intended to simulate an adult's breathing pattern. A different breathing pattern may be used when appropriate; e.g., drug products specifically intended for use by children may be tested using a breathing pattern appropriate for a child.

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Table 1. Breath simulator specification

Item	Specification
Tidal volume	500 mL
Frequency	15 cycles/min
Waveform	Sinusoidal
Inhalation:exhalation ratio	1:1

Filter system

The test uses a suitably validated low-resistance filter (*4*) that is capable of quantitatively collecting the aerosol and is suitable for ensuring recovery of the drug with an appropriate solvent. The dead volume of the filter casing should not exceed 10% of the tidal volume used in the breath simulation.

1b. Method

Attach the filter contained in filter holder (A) to the breath simulator (B) according to the scheme shown in *Figure 1*. Fill the nebulizer with the volume of the drug product specified in the patient instructions. Attach the mouthpiece of the nebulizer to the inhalation filter using a mouthpiece adapter, if required, ensuring that connections are airtight. Make sure the nebulizer is positioned in the same orientation as intended for use. This may require tilting the breath simulator and filter holder. Ensure that environmental conditions are within the limits specified in *Table 2*. Set the breath simulator to generate the specified breathing pattern.

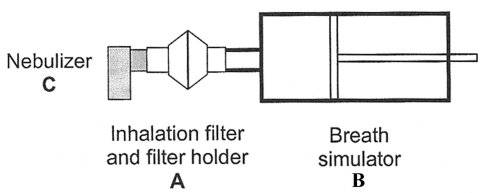

Figure 1. Experimental set-up for breath simulator testing

Table 2. Environmental conditions

Item	Specification range
Temperature	23 ± 2 °C
Pressure	86–106 kPa
Relative humidity (RH)	45%–75% RH

Start the breath simulator and then, at the beginning of an inhalation cycle, start the nebulizer. Operate the nebulizer for the defined initial time, and collect the nebulized drug aerosol on the filter during the inhalation phase of the breathing cycle. The length of the time interval ensures that sufficient drug will be deposited on the inhalation filter for quantitative analysis. A time of 60 ± 1 s typically enables direct determination of the drug delivery rate. If necessary, the length of the time interval for aerosol collection can be increased if there is insufficient drug deposition on the inhalation filter to allow quantitative analysis over the 60-s period. At the end of the initial period, stop the nebulizer, dismantle the filter holder, and recover the drug from the filter and the filter holder using a suitable solvent.

Place a fresh filter and filter holder in position, and continue until nebulization ceases. Interrupt nebulization and exchange filters if necessary to avoid filter saturation. The end of nebulization for gas-powered nebulizers is 1 min after the beginning of sputtering, and for electronic nebulizers it is at the end of operation.

Results

Using a suitable method of analysis, determine the quantity of drug mass collected on the filters during each time interval. Determine the Drug Delivery Rate by dividing the drug mass collected on the first inhalation filter by the time interval used for collection. Determine the Total Mass of Drug Delivered by summing the drug mass collected on all inhalation filters.

2. Aerodynamic Assessment of Nebulized Aerosols

Particle sizes in nebulized products should be characterized at flow rates lower than those in the range that is normally used for dry-powder and metered-dose inhalers. The CEN standard (*1*) recommends a flow rate of 15 L min^{-1} because this value represents a good approximation of the midinhalation flow rate achievable by a tidally breathing healthy adult, who typically has a 500-mL tidal volume.

Although low-angle laser light-scattering instruments (laser diffractometers) can provide rapid size-distribution measurements of nebulizer-generated aerosols, these techniques do not detect the active substance, but rather they measure the size distribution of the droplets irrespective of their content. This may not be a problem for homogeneous solutions but can result in significant error if the nebulized product is a suspension or if droplet evaporation is significant, as can be the case with certain nebulizer types. Cascade impactors enable laboratory technicians to unambiguously characterize the aerosol in terms of the mass of active substance as a function of aerodynamic diameter.

Apparatus E, the Next Generation Impactor (NGI), is a cascade impactor that has been calibrated at 15 L min^{-1} specifically to meet the recommendation of the CEN standard, and it is therefore used for this test (*5*). Researchers also recognize that controlling the evaporation of droplets produced by nebulizers may be critical to avoid bias in assessing droplet size. The method describes an approach by which evaporation is standardized by operating with air or other driving gas that is within a defined range of water vapor content. Determination of mass balance for metered-dose and dry-powder inhalers is not straightforward because in these cases the dose is captured as a continuous output, and hence this method is not included for use with nebulizers. As a part of method development, recovery experiments should be performed to validate the method.

The droplets produced by certain types of nebulizer (e.g., non–air-entrainment versions) may be more susceptible to evaporation caused by heat transfer from the impactor during the measurement process (*6*). As part of method development it is good practice to check if the nebulized aerosol is significantly affected by evaporation. Analysts can do this by comparing the size distributions of aerosols generated by an impactor operated at ambient temperature and comparing such

aerosols with those produced by a cooled impactor. If there is a significant difference, the operating conditions described in the monograph may not be suitable. In such cases, cool the impactor to between +5° and +10 °C before making further measurements of the droplet size distribution.

2a. Procedure for Aerodynamic Assessment of Fine Droplets (Particles)

Detailed descriptions of Apparatus E, the NGI, and the Induction Port are contained in the *European Pharmacopoeia,* Chapter 2.9.18, and in *USP* General Chapter ⟨601⟩ and include details of critical dimensions and the qualification process for the impactor (stage mensuration).

2b. Method Validation

Impactor stage overloading

During method development and validation, it is important to confirm that the volume of liquid sampled from the nebulizer does not overload the impactor. Visual inspection of the collection surfaces on stages collecting most of the droplets normally will reveal streaking if overloading has occurred. This phenomenon is also usually associated with an increase in the mass of drug collecting on the final stage and back-up filter. Reducing the sampling period (T_0) is the most effective way to avoid overloading in any given system, balancing overloading with analytical sensitivity.

Re-entrainment

Droplet bounce and re-entrainment are less likely with nebulizer-produced droplets than with solid particles from other types of inhaler. However, it is important to assess the need for coating as part of method development and to check if coating can be omitted if justified and authorized. When necessary to ensure efficient particle capture, coat each cup with silicone oil or similar high-viscosity liquid, typically deposited from a volatile solvent.

Impactor configuration

A back-up filter in addition to the micro-orifice collector (MOC) must be used to ensure quantitative recovery of drug from the nebulized aerosol at the specified flow rate of 15 L min^{-1}. The MOC may be removed for the purpose of nebulizer testing. However, if it is retained, the filter may be located below the MOC (internal filter option), or an external filter may be used to capture any fine droplets that pass beyond the last size-fractionating stage. The pre-separator is not used for testing nebulizer-generated aerosols (*5*).

2c. Method

Locate the test system in an environment in which the ambient air is at a temperature of 23 ± 2 °C at an RH between 45% and 75% (or cool the impactor to between 5° and 10 °C if method development has demonstrated the need to control droplet size changes caused by heat transfer from the impactor to the incoming aerosol).

Attach the induction port to the impactor, and connect the outlet of the impactor to a vacuum source that is capable of withdrawing air through the system at 15 L min^{-1} as specified in *Figure 2*. Locate a three-way gate valve between the impactor and vacuum source, and set the valve so that flow is sampled from the impactor. Insert a suitable filter (e.g., a glass fiber filter) capable of quantitatively collecting the active ingredient in either the internal or external filter holder.

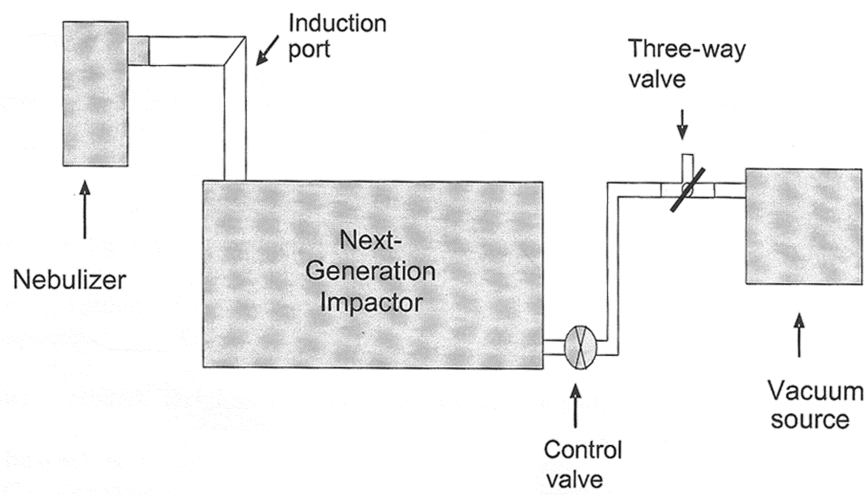

Figure 2. Apparatus E for measuring the size distribution of products for nebulization

Connect a flow meter, calibrated for the volumetric flow leaving the meter, to the induction port. Adjust the flow control valve located between the impactor and three-way valve to achieve steady flow through the system at 15 L min^{-1} (± 5%). Turn off the flow, and set the three-way valve so that flow to the vacuum source bypasses the impactor. Remove the flow meter.

Set up the nebulizer with a supply of driving gas (usually air or oxygen) at the pressure and flow rate specified by the manufacturer. Take precautions to ensure that the gas supply line does not become detached from the nebulizer when under pressure. Fill the nebulizer with the volume of the drug product as specified in the patient instructions.

Set the three-way valve so that the flow bypasses the impactor. Switch on flow from the vacuum source downstream of the impactor, and then switch on the flow of driving gas to the nebulizer at the steady predetermined value. When the flow rate is stable, attach the mouthpiece of the nebulizer to the induction port, using a mouthpiece adapter if required and ensuring that the mouthpiece is aligned on-axis with the induction port. Set the three-way valve so that the flow passes through the impactor. Sample for a predetermined time (T_0). Once determined, this time (T_0) must be defined and used in the analytical method for a particular drug product to ensure that mass fraction data for a given drug product are comparable. At the end of the sampling period, remove the nebulizer from the induction port and switch off flow from the vacuum source to the impactor. Switch off the driving gas flow to the nebulizer.

Dismantle the impactor and, using a suitable method of analysis, determine the mass of drug collected in the induction port and on each stage and on the back-up filter as described for Apparatus E in *USP* General Chapter ⟨601⟩ and in the *European Pharmacopoeia,* Chapter 2.9.18. If the MOC is retained, add the mass of drug collected in the MOC to that deposited on the back-up filter, and treat this mass as a single sample for the purpose of subsequent calculations.

Calculate the mass fraction ($F_{m,comp}$) of the drug deposited on each component of the impactor, commencing with the induction port and proceeding in order through the impactor in accordance with the relationship:

$$F_{m,comp} = \frac{m_{comp}}{M}$$

where m_{comp} refers to the mass associated with the component under evaluation and M is the total mass collected by the system.

Present $F_{m,comp}$ in order of location within the measurement equipment, beginning at the induction port and ending with the back-up filter of the impactor (see *Figure 3*). When appropriate, $F_{m,comp}$ for adjacent stages of the impactor may be combined in order to report the mass fraction collected on a group of stages as a single value.

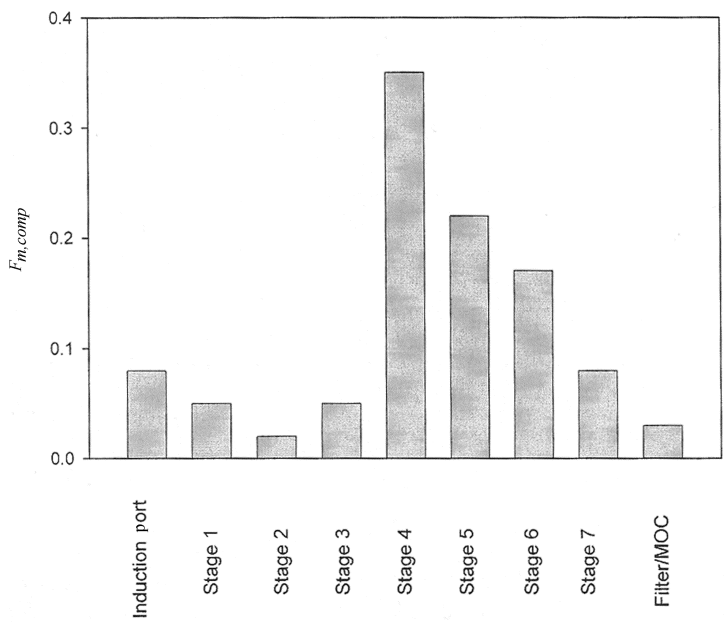

Figure 3. Example of mass fraction of droplets presented in terms of location within the sampling system

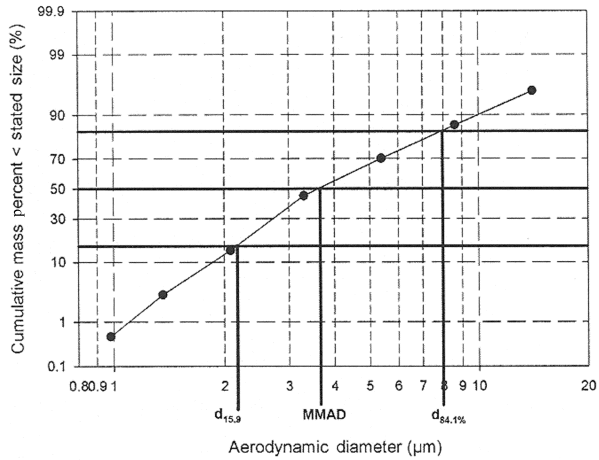

Figure 4. Cumulative mass-weighted size distribution from NGI-measured data: geometric standard deviation (GSD) = $\sqrt{(d_{84.1\%}/d_{15.9\%})}$ for a log-normal size distribution; MMAD = mass median aerodynamic diameter

Determine the cumulative mass-weighted particle-size distribution of the aerosol size-fractionated by the impactor in accordance with the procedures given in *USP* General Chapter ⟨601⟩ and in the *European Pharmacopoeia,* Chapter 2.9.18. Starting at the filter, derive a cumulative mass vs. cut-off diameter of the respective stages (see *Table 3* for the appropriate cut-off diameters at 15 L min^{-1}). Plot the cumulative fraction of active ingredient versus cut-off diameter in a suitable format, e.g., logarithmic or log-probability format (see *Figure 4*). As appropriate, use this plot to determine by interpolation the fraction either less than a given size or between an upper and lower size limit. If necessary, and when appropriate, use this plot to determine values for the mass median aerodynamic diameter and the geometric standard deviation. Suitable computational methods also may be used.

Table 3. Cut-off sizes for Apparatus E at 15 L min^{-1} (*6*)

Stage	Cut-off diameter (µm)
1	14.1
2	8.61
3	5.39
4	3.30
5	2.08
6	1.36
7	0.98

CONCLUSION

The methodology presented in this article provides a standardized approach to the assessment of products for nebulization. This methodology has not been previously described in either *USP* or *EP*. The test methodology has been assessed in a number of laboratories, and a collaborative study involving the European Pharmaceutical Aerosol Group (EPAG) will take place in 2006. The apparatus used, specifically the Next Generation Impactor, has been suitably qualified and is already described within \the two pharmacopeias. All apparatus described is commercially available.

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Correction Formula for the Boiling Point Temperatures in USP General Chapter Distilling Range ⟨721⟩

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ABSTRACT Boiling point is a test used by some pharmacopeias as a quality attribute, with associated test, procedure, and acceptance criteria. Because of variations in atmospheric pressure, correction to a standard pressure is performed prior to application of the standard. The current *United States Pharmacopeia (USP)* General Chapter *Distilling Range* ⟨721⟩ (*4*) uses a single correction factor for all boiling temperatures, namely 0.037 °C per mm Hg variation from standard atmospheric pressure. This value is added to or subtracted from the boiling point when it is lower or higher than 760 mm Hg, respectively. An improved approach used both in *Lange's Handbook* and adopted by the *European Pharmacopoeia (EP)* (*3*) relies on tables that relate the correction factor with temperature ranges to provide an average correction factor for a number of individual substances. Even this approach, however, is a rough approximation. We applied both the USP and EP approaches as well as two additional ones, one of which involves use of the Antoine equation, to tabulated ranges from differing sources. The general goal of this effort resulted in a single equation utilizing readily determined variables to correct observed boiling point temperature. Comments are requested on the use of this equation as a means of adjusting an observed boiling point to standard pressure.

INTRODUCTION

Boiling point is defined as the temperature at which the vapor pressure of a liquid equals the external atmospheric pressure. The standard boiling point is the temperature at which the vapor pressure of a liquid equals the standard atmospheric pressure, which is defined as 760 mm Hg or 101.325 kPa. In addition, the distillation range of a solvent is a measurement of purity and quality, which in turn can be assessed by its boiling point. Distillation is a technique used for the separation of the components of a mixture on the basis of different boiling points, whereby the mixture is heated until some of the components are vaporized. When the boiling point (or the distillation range) is determined at an atmospheric pressure that is different from standard (760 mm Hg), a correction is usually made to reflect the effect of this parameter on the vapor pressure of the liquid. Several approaches of varying degrees of complexity have been employed, and selection of a particular approach typically is related to the accuracy required in the corrected value (*1*).

When a high degree of accuracy for a prediction model is not required, simpler approaches may be used. For example, the Clausius-Clapeyron equation assumes that the change in volume upon vaporization equals the ideal gas volume of the vapor. The Clausius-Clapeyron equation is:

$$\Delta t / \Delta p \;=\; RT_b^2 / p_0 \Delta_{vap} H(T_b)$$

where $\Delta t/\Delta p$ is the temperature variation due to pressure variation, R is the molar gas constant [8.3145 joules per kelvin per mole ($J \cdot K^{-1} \cdot mol^{-1}$)], T_b is the absolute temperature for the normal boiling point, p_0 is the standard pressure, and $\Delta_{vap}H(T_b)$ is the molar enthalpy of vaporization at T_b.

However, a more accurate and therefore most widely used approach involves the application of the Antoine equation. This equation generally is accurate to 0.1–0.2 °C if the atmospheric pressure is ±10% of the standard atmospheric pressure of 760 mm Hg. The formula is:

$$\log p = A - \frac{B}{t + C}$$

Antoine's equation uses three parameters fit to experimental vapor pressures, measured over a restricted temperature range. The variables p and t refer to pressure and temperature, respectively. *A, B,* and *C* are Antoine coefficients that vary for each chemical substance and are determined experimentally. They depend on several intrinsic factors, including the molecular weight of the substance, its functional groups, and number of carbon atoms. Antoine *A, B,* and *C* values for several inorganic and organic substances can be found in *Lange's Handbook of Chemistry* (*2*).

Another approach is the use of the Dreisbach method, which is a derivation of Antoine's equation and evaluates the rate of change of the boiling point with atmospheric pressure (symbols have the same meaning as in Antoine's equation):

$dt/dp = B/[2.3026\ p\ (A - \log p)^2]$

However, this formula should not be used to correct boiling points at different atmospheric pressures because the value of dt/dp itself varies with pressure (*2*).

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EXPERIMENTAL

In an attempt to add accuracy while maintaining the simplicity of the compendial measurement, the authors studied published experimental data to establish a set of correction factors that depend on the boiling point. We compared three published data sets based on Antoine's equation. The sets were published in *Lange's Handbook of Chemistry,* the *EP,* and the *CRC Handbook of Chemistry and Physics* (*5*).

Figure 1 is an example of the data sets examined and shows the compilation of data published in *CRC* for the correction factor in two units of measurement, one used by *EP* (°C/kPa), and one used by *USP* (°C/mm Hg).

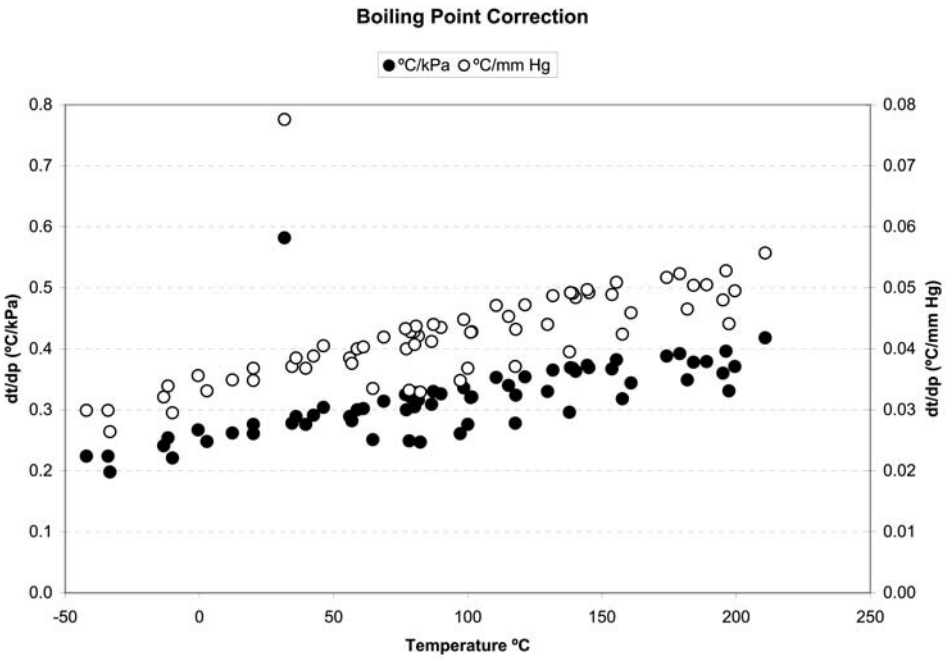

Figure 1. Correction factors for the complete set of substances disclosed in *CRC* (*5*). The out-of-trend data belong to methyl formate and could not be confirmed from the source.

The *EP* Data Set

The *EP* data set was created by the application of *EP's* correction formula:

$t_c = t_0 + k\ (101.3 - b)$

where t_c is the corrected temperature of the boiling point, t_0 is the measured temperature, k is the correction factor, and b is the atmospheric pressure expressed in kPa. The correction factor is shown in *Table 1*.

Table 1. Temperature Correction in Relation to Pressure*

Distillation Temperature	Correction Factor, k (°C/kPa)
Up to 100 °C	0.30
Above 100 up to 140 °C	0.34
Above 140 up to 190 °C	0.38
Above 190 up to 240 °C	0.41
Above 240 °C	0.45

* From *EP,* Table 2.2.11.1.

Lange's Data Set

Correction factors also are found in *Lange's* (*Table 10-10*). The correction factors are presented in narrower bands (20 °C each) and in a wider overall range (from 10 to 410 °C) than in *EP*. The correction is added to or subtracted from the experimental temperature when the atmospheric pressure is below or above the normal pressure, respectively.

The CRC Data Set

The application of the *CRC* correction factors (''Dependence of Boiling Point on Pressure,'' pp. 15–26) using the same ranges proposed by *EP* (*Tables 2–5*) give slightly different factors, as illustrated in *Figure 2*. *CRC* does not report on substances that boil above 240 °C.

Table 2. Range: up to 100 °C*

Compound	*t* °C	°C/kPa	°C/mm Hg
Propane	–42.1	0.224	0.0299
Chlorine	–34.0	0.224	0.0299
Ammonia	–33.3	0.198	0.0264
Chloroethylene	–13.3	0.241	0.0321
Isobutane	–11.7	0.254	0.0339
Sulfur dioxide	–10.1	0.221	0.0295
Butane	–0.5	0.267	0.0356
Trimethylamine	2.8	0.248	0.0331
Chloroethane	12.3	0.262	0.0349
Acetaldehyde	20.1	0.261	0.0348
Hydrogen fluoride	20.1	0.276	0.0368
Methyl formate	31.7	0.582	0.0776
Diethyl ether	34.5	0.278	0.0371
Pentane	36.0	0.289	0.0385
Dichloromethane	39.6	0.276	0.0368
Iodomethane	42.5	0.291	0.0388
Carbon disulfide	46.2	0.304	0.0405
Acetone	56.0	0.289	0.0385
Methyl acetate	56.8	0.282	0.0376
Bromine	58.8	0.300	0.0400
Trichloromethane	61.1	0.302	0.0403
Methanol	64.6	0.251	0.0335
Hexane	68.7	0.314	0.0419
Tetrachloromethane	76.8	0.325	0.0433
Ethyl acetate	77.1	0.300	0.0400
Ethanol	78.2	0.249	0.0332
1-Chlorobutane	78.6	0.321	0.0428
Benzene	80.0	0.321	0.0428
Hexafluorobenzene	80.2	0.305	0.0407
Cyclohexane	80.7	0.328	0.0437
Acetonitrile	81.6	0.316	0.0421
2-Propanol	82.3	0.247	0.0329
Pyrrolidine	86.5	0.309	0.0412
Trichloroethylene	87.2	0.330	0.0440
Dipropyl ether	90.0	0.326	0.0435
1-Propanol	97.2	0.261	0.0348
Heptane	98.5	0.336	0.0448
MAX		0.582	0.078
MIN		0.198	0.026
AVERAGE		0.289	0.039

* Data from *CRC.*

Table 3. Range: above 100 °C up to 140 °C*

Compound	*t* °C	°C/kPa	°C/mm Hg
Water	100.0	0.276	0.0368
Nitromethane	101.1	0.320	0.0427
1,4-Dioxane	101.5	0.321	0.0428
Toluene	110.6	0.353	0.0471
Pyridine	115.2	0.340	0.0453
1-Butanol	117.7	0.278	0.0371
Acetic acid	117.9	0.324	0.0432
Tetrachloroethylene	121.3	0.354	0.0472
Pyrrole	129.7	0.330	0.0440
Chlorobenzene	131.7	0.365	0.0487
1-Pentanol	137.9	0.296	0.0395
p-Xylene	138.3	0.369	0.0492
m-Xylene	139.1	0.368	0.0491
MAX		0.369	0.049
MIN		0.276	0.037
AVERAGE		0.330	0.044

* Data from *CRC.*

Table 4. Range: above 140 °C up to 190 °C*

Compound	*t* °C	°C/kPa	°C/mm Hg
Dibutyl ether	140.2	0.363	0.0484
o-Xylene	144.5	0.373	0.0497
Styrene	145.1	0.369	0.0492
Anisole	153.7	0.367	0.0489
Cyclohexanone	155.4	0.382	0.0509
1-Hexanol	157.6	0.318	0.0424
Cyclohexanol	160.8	0.344	0.0459
Decane	174.1	0.388	0.0517
Benzaldehyde	179.0	0.392	0.0523
Phenol	181.8	0.349	0.0465
Aniline	184.1	0.378	0.0504
Dimethyl sulfoxide	189.0	0.379	0.0505
MAX		0.392	0.052
MIN		0.318	0.042
AVERAGE		0.367	0.049

* Data from *CRC.*

Table 5. Range: above 190 °C up to 240 °C*

Compound	*t* °C	°C/kPa	°C/mm Hg
1-Octanol	195.1	0.360	0.0480
N-Methylaniline	196.2	0.396	0.0528
Ethylene glycol	197.3	0.331	0.0441
N-Methylformamide	199.5	0.371	0.0550
Nitrobenzene	210.8	0.418	0.056
MAX		0.418	0.056
MIN		0.331	0.044
AVERAGE		0.375	0.051

* Data from *CRC.*

The Current *USP* Data Set

The current *USP* General Chapter ⟨721⟩ strategy is based on a single correction factor regardless of pressure.

Figure 2 shows the differences among the four data sets. Aside from demonstrating the difference in correction magnitudes, *Figure 2* also shows that the three approaches based on Antoine's equation give similar but not identical results. The most complete data set is represented by the Lange Data Set. These data clearly show that a linear regression would yield a simple equation resulting in a straight line as shown in *Figure 3*.

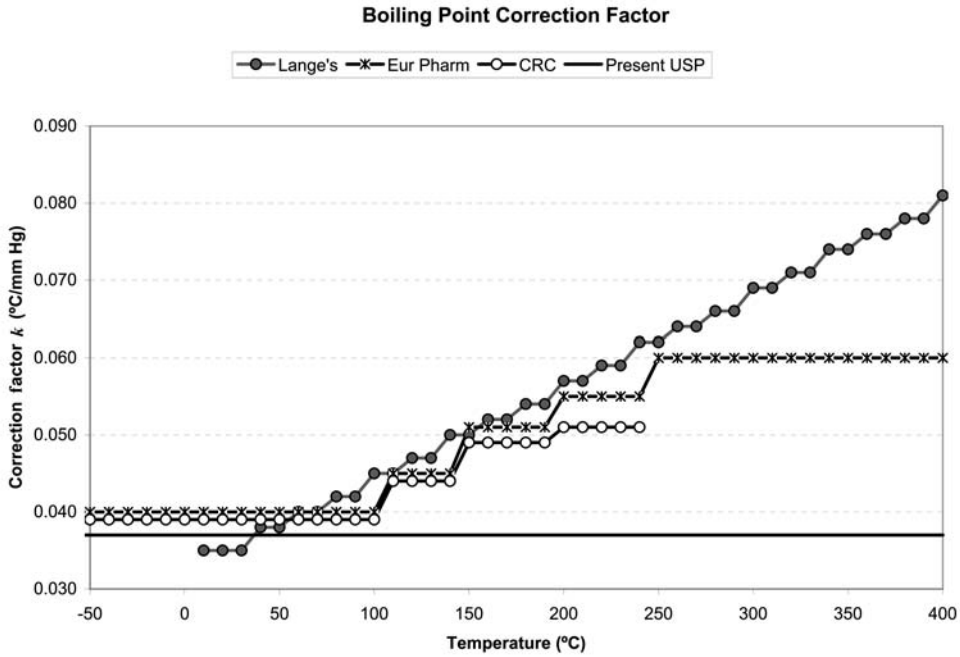

Figure 2. Comparison of correction factors as a function of temperature using *Lange's* (*2*), *EP* (*3*), *CRC (5),* and the present *USP (4)* approach. For comparison purposes, *CRC* data were ordered as in *EP* tables.

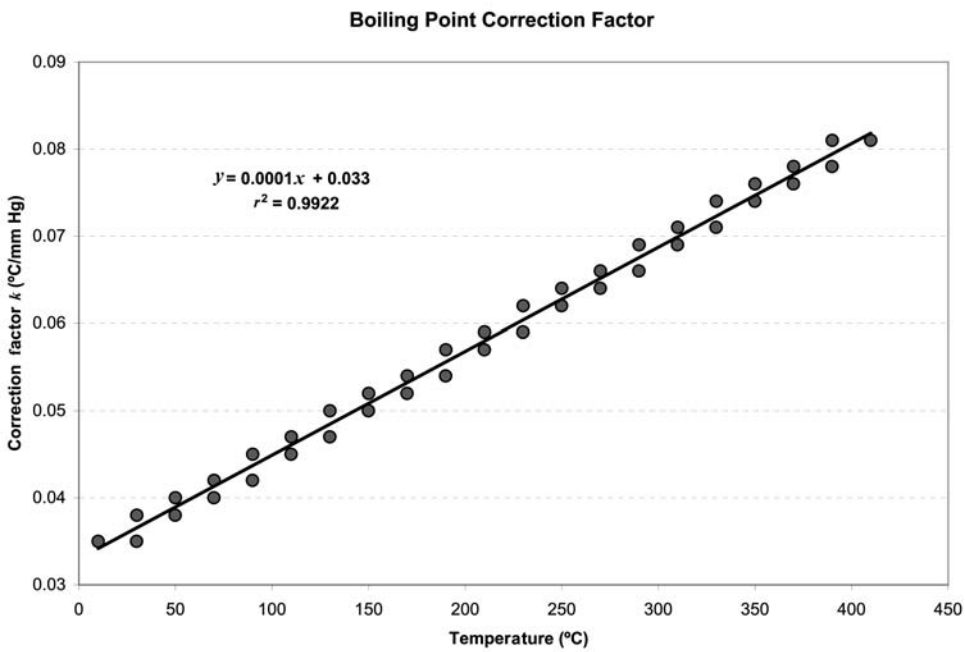

Figure 3. Linearization of *Lange's* data table based on an American Society for Testing and Materials method. The correction factor, *k* was calculated from the graph and was applied to a correction formula.

A NEW APPROACH

The general approach and equation presented in *EP* appear to give results that are similar to those from the much more complicated Lange approach. However, the use of a table to specify k is not as accurate a means to approximate the effects of pressure on the measurement. The linear regression presented in *Figure 3* yields a better way to derive the correction factor, k. Therefore, the *EP* equation, converted to mm of Hg,

$$t = t_0 + k\,(760 - p),$$

is solved using the the linear regression formula:

$$k = 0.0001t_0 + 0.033$$

to yield the final equation

$$t = t_0 + [(t_0 10^{-4} + 0.033)\,(760 - p)].$$

This formula would be used as the correction equation in *USP* ⟨721⟩, where t is the corrected boiling point temperature, t_0 is the measured boiling point temperature, and p is the atmospheric pressure at the time of measurement [NOTE—In the previous equations, k is the correction factor].

The Dreisbach method cited above also proposed a formula for the correction of the temperature but was considered of little value in *Lange's,* probably because of a lack of fit with experimental data. The formula and approach proposed here are based on experimental comparisons and thus should be applicable for correction of the boiling temperature based on the difference between atmospheric pressure and the standard pressure.

Figure 4 compares results from all four approaches. The proposed method yields a line in a central position between *EP* and *CRC* but is extended for a wider range. Its slope is slightly lower than *Lange's,* probably because the last digit of the slope was rounded to fit better with substances more polar than the nonpolar hydrocarbons used in *Lange's*.

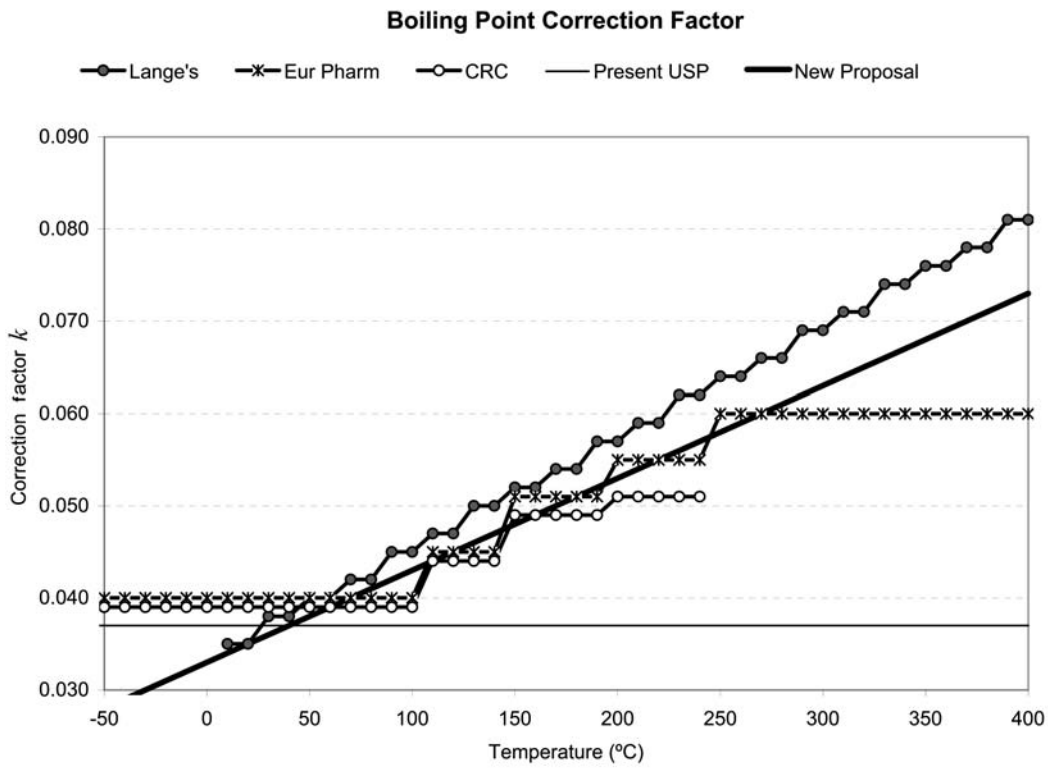

Figure 4. Comparison of the proposed approach with the correction factors as a function of temperature using *Lange's* (*2*), *EP* (*3*), *CRC* (*5*), and the current *USP* (*4*) approach.

CONCLUSION

Several approaches are used to correct the boiling point when it is measured at an atmospheric pressure different from the normal barometric pressure of 760 mm Hg. The proposed approach seems to be both accurate and simple and offers a broader application range by comparison with other methods. Comments regarding the proposed revision to *USP* General Chapter ⟨721⟩ should be sent before 16 October 2006 to Antonio Hernández Cardoso, Scientist and Latin American Specialist, Department of Standards Development, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD, 20852-1790; e-mail: ahc@usp.org.

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Bioassay Glossary

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ABSTRACT The United States Pharmacopeia (USP) has empanelled biological and statistical experts to develop chapters pertaining to the practice of biological assays. These include a rewrite of General Chapter *Design and Analysis of Biological Assays* ⟨111⟩ and the development of two new General Chapters, *Design of Biological Assays* ⟨1032⟩ and *Validation of Biological Assays* ⟨1033⟩. These experts have come to realize a need for clear and uniform terminology in their discussions, throughout the three chapters, and, indeed, throughout all portions of *USP–NF* that relate to biological assays. Accordingly, they have developed a glossary pertinent to biological assays. The purpose of this *Stimuli* article is to share this nascent glossary with the USP audience and to resolve and/or clarify differences in measurement terminology for well- (small molecules) and poorly characterized (biologicals and biotechnological moieties), hereafter referred to collectively as drug substances. In many cases the terms developed herein have common usages or appear elsewhere, for example in contemporary references by the International Conferences on Harmonization [ICH, for example Guideline Q2A, *Text on Validation of Analytical Procedures (1)*], Food and Drug Administration (FDA), and USP. For some of the terms in this document, the derivation may be clear. Rather than claim originality, the authors seek to associate with this work a compendial perspective that will provide clarity going forward, consistency with previous authoritative usage, and a useful focus on the bioassay context.

I. GENERAL TERMS RELATED TO BIOASSAYS

Analytical procedure—detailed description of the steps necessary to perform the assay.

Notes: 1. The description may include but is not limited to the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the standard curve, use of the formulae for the calculation, etc. 2. The FDA Guidance provides a list of information that typically should be included in the description of an analytical procedure *(2)*.

Assay—analysis (as of a drug) to determine the quantity of one or more components or the presence or absence of one or more components.

Notes: 1. *Assay* often is used as a verb synonymous with *to determine,* as in, "I will assay the material for impurities." In this glossary, *assay* is a noun and is synonymous with the *analytic procedure (protocol).* 2. The phrase, "to run the assay" means to perform the analytical procedure(s) as specified.

Assay data set—the set of data used to determine a single potency or relative potency for all samples included in the bioassay.

Notes: 1. The definition of an assay data set can be subject to interpretation as necessarily a *minimal* set. It is important to understand that it may be possible to determine a potency or relative potency from a set of data but not to do this well. It is *not* the intent of this definition to mean that an assay data set is the *minimal* set of data that can be used to determine a relative potency. In practice, an assay data set should include, at least, sufficient data to assess similarity (q.v.). It also may include sufficient data to assess other assumptions. 2. It is also not an implication of this definition that assay data sets used together in determining a reportable value (q.v.) are necessarily independent from one another, although it may be desirable that they be so. When a run (q.v.) consists of multiple assay data sets, independence of assay sets within the run must be evaluated.

Bioassay, biological assay (these terms are interchangeable)—analysis (as of a drug) to quantify the biological activity(ies) of one or more components by determining its capacity for producing an expected biological activity, expressed in terms of units.

Notes: 1. Typically a bioassay involves controlled administration of the drug substance to living matter, in vivo or in vitro, followed by observation and assessment of the extent to which the expected biological activity has been manifested. 2. The description of a bioassay includes the analytic procedure, which should include the statistical design for collecting data, and the method of statistical analysis that eventually yields the estimated potency or relative potency. 3. Bioassays can be either direct or indirect.

> **Direct bioassays** measure the concentration of a substance that is required to elicit a specific response. For example, the potency of digitalis can be directly estimated from the concentration required to stop a cat's heart. In a direct assay, the response must be distinct and unambiguous. The substance must be administered in such a manner that the exact amount (threshold concentration) needed to elicit a response can be readily measured and recorded.

> **Indirect bioassays** compare the magnitude of responses for nominally equal concentrations of reference and test preparations, rather than test and reference concentrations

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that are required to achieve a specified response. Most biological assays in *USP* are indirect assays that are based on either quantitative or quantal (yes/no) responses.

Potency—the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

Notes: 1. A wholly impotent sample has no capacity to produce the expected response, as a potent sample would. Equipotent samples produce equal responses at equal dosages. Potency is typically measured relative to a reference standard or preparation that has been assigned a single unique value (e.g., 100%) for the assay; see *relative potency.* At times, additional qualifiers are used to indicate the physical standard employed (e.g., ''international units''). 2. Some biological products have multiple uses and multiple assays. For such products there may be different reference lots that do not have consistently ordered responses across a collection of different relevant assays.

Relative potency—a measure obtained from the comparison of a test to a reference drug substance on the basis of capacity to produce the expected biological activity.

Notes: 1. A frequently invoked perspective is that relative potency is the degree to which the test preparation is diluted or concentrated relative to the standard. 2. Relative potency is unitless and is given definition, for any test material, solely in relation to the reference material and the assay.

Reportable value—the potency or relative potency estimate of record that is intended to achieve such measurement accuracy and precision as are required for use.

Notes: 1. The reportable value is the value that will be compared to a product specification. The specification may be in the *USP* monograph, or it may be set by the company, e.g., for product release. 2. The term *reportable value* is inextricably linked to the ''intended use'' of an analytical procedure. Tests are performed on samples in order to yield results that can be used to evaluate some parameter of the sample in some manner. One type of test may be configured in two different ways because the resulting data will be used for two different purposes (e.g., lot release vs. stability). The reportable value would likely be different even if the mechanics of the test itself were identical. Validation is required to support the properties of each type of reportable value. In practice there may be one physical document that is the analytical procedure used for more than one application, but each application must be detailed separately within that document. Alternatively, there may be two separate documents for the two applications. 3. When the inherent variability of a biological response, or that of the log potency, precludes a single assay data set's attaining a value sufficiently accurate and precise to meet an assay specification, the assay, or analysis data set, may consist of multiple assay data sets, as necessary. The number of assay data sets needed depends on the assay's accuracy and precision and on the intended use and hence the properties of the reported value and is influenced by factors such as the type and variability of the biological activity being studied.

Run—that performance of the analytical procedure that can be accomplished by a laboratory team in a set time with a given unique set of assay factors (e.g., standard preparations).

Notes: 1. There is no necessary relationship of *run* to *assay data set* (q.v.). The term *run* is laboratory specific; *run* relates to the physical capability of a team and its physical environment. An example of a *run* is given by one analyst's simultaneous assay of several samples in one day's bench work. During the course of a single run, it may be possible to determine multiple reportable values. Conversely, a single assay or reportable value may include data from multiple runs. 2. From a statistical viewpoint, a run is one realization of the factors associated with intermediate precision (q.v.). It is good practice to associate runs with factors that are significant sources of variation in the assay. For example, if cell passage number is an important source of variation in the assay response obtained, then each change in cell passage number initiates a new run. If the variance associated with all factors that could be assigned to runs is negligible, then the influence of runs can be ignored in the analysis and the analysis can focus on combining independent analysis data sets. 3. When a run contains multiple assays, caution is required regarding the independence of the assay results. Factors that are typically associated with runs and that cause lack of independence include cell preparations, groups of animals, analyst, day, a common preparation of reference material, and analysis with other data from the same run. Even though a strict sense of independence may be violated because some elements are shared among the assay sets within a run, the degree to which independence is compromised *may* have negligible influence on the reportable values obtained. This would need to be verified and monitored.

Similar preparations (similarity)—the property of two preparations such that each behaves as a dilution (or concentration) of the other.

Notes: 1. Similarity is fundamental to methods for determination of relative potency. Bioassay similarity requires that the reference and test samples should be sufficiently similar for legitimate calculation of relative potency. Given demonstration of similarity, a relative potency can be calculated, reported, and interpreted. Relative potency is valuable in assessing consistency and also intra- and inter-manufacturer comparability in the presence of change. In the absence of similarity, a meaningful relative potency cannot be reported or interpreted. 2. The practical *consequence* of similarity is a comparable form of dose and/or concentration–response behavior. 3. Failure to statistically demonstrate dissimilarity between a reference and a test sample does not amount to demonstration of similarity. To assess similarity it is not sufficient to fail to find evidence that a reference and a test sample are not similar.

II. TERMS RELATED TO RUNNING A BIOASSAY

Configuration, assay—the arrangement of experimental units (q.v.) by number, position, location, temporal treatment, etc. and the corresponding test, control, or reference sample dilution that will be applied to each.

Notes: 1. The assay configuration must be specified in the formalized assay protocol. 2. Assay configuration can include nested dimensions like plate design, multiple plates per day, single plates on multiple days, etc. The configuration will depend on what the variance analysis (performed during assay development) reveals regarding sources of variability on assay response.

Sample suitability—a sample is suitable (may be described as having a potency) if its response curve satisfies certain properties defined in the protocol.

Note: Most significant of these properties is that of similarity to the reference standard response curve. If this property of similarity is satisfied, then the sample is suitable for the assay and can be described via a relative potency estimate.

System suitability—the provision of assurance that the laboratory control procedure is capable of providing legitimate measurements as defined in the validation report.

Notes: 1. System suitability may be thought of as an assessment of current validity achieved at the time of assay performance. An example is provided by positive and negative controls giving values within their normal ranges, ensuring that the assay system is working properly. 2. As described in USP General Chapter *Validation of Compendial Methods* ⟨1225⟩ and ICH Q2B, system suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated. *USP–NF* is a source of many system suitability tests.

III. TERMS RELATED TO PRECISION AND ACCURACY

Accuracy—an expression of the closeness of agreement between the value that is accepted either as a conventional true value or an accepted reference value and the value found.

Notes: 1. ICH and ISO give the same definition of accuracy. However, ISO specifically regards accuracy as having two components, bias and precision *(3)*. That is, to be accurate as used by ISO, a measurement must be both ''on target'' (have low bias) and precise. In contrast, ICH Q2A says that accuracy is sometimes termed ''trueness'' but does not define trueness. ISO defines trueness as the ''closeness of agreement between the average value obtained from a large series of test results and an accepted reference value'' and indicates that ''trueness is usually expressed in terms of bias.'' The 2001 FDA guidance on Bioanalytical Method Validation defines accuracy in terms of ''closeness of *mean* test results'' (emphasis added) and is thus consistent with the ICH usage. This glossary adopts the ICH approach. That is, it uses the term *accurate* to indicate low bias and the term *precise* to indicate low variability. 2. Considerable caution is needed when using or reading the term *accuracy*. In addition to the inconsistency between ICH and ISO, common usage is not consistent.

Error, types of—Two sources of uncertainty that affect the results of a biological assay are systematic and random error.

A **systematic error** is one that happens with similar magnitude and consistent direction repeatedly. This introduces a *bias* in the determination. Effective experimental design, including randomization and/or blocking, can reduce systematic error.

A **random error** is one whose magnitude and direction vary without pattern. Random error is an inherent variability or uncertainty of the determination. Transformation of systematic into random error will increase the robustness of a biological assay and allow a comparatively simple analysis of assay data.

Intermediate precision—expresses within-laboratory precision associated with changes in operating conditions.

Notes: 1. Factors contributing to intermediate precision involve anything that can change within a given laboratory and that may affect the assay, including different days, different analysts, different equipment, etc. Intermediate precision is thus ''intermediate'' in scope between the extremes of repeatability and reproducibility. 2. Any statement of intermediate precision should include clarification about which factors varied. For example, ''The intermediate precision associated with changing equipment and operators is . . .'' 3. There can also be value in separately identifying the precision associated with each source, e.g., interanalyst precision. This may be part of assay development and validation, when there is value in identifying which are the important contributors to intermediate precision. 4. When reporting intermediate precision, particularly for individual sources, analysts should take care to distinguish between intermediate precision variance and components of that variance. The variance includes repeatability and thus must be necessarily at least as large as the repeatability variance. A variance component, e.g., for analyst, is also a part of the intermediate precision variance for analyst, but it could be negligible and need not be larger in magnitude than the repeatability variance.

Precision—the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Notes: 1. Precision may be considered at three levels: repeatability (q.v.), intermediate precision (q.v.), and reproducibility (q.v.). 2. Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample, precision may be investigated using artificially prepared samples or a sample solution. 3. Precision is usually expressed as the variance, standard deviation, or coefficient of variation.

Repeatability—the expression of the precision under the same operating conditions over a short interval of time.

Notes: 1. ICH Q2A says that repeatability is also termed ''intra-assay'' precision. In the bioassay context, the better term is ''intrarun,'' and a ''short interval of time'' is meant

to connote "within-run." 2. The idea of a "short interval of time" can be problematic with bioassay. If a run takes multiple weeks and consists of a single assay set, then intrarun precision cannot be determined. Alternatively, if a run consists of two assay data sets and a run can be done in a single day, repeatability of the relative potency determination can be assessed. 3. Operating conditions will include, but not be limited to, equipment and analyst.

Reproducibility—expresses the precision between laboratories.

Notes: 1. Reproducibility includes contributions from repeatability and all factors contributing to intermediate precision as well as any additional contributions from interlaboratory differences. 2. Reproducibility will apply to collaborative studies, such as those for standardization or portability of methodology. Depending on the design of the collaborative study, it may be possible to separately describe variance components associated with intra- and interlaboratory sources of variability.

Specificity—the ability to assess unequivocally the analyte in the presence of components that may be expected to be present.

Note: Typically these components may include impurities, degradants, matrix, etc.

IV. TERMS RELATED TO CHARACTERIZATION AND VALIDATION

Detection limit—the lowest amount of analyte in a sample that can be detected but not necessarily quantified or quantified to any given level of precision and accuracy.

Linearity, bioassay—the ability (within a given range) of a bioassay to obtain log relative potencies that are directly proportional to the log relative potency of the sample.

Notes: 1. Bioassay linearity, sometimes called dilutional linearity, is demonstrated across a range of known relative potency values by considering a plot of true log potency vs. observed log potency. If that plot yields an essentially straight line with a y-intercept of 0 and a slope of 1, the assay has direct proportionality. If that plot yields an essentially straight line but either the y-intercept is not 0 or the slope is not 1 (or both), the assay has a proportional linear response. 2. To assess whether the slope is (near) 1.0 requires an a priori equivalence or indifference interval. It is not proper statistical practice to test the null hypothesis that the slope is 1.0 against the alternative that it is not 1.0 and conclude a slope of 1.0 if this is not rejected. Assay linearity is separate from consideration of the shape of the concentration–response curve. Linearity of concentration–response is *not* a requirement of assay linearity. Linearity as discussed in ICH Guideline Q2B is concentration–response linearity.

Quantitation limits—the limits of true relative potencies between which the assay has suitable precision and accuracy.

Note: This applies to assay results (log potency) rather than the reportable value.

Range—the interval between the upper and lower relative potencies for which the bioassay is demonstrated to have a suitable level of precision, accuracy, and assay linearity.

Note: This applies to assay results (log potency) rather than the reportable value.

Robustness—a measure of an analytical procedure's capacity to remain unaffected by small but deliberate variations in method parameters.

Notes: 1. Robustness is an indication of a bioassay's reliability during normal usage. For example, a cell culture assay system that is robust to the passage number of the cells would provide potency values with equivalent accuracy and precision across a consistent range of passage numbers. 2. ICH Q2B states:

> the evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the reliability of an analysis with respect to deliberate variations in method parameters. If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled, or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness should be that a series of system suitability [q.v.] parameters is established to ensure that the validity of the analytical procedure is maintained whenever used.

Validation, assay—a formal, archived demonstration of the analytical capacity of an assay that provides justification for use of the assay for an intended purpose and a range of acceptable potency values.

Note: Formal validations are conducted prospectively according to a written, approved plan.

V. TERMS RELATED TO STATISTICAL DESIGN AND ANALYSIS

Blocking—the grouping of related experimental units in experimental designs.

Notes: 1. Blocking is often used to reduce the variability of a measure of interest. 2. Blocks may consist of groups of animals (a cage, a litter, or a shipment), individual 96-well plates, sections of 96-well plates, or whole 96-well plates grouped by analyst, day, or batch of cells. 3. The goal is to isolate a systemic effect, such as cage, so that it does not obscure the effects of interest.

> A **complete block design** occurs when all levels of a treatment factor (in a bioassay, the primary treatment factors are sample and concentration) can be applied to experimental units for that factor within a single block. Note that the two treatment factors, sample and concentration, may have different experimental units. For example, if the

animals within a cage are all assigned the same concentration but are assigned unique samples, then the experimental unit for concentration is cage and the experimental unit for sample is animal; cage is a blocking factor for sample.

An **incomplete block design** occurs when the number of levels of a treatment factor exceeds the number of experimental units for that factor within the block.

Confounded design—two factors are confounded if their levels vary together (they are not crossed).

Notes: 1. For example, in a bioassay validation experiment in which one analyst performs assays on a set of samples for three days using cells from one passage number, then another analyst performs assays on the same set of samples for another three days using cells from a different passage number, the passage number of the cells and the analysts are confounded. [Also note that days are nested (q.v.) within analyst and cell passage number.] When factors are confounded, one cannot tell which of the factors has caused an observed experimental difference. 2. Fractional factorial designs (q.v.), in which factors are only partially crossed, also are partially confounded. A full factorial design also can be confounded if the number of treatment combinations (sample and concentration) is greater than the block size.

Crossed (and partially crossed)—two factors are crossed (or fully crossed) if each level of each factor appears with each level of the other factor. Two factors are partially crossed when they are not fully crossed but multiple levels of one factor appear with a common level of the other factor.

Notes: 1. For example, in a bioassay in which all samples appear at all dilutions, samples and dilutions are (fully) crossed. In a bioassay validation experiment in which two of four analysts each perform assays on the same set of samples on each of six days and a different pair of analysts is used on each day, the analysts are partially crossed with days. 2. Each factor may be applied to different experimental units, and the factors may be both fully crossed and nested (q.v.), creating a split-unit or split-plot design (q.v.). 3. Experiments with factors that are partially crossed require particular care for proper analysis. 4. A randomized complete block design (RCBD) (q.v.) is a design in which the block factor (which often is treated as a random effect) is crossed with the treatment factor (which is usually treated as a fixed effect).

Experimental design—the structure of assigning treatments to experimental units.

Note: Blocking (q.v.), randomization (q.v.), replication (q.v.), and specific choice of design (to be covered in the planned General Chapter *Design of Biological Assays* ⟨1032⟩ are some aspects of experimental design. Important components of experimental design include the number of samples, the number of concentrations, and how samples and concentrations are assigned to experimental units and are grouped into blocks.

Experimental unit—the smallest unit to which a distinct level of a treatment is randomly allocated.

Notes: 1. Randomization of treatment factors to experimental units is essential in bioassays. 2. An experimental unit needs to be distinguished from a sampling unit, the smallest unit on which a distinct measurement is recorded (e.g., a well). Because the sampling unit is often smaller than the experimental unit, it is an easy mistake to treat sampling units as if they are experimental units; this mistake is called pseudoreplication (q.v.). 3. Different treatment factors can be applied to different experimental units. For example, samples may be assigned to rows on a 96-well plate while dilutions are assigned to columns on the plate. In this case, rows are the experimental units for samples, columns are the experimental units for concentrations, and wells are the experimental units for the interaction of sample and concentration.

Factor—an assay design element that may affect assay response and that varies in an experiment.

Note: In a bioassay there will be at least two treatment factors—sample and concentration.

A **fixed factor** is a factor that is deliberately set at specific levels in an experiment; inference is made only to the levels used in the experiment. In a bioassay, sample and concentration are both fixed factors.

A **random factor** is one for which its levels represent a sample of ways in which that factor might vary. In a bioassay, the test organisms, plate, and day often are considered random factors.

Factorial design—one in which there are multiple factors and the factors are partially or fully crossed.

In a **full factorial design**, each level of a factor appears with each combination of levels of all other factors. For example, if factors are sample (test and reference), concentration, and analyst, for a full factorial design each analyst must analyze all combinations of sample and concentration.

A **fractional factorial design** is one in which some factors are deliberately partially confounded with interactions associated with other combinations of factors.

Independence—For two measurements or observations A and B (raw data, assay sets, or relative potencies) to be independent, values for A must be unaffected by B's responses and vice versa.

Note: In practice this means that if two potency or relative potency measurements share a common analyst, cell preparation, incubator, group of animals, or aliquot of reference sample, then the assumption must be that they cannot be assumed to be independent. The same holds true if the two potency or relative potency measurements are estimated together from the same model or are in any way associated. In some bioassays, ongoing evidence from data can be used to show that it is reasonable to treat potency measures as independent even if they share a common level of a factor such as cell preparation.

Interaction—two factors are said to interact if the effect of one factor depends on the level of the other factor.

Level—a location on the scale of measurement of a factor.

Notes: 1. Factors have two or more distinct levels. For example, if a bioassay contains two samples, test and reference, then there are two levels for the factor sample. 2. Levels of a factor in a bioassay may be quantitative, such as concentration, or categorical, such as sample (i.e., test and reference).

Modeling, statistical—the mathematical specification of the concentration–response relationship and important sources of variation in the bioassay.

Notes: 1. Modeling includes methods to capture the dependence of the response on the samples, concentration, and groups or blocking factors in the assay configuration. 2. Modeling of bioassay data includes making many choices, some of which are driven by data. With continuous data there is a choice between linear and nonlinear models. With discrete data there is a choice among logit/log models within a larger family of generalized linear models. In limiting dilution assays there is published literature advocating Poisson models and Markov chain binomial models. One can use either fixed-effects models or mixed-effects models for bioassay data. The fixed-effects models are more widely available in software and are somewhat less demanding for statisticians to set up. On the other hand, mixed models have advantages over fixed ones. The former are more accommodating of missing data and, more importantly, can allow each block to have different slopes, asymptotes, median effective concentrations required to induce a 50% effect (EC50s), or relative potencies. Particularly when the analyst is using straight-line models fit to nonlinear responses, or in assay systems in which the concentration–response curve varies from block to block, the mixed model captures the behavior of the assay system in a much more realistic and interpretable way. 3. It is essential that any modeling approach for bioassay data use all available data simultaneously to estimate the variation (or, in a mixed model, each of several sources of variation). It may be necessary to transform the observations before this modeling; to include a variance model; or to fit a "means" model (in which there is a predicted effect for each combination of sample and concentration) to get pooled estimate(s) of variation.

Nested—a factor *A* is nested within another factor *B* if the levels of *A* are different for every level of *B*.

Notes: 1. For example, in a bioassay validation experiment two analysts may perform assays on the same set of samples on each of six days when no analyst performs the assay on more than one day (this requires 12 analysts who are qualified to perform the assay); these analysts are nested within days. 2. Nested factors have a hierarchical relationship. 3. For two factors to be nested they must satisfy the following: (a) be applied to different-sized experiment units; (b) the larger experimental unit contains more than one of the smaller experimental units; and (c) the factor applied to the smaller experimental unit is not fully crossed with the factor applied to the larger experimental unit. When conditions (a) and (b) are satisfied and the factors are partially crossed, then the experiment is partially crossed and partially nested. Experiments with this structure require particular care for proper analysis.

Parallelism (of concentration–response curves)—the concentration–response curves of the test and standard are identical in shape and differ only in a constant horizontal difference.

Notes: 1. When test and reference preparations are similar (q.v.) and assay responses are plotted against log concentrations, the resulting curve for the test preparation will be the same as that for the standard but shifted horizontally by an amount that is the logarithm of the relative potency. Because of this relationship, similarity (q.v.) is generally referred to as *parallelism*. Note that similarity is the primary concept and that parallelism is not necessary for similarity; see slope ratio models in the General Chapter *Design and Analysis of Biological Assays* ⟨111⟩, in which samples with similar concentration–response relationships have a common (or nearly common) *y*-intercept, but may differ in their slopes. 2. In practice, it is not possible to demonstrate that the shapes of two curves are exactly the same. Instead, the two curves are shown to be sufficiently similar (equivalent) in shape. Note that *similar* should be interpreted as "we have evidence that the two values are close enough" rather than "we don't have evidence that the two values are different." 3. The assessment of parallelism depends on the type of function used to fit the response curve. Parallelism for a nonlinear assay using a four-parameter logistic fit means that (a) the slopes of the rapidly changing parts of the sample and reference standard curves (that is, slope at tangent to the curve, where the first derivative is at a maximum) should be similar and (b) the upper and lower asymptotes of the response curves (plateaus) should be similar. For straight-line analysis, the slopes of the lines should be similar.

Randomization—a process of assignment of treatment to experimental units based on chance so that all equal-sized groups of units have an equal chance of receiving a given treatment.

Notes: 1. The chance mechanism may be an unbiased physical process (rolling unbiased dice, flipping coins, drawing from a well-mixed urn), random-number tables, or computer-generated randomized numbers. Care must be taken in the choice and use of method. Good practice is to use a validated computerized random-number generator. 2. The use of randomization results in systematic error becoming random error not associated with particular samples or a dilution pattern but distributed throughout the assay. In 96-well bioassays, plate effects can be substantial and cause bias or trending, particularly in assays involving long-term cell culturing or multiple addition and wash steps. In animal studies, a variety of factors associated with individual animals can influence responses. If extraneous factors that influence either plate assays or animal assays are not routinely demonstrated to have been eliminated or minimized so as to be negligible, randomization that removes the influence of the biasing factor is essential to obtain unbiased data required for the calculation of true potency. Randomization is central to the experimental design and analysis of data obtained from most biological assays.

Replication—a process in which multiple independent experimental units receive the same level of a treatment factor.

Notes: 1. The purpose of replication is to minimize the effects of uncontrollable sources of random variability. 2. Replication can occur either completely at random or across blocks. Generally, replication within blocks is pseudoreplication (see below).

> **True replicates**—samples based on independent experimental units.
>
> **Pseudoreplication** is the identification of samples from experimental units as independent and thus true replicates when they are actually not independent.

Notes: 1. Pseudoreplication results in wrong inferences and the appearance of more replicates than are actually present. 2. Pseudoreplication is dangerous because it is an easy mistake to make, it is easy to overlook, and the consequences can be serious. For example, pseudoreplicates commonly arise when analysts are making a dilution series for each sample in tubes (the dilution series can be made with serial dilutions, by single-point dilutions, or with any convenient dilution scheme). The analyst then transfers each dilution of each sample to several wells on one or more assay plates. The wells are then pseudoreplicates because they are simply aliquots of a single dilution process. 3. In general, pseudoreplication should be avoided because, unless it is properly addressed in the analysis, it leads to underestimation of replicate variance. 4. The simple way to analyze data from pseudoreplicates is to average over the pseudoreplicates (if a transformation of the observed data is used, the transformation should be applied before averaging over pseudoreplicates) before fitting any sort of concentration–response model. In many assay systems averaging over pseudoreplicates will leave the assay without any replication. A more complex way to use data containing pseudoreplicates is to use a mixed model that treats the pseudoreplicates as a separate random effect. The only case in which pseudoreplication is useful is when the pseudoreplicate (i.e., well-to-well) variation is very large compared to the variation associated with replicates and when the cost of pseudoreplicates is much lower than the cost of replicates.

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Proposed Revisions to *USP* Standards for Containers—Glass

C. Jeanne Taborsky, *SciRegs International;* Edward McKinley, *Owens-Illinois;* Brian Reamer, *SciRegs International;* Michael Röβler, *Schott AG;* Desmond Hunt,* *USP;* and Claudia Okeke, *USP*

ABSTRACT All glasses do not behave identically in the presence of pharmaceutical products. For example, some drugs fail stability tests when manufacturers change Type 1 glass suppliers or Type 1 glass formulations *(Table 1)*. Neutral parenteral preparations may interact with the inner surface of glass containers. A small amount of alkali and other ions may leach into and react with the drug product, rendering it unacceptable for use. The intensity of the degradation depends on the nature of the drug product, the composition of the glass, its surface treatment, and the method of the glass manufacture. This *Stimuli* article discusses glass components, compositions, and evaluations and outlines proposed revisions to current *USP* standards to better qualify glass components for use with pharmaceutical products. Current *USP* General Chapter *Containers* ⟨661⟩ standards have been in effect without substantive revisions for an extensive period (*1*) and may benefit from comparative and cooperative international compendial revision (*2*).

INTRODUCTION

USP XII (1942) contained the first chemical specifications for glass containers for certain parenteral products (*3*). In *USP XVIII* and *NF XIII* the standards for glass were expanded, and glass was classified based on its composition and hydrolytic chemical durability (*4*), defined as the ability of glass grains to resist the release of soluble mineral substances into water under prescribed conditions of contact with water (see *Appendix: Proposed Definition*s, for further terminology and definitions) (*5, 6*). No single formula or method of manufacture is established for each type of glass. Currently in *USP* General Chapter *Containers* ⟨661⟩ the types of glass are measured by hydrolytic resistance using the powdered glass test, which measures the titration of released alkali. In this test the glass is ground, sieved, and titrated to an endpoint. Glass types are summarized in *Tables 1* and *2* below.

Until the 1970s glass was the most widely used packaging material. During this time containers were manufactured of glass or polystyrene with metal or plastic screw closures for tablets and capsules. Glass was used for vials for parenteral products, bottles for oral liquids and solids, and large bottles for intravenous solutions, blood and blood components, anticoagulants, cartridges, droppers, and ampuls. Today glass is still the primary packaging material for vials for injectable drugs and prefilled syringes. Plastics are used for most solid oral dosage forms, oral liquids, ophthalmic solutions, parenteral solutions, and ampuls in the form of nebules.

Glass has the advantage of transparency, ease of cleaning, and amenability to heat sterilization. Glass is resistant to most liquids, relatively inert, and totally impermeable to gases. Weight loss by diffusion through the container is nonexistent, although closure integrity can be an issue because of loss at the container–closure interface. Some disadvantages of using glass include its density (2.0–2.5 g/cm^2) and brittle nature. Glass requires thick container walls in order to remain durable and is therefore heavier than similar containers manufactured from plastic (*7*). Because glass containers are heavier, they are more expensive to ship. Glass also is more prone to stress cracks, breakage, and shattering into small, sharp fragments. Some glass defects are not visible until the container is filled with drug product, and over time the surface can flake into the drug.

Types of Glass

Glass as an amorphous, inorganic, super-cooled liquid has an ultra-high viscosity at room temperature (*5, 7*). Conventional inorganic glass consists of a mixture of crystalline oxides, carbonates, etc., melted by heating to a viscous liquid state. Glass consists mainly of silica dioxide, but the composition varies widely within each type. The types are based on chemical resistance (*Table 1*).

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Table 1. Types of Glass in ⟨661⟩

	Type I	Type II	Type III	Type NP*
Composition	Borosilicate	Soda–lime	Soda–lime	General purpose
Reactivity	Neutral glass; high hydrolytic resistance	High hydrolytic resistance resulting from dealkalization	Average hydrolytic resistance	Potentially reactive
USP *Powdered Glass Test:* mL of 0.02 N acid	NMT† 1.0	(Water attack) NMT 0.7 or 0.2	NMT 8.5	NMT 15.0
Color	Clear amber	Clear amber	Clear amber	Assorted
Use	Most products including parenterals	Most acidic and neutral aqueous preparations including some parenterals	Nonaqueous parenterals, powders (excluding freeze-dried preparations), and nonparenterals	Nonparenterals

* NP=Nonparenteral
† NMT=Not more than

Medical glass is composed of borosilicate or soda–lime glass. The composition and relative concentration of the various elements change the properties, including melting and processing temperature. Typical proportions of atoms are provided in *Table 2*.

Table 2. Typical Composition of Medical Glass: Proportions of Atoms (*6*)

Element	Type I	Type II	Type III
Boron	6	0	0
Silica	25	24	24
Aluminum	2	1	1
Sodium	4	2	10
Calcium	0	5	5
Oxygen	63	56	60

Type I glass is composed of approximately 80% silicon dioxide and 20% boron oxide. It is preferred for sterile injectable products because of its high chemical resistance, and it is available in both amber and clear glass. Type II glass containers are fabricated of a high-grade commercial soda–lime glass, the inner glass surface of which is dealkalized by treatment, e.g., with ammonium sulfate or sulfur dioxide, followed by washing with water. This glass is suitable for most acidic and neutral aqueous preparations, including some parenteral products. Type III glass is a level above common commercial glass in resistivity to chemical attack. This glass may be suitable for some parenteral products, solids, oral liquids, and beverages.

GLASS INTERACTIONS

The quality of the contact surface of glass containers is critical to the stability of pharmaceutical products therein. Chemicals, most commonly sodium, silicon, boron, aluminum, and calcium ions, can leach or migrate from the glass to the product, causing a pH shift in unbuffered solutions. Migrants also can cause precipitation, aggregation, and degradation of product, rendering it unacceptable for use. In all types of glass, all of the ingredients have a potential to leach into the product. Neutral or acid solutions can attack the glass surface and result in ion exchange. Alkali attacks glass by dissolution. Physical attacks of the glass by the pharmaceutical product can result in sloughing or delamination, producing glass particles. Product can adsorb on the glass, and the glass can physically degrade (slough or weather). The manufacturer of the component can control the quality of the surface by controlling the composition, forming process, and secondary processes. Ultimately the packager or finished pharmaceutical product manufacturer must determine the suitability for use of the glass component in a system with a particular product (*5, 6, 7*).

INTERIOR SURFACE TREATMENTS

Several factors affect the surface quality of glass components, including composition, forming process, and secondary processing or treatments. Drug interactions with glass are due mostly to the migration or leaching of ions, e.g., sodium. Reduction of sodium atoms will increase chemical resistance to most, but not all, attacks. The sodium content of Type I borosilicate glass is inherently low, so it resists reactions with neutral and acidic drugs but may be less stable in the presence of alkaline solutions. The compatibility of any type of glass with alkaline solutions must be tested and evaluated on a case-by-case basis. Treatment of Type II glass is common to achieve chemical compatibility with pharmaceutical products. Alkali atoms can be removed from the surface of glass by several methods. Soaking or rinsing with water can remove some alkali from the immediate surface. In contact with water, elemental components that migrate are present in proportions identical to those in molded glass components. The most effective method is to treat the surface of the glass with ammonium sulfate or sulfur dioxide, which removes alkali to a deeper level below the immediate surface than does water treatment alone. Using this method during the manufacturing process at high temperatures allows other atoms to fill the voids left by the alkali and maintains the density of the glass at the inner surface. Glass for parenteral use is washed and must be presterilized before it can be used for an aseptically

filled pharmaceutical product. All washings and treatments should be documented, and their effects on the reactivity and stability of the glass component must be known (*5 ,6 ,7*).

Type I glass also is available with a silicon dioxide coating (silica) on the inner surface to reduce the risk of migration and interaction, further increasing chemical resistance. The coating forms a strong chemical bond without the use of solvents and reduces ion release from the glass by orders of magnitude. These containers are designed for packaging products of extreme sensitivity, high pH or aggressive buffer systems, complex agents, radiopharmaceuticals, or pharmaceutical products that have a tendency to adsorb to glass surfaces.

STABILITY OF GLASS CONTAINERS

The composition, manufacturing process, treatment, and storage conditions of glass components affect the stability of glass. Some typically assume that tubing glass has less physical stability because it has more heat histories, but this is a general premise that should be evaluated and tested. Type I glass is inherently the most stable. Type II components that have been sulfur treated can display stability problems because of environmental issues. Sodium sulfate on the surface can interact with surface moisture and subsequently recrystallize as a white deposit. These deposits can easily be removed by washing. Within 6 months of storage, under uncontrolled conditions, components made of other types of glass can show signs of weathering. High humidity and temperature and cycling conditions have the greatest influence because of condensation and subsequent evaporation.

SIMILARITIES AND DIFFERENCES BETWEEN PHARMACOPEIAS

The authors reviewed and compared standards for glass in *USP,* the *European Pharmacopoeia (EP),* and the *Japanese Pharmacopoeia (JP)* and are recommending only staged changes or additions that are appropriate for the improvement of *USP*'s glass standards. The first stage is to move glass standards to their own chapter, *USP* General Chapter *Containers—Glass* ⟨660⟩. The second stage is to incorporate the surface test. The third stage is to conduct studies to determine which of the tests in *USP, EU,* and *JP* should be used for the *Powdered Glass Test*.

Currently, *USP, EP,* and *JP* conduct similar *Powdered Glass Tests* but with several variations. The dissimilarities can be found in the cleaning process, the test samples, size of the sieves, acid used for titration, amount of methyl red included in the solution, and limits. The differences between tests for glass containers are summarized in *Table 3*.

Table 3. Comparison of *USP, EP,* and *JP* Tests for Glass Containers

Test	*USP 29* ⟨661⟩	*EP 5.0* Section 3.2.1	*JP XIV* GT 57
Definitions	Glass types	Colourless glass Coloured glass Neutral glass Soda–lime glass	None listed
Introduction	Comparable	Comparable	N/A
Glass types	Types I, II, III, and NP	Types I, II, and III (Type IV deleted)	None listed
Hydrolytic resistance A. Inner surface	Proposed	Existing test	Existing test
Hydrolytic resistance B. Glass grains	(Powdered glass test)	(Glass grains test)	(Powdered glass test)
	Cleaning process: air dry	Cleaning process: oven dry	Cleaning process: doesn't specify
	Samples: max. particle size is 25 mm, separated into 3 equal portions	Samples: max. particle size is 30 mm, separated into 2 equal portions	Samples: max. particle size not specified
	Equipment: sieve numbers are different (20, 40, and 50) and sieve sizes: 850, 425, and 300 µm	Equipment: sieve numbers are different (710, 425, and 300) and sieve sizes: 710, 425, and 300 µm	Equipment: sieve numbers are different (12, 18, and 50) and sieve sizes: 1400, 850, and 300 µm
	Procedure: titrate with 5 drops of methyl red and 0.020 N sulfuric acid	Procedure: titrate with 0.05 mL of methyl red and 0.02 M hydrochloric acid	Procedure: titrate with 5 drops of methyl red and 0.01 M sulfuric acid
	Limits: Type I NMT 1.0 mL, type II NMT (100 or less) 0.7 (over 100) 0.2, type III NMT 8.5 mL, and type NP NMT 15.0 mL	Limits: type I NMT 1.0 mL, and type II and III NMT 8.5 mL	Limits: containers to be fused 0.30 mL, and containers not to be fused 2.0 mL
Hydrolytic resistance C. Etching test	Test absent	Existing test	Existing test

Table 3. Comparison of *USP, EP,* and *JP* Tests for Glass Containers *(Continued)*

Test	*USP 29* ⟨661⟩	*EP 5.0* Section 3.2.1	*JP XIV* GT 57
Hydrolytic resistance (Surface glass test) by flame absorption spectrometry	Test absent	Test present in Annex	Test absent
Fill volume	Test absent	Determination of the filling volume	Determination of the filling volume
Arsenic	(Use *Arsenic* ⟨211⟩ *Method I*) titrimetric	Hydride generation atomic absorption spectrometry	Test absent
Light resistance	Light transmission	Spectral transmission	Light transmission
Etching test	Not proposed for addition	Test C to determine whether the containers have been surface treated (Etching test)	Test absent
Water attack at 121°	Existing test	Test absent	Test absent

PHARMACOPEIAL CHANGES

Proposed Changes to *USP*

In order to make the container standards in *USP* clearer, the testing for glass should be moved to a separate chapter titled *USP* General Chapter *Containers—Glass* ⟨660⟩. The testing for plastic components should remain in ⟨661⟩. Compendial scientists seem to agree that the hydrolytic resistance test of the inner surface of glass containers should be added to *USP* because this test already is being conducted by many US companies and its addition to *USP* appears to be noncontroversial. *EP* also includes an *Etching Test,* which is implemented using the results of the surface test to determine if glass has been surface treated. The authors recommend that this test also be incorporated into ⟨660⟩. To the best of our knowledge, Type NP glass is no longer being used for pharmaceuticals, and thus we propose its deletion.

EP 5.0 Section 3.2.1. Glass containers for pharmaceutical use

As part of *EP*'s recent revision and update to the introduction to the general chapter, Type IV glass, which is comparable to *USP* NP, has been deleted. In addition, a new passage was added discussing possible interactions between glass components and pharmaceutical products. For the *Hydrolytic Resistance* test, which measures the alkali release of the inner surface, the exact definition for fill volume is provided. The fill volumes for cartridges and syringes have been defined, and additional set times for rinsing are stipulated (20–25 min). Recent laboratory studies have shown that the results obtained using the titrimetric or the flame atomic absorption spectrometry method are not always comparable. Both methods cannot be considered equivalent or comparable, so *EP* has recommended that the current titrimetric method be kept as the official method.

For the *Glass Grains* test, the mesh size of sieve No. 250 was changed to sieve No. 300 in accordance with ISO 720 and *USP*. The quantity of glass powder was reduced from 20 g to 10 g. The quantity of water used for extraction was reduced from 100 mL to 50 mL. The concentration of the acid used in the titration was doubled, and the limit was reduced to half the previous value. For containers produced from tubular glass, the result of the glass grains test carried out on the corresponding glass tubing is sufficient to qualify the finished molded part. Therefore it is not necessary to carry out a separate test on finished containers.

The *Glass Grains* test was renamed the *Hydrolytic Resistance of Glass Grains* and measures the durability or chemical resistance of glass particles. The sample is crushed to a defined particle size and autoclaved in water. The liquid is titrated with acid to determine the alkali content. This test is not sensitive to surface features. The effectiveness of this surface treatment cannot be sufficiently evaluated by the glass grains test.

JP

To the best of the authors' knowledge, no changes are proposed to glass testing in *JP* at this time.

CONCLUSIONS

This *Stimuli* article has examined the history of and recent progress in packaging pharmaceutical products in various types of glass. Because of advances in both materials science and analytical technologies, container components have become more amenable to precise pharmaceutical characterization, leading to a better understanding of interactions between pharmaceutical products and glass container systems. This knowledge may warrant both a separate *USP* chapter for glass containers and activities to harmonize, when possible, with other pharmacopeias to improve the precision, utility, and scope of pharmacopeial glass container testing. USP welcomes comments, which should be sent to Desmond Hunt, Ph.D., dgh@usp.org before 30 September 2006.

APPENDIX: PROPOSED DEFINITIONS

Fill Capacity—The rated fill amount or volume inside a component.
Overflow Capacity—The total volume inside a component measured to the meniscus.
Durability—The lasting physical and chemical quality of a glass surface. It is frequently evaluated after prolonged weathering or storing in terms of chemical and physical changes in the glass surface or in terms of changes to the contents of a vessel.
Finish—The material forming the opening of a container shaped to accommodate a specified closure system.
Glass—An amorphous inorganic super-cooled liquid.
Clear flint glass—Glass that is highly transparent in the visible spectrum.
Light-resistant glass—Glass that is obtained by the addition of small amounts of metal oxides, chosen according to the desired spectral absorbance.
Neutral glass—A borosilicate glass containing significant amounts of boric oxide, aluminum oxide, alkali, and/or alkaline earth oxides. Because of its composition, neutral glass has a high hydrolytic resistance and a high thermal shock resistance.
Soda–lime silica glass—A silica glass containing alkali metal oxides, mainly sodium oxide and alkaline earth oxides, mainly calcium oxide. Because of its composition, soda–lime silica glass has only a moderate hydrolytic resistance.
Haze—The degree of cloudiness in a material.
Headspace—The volume between the fill level capacity and the overflow capacity.
Stability—The ability of the material to maintain its chemical and physical properties from manufacture through the shelf life of the article.
Hermetic—A container that is impervious to air or other gases under the ordinary and customary conditions of use.

References

1. USP. *USP 28–NF 23*. General Chapter *Containers* ⟨661⟩. Rockville, MD: United States Pharmacopeial Convention; 2005:2396–2399.
2. USP. *USP XII*. General Chapter *Containers for Injection* ⟨661⟩. Rockville, MD: United States Pharmacopeial Convention; 1942:567–576.
3. EMEA. *European Pharmacopoeia*. 5th ed. 3.2.1. Glass containers for pharmaceuticals. 2005.
4. ATSM. *Annual Book of ASTM Standards.* Standard C162-88. Standard definitions of terms relating to glass and glass products. West Conshohocken, PA: ASTM; 1999:1–14
5. Bansal R, Doremus R. *Handbook of Glass Properties*. New York, NY: Academic Press; 1986.
6. Abendroth RP. Glass as a packaging material for pharmaceuticals. In *Encyclopedia of Pharmaceutical Technology.* Swarbrick J, Boylan JC, eds., New York, NY: Marcel Dekker, Inc.; 1993:99–102.
7. Okeke, C. Glass as a packaging material for pharmaceuticals. In *Encyclopedia of Pharmaceutical Technology.* 2nd ed. Swarbrick J, Boylan JC, eds., New York, NY: Marcel Dekker, Inc.; 2002:1372–1389.

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

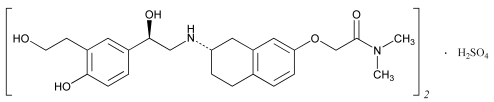
USP Dictionary of USAN and International Drug Names
2006 USP DICTIONARY SUPPLEMENT 2

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2006 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2005) edition will be included in the next complete edition of the Dictionary.

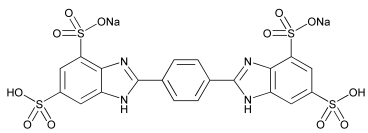
Newly Approved United States Adopted Names (USAN), Released for Publication

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

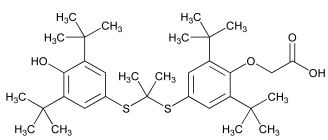
Bedoradrine Sulfate [*2006*] (bed or′ a dreen). $2C_{24}H_{32}N_2O_5.H_2O_4S$. 955.12. (1) Acetamide, *N,N*-dimethyl-2-[[(7*S*)-5,6,7,8-tetrahydro-7-[[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-2-naphthalenyl]oxy]-, sulfate; (2) Bis[2-[[(7*S*)-7-[[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-5,6,7,8-tetrahydronaphthalen-2-yl]oxy]-*N,N*-dimethylacetamide] sulfate. *CAS-194785-31-4*. *Tocolytic for the acute management of imminent pre-term birth.* (Medical Arts) ✧*KUR-1246; MN-221*



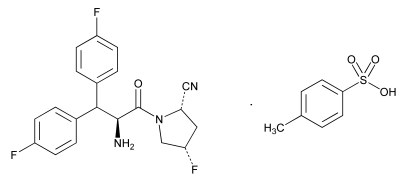
Bisdisulizole Disodium [*2006*] (bis dye su′ li zole). $C_{20}H_{12}N_4Na_2O_{12}S_4$. 674.57. (1) 1*H*-Benzimidazole-4,6-disulfonic acid, 2,2′-(1,4-phenylene)bis-, disodium salt; (2) Disodium dihydrogen 2,2′-(1,4-phenylene)bis(1*H*-benzimidazole-4,6-disulfonate). *CAS-180898-37-7*. *Sunscreen.* Neo Heliopan AP (Symrise GmbH)



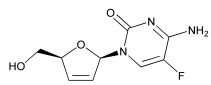
Camobucol [*2006*] (kam oh bue′ kol). $C_{33}H_{50}O_4S_2$. 574.88. (1) Acetic acid, [4-[[1-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-1-methylethyl]thio]-2,6-bis(1,1-dimethylethyl)phenoxy]-; (2) [4-[[1-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]sulfanyl]-1-methylethyl]sulfanyl]-2,6-bis(1,1-dimethylethyl)phenoxy]acetic acid. *CAS-216167-92-9*. *Treatment of inflammatory diseases.* (AtheroGenics) ✧*AGIX-4207*



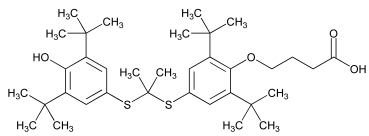
Denagliptin Tosylate [*2006*] (den a glip′ tin). $C_{20}H_{18}F_3N_3O.C_7H_8O_3S$. 545.57. [Denagliptin is INN.] (1) 2-Pyrrolidinecarbonitrile, 1-[(2*S*)-2-amino-3,3-bis(4-fluorophenyl)-1-oxopropyl]-4-fluoro-, (2*S*,4*S*)-, mono(4-methylbenzenesulfonate); (2) (2*S*,4*S*)-1-[(2*S*)-2-Amino-3,3-bis(4-fluorophenyl)propanoyl]-4-fluoropyrrolidine-2-carbonitrile 4-methylbenzenesulfonate. *CAS-811432-66-3; CAS-483369-58-0* [denagliptin]. *Treatment of Type 2 diabetes.* (GlaxoSmithKline) ✧*GW823093C*



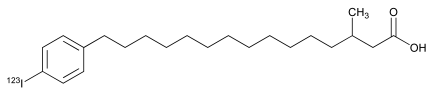
Dexelvucitabine [*2006*] (dex″ el vue sye′ ta been). $C_9H_{10}FN_3O_3$. 227.19. (1) Cytidine, 2′,3′-didehydro-2′,3′-dideoxy-5-fluoro-; (2) (+)-4-Amino-5-fluoro-1-[(2*R*,5*S*)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]pyrimidin-2(1*H*)-one. *CAS-134379-77-4*. *Treatment of HIV-1 and HIV-2 infection.* Reverset (Incyte) ✧*INCB-8721; DPC-817; YZ-817*



Elsibucol [*2006*] (el si bue′ kol). $C_{35}H_{54}O_4S_2$. 602.93. (1) Butanoic acid, 4-[4-[[1-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-1-methylethyl]thio]-2,6-bis(1,1-dimethylethyl)phenoxy]-; (2) 4-[4-[[1-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]sulfanyl]-1-methylethyl]sulfanyl]-2,6-bis(1,1-dimethylethyl)phenoxy]butanoic acid. *CAS-216167-95-2*. *Prevention of solid organ transplant rejection.* (AtheroGenics) ✧*AGI-1096*

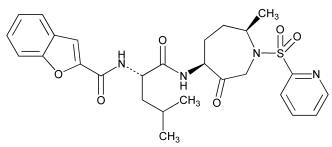


Iodofiltic Acid I 123 [*2006*] (eye oh doe fil′ tic). $C_{22}H_{35}[^{123}I]O_2$. 454.40. (1) Benzenepentadecanoic acid, 4-(iodo-^{123}I)-β-methyl-; (2) (3*RS*)-15-(4-[^{123}I]iodophenyl)-3-methylpentadecanoic acid. *CAS-123748-56-1. Metabolic imaging pharmaceutical for detection of ischemic myocardium.* Zemiva (Molecular Insight) ✧*BMIPP*



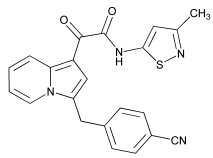
Lexatumumab [*2006*] (lex″ a too′ moo mab). $C_{6346}H_{9832}N_{1720}O_{2002}S_{42}$. (1) Immunoglobulin G1, anti-(human cytokine receptor TRAIL-R2) (human monoclonal HGS-ETR2 heavy chain), disulfide with human monoclonal HGS-ETR2 λ-chain, dimer; (2) Immunoglobulin G1, anti-(human tumor necrosis factor receptor superfamily member 10B (Death receptor 5 or TRAIL-R2)) (human monoclonal HGS-ETR2 heavy chain), disulfide with human monoclonal HGS-ETR2 λ-chain, dimer. Molecular weight is approximately 143,600 daltons. *CAS-845816-02-6. Treatment of cancer.* (Human Genome Sciences) ✧*HGS-ETR2; HGS1018*

Relacatib [*2006*] (rel′ a ka tib). $C_{27}H_{32}N_4O_6S$. 540.63. (1) 2-Benzofurancarboxamide, *N*-[(1*S*)-1-[[[(4*S*,7*R*)-hexahydro-7-methyl-3-oxo-1-(2-pyridinylsulfonyl)-1*H*-azepin-4-yl]amino]carbonyl]-3-methylbutyl]-; (2) *N*-[(1*S*)-3-Methyl-1-[[(4*S*,7*R*)-7-methyl-3-oxo-1-(pyridin-2-ylsulfonyl)hexahydro-1*H*-azepin-4-yl]carbamoyl]butyl]benzofuran-2-carboxamide; (3) *N*-[(1*S*)-3-Methyl-1-({[(4*S*,7*R*)-7-methyl-3-oxo-1-(2-pyridinylsulfonyl)hexahydro-1*H*-azepin-4-yl]amino}carbonyl)-butyl]-1-benzofuran-2-carboxamide. *CAS-362505-84-8*. INN. *Treatment of osteoporosis.* (GlaxoSmithKline) ✧*SB-462795*

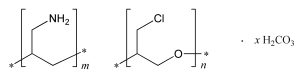


Rilonacept [*2006*] (ri lon′ a sept). $C_{9030}H_{13932}N_{2400}O_{2670}S_{74}$. (1) Interleukin 1 receptor accessory protein (human extracellular domain fragment) fusion protein with type I interleukin 1 receptor (human extracellular domain fragment) fusion protein with immunoglobulin G1 (human Fc fragment), homodimer; (2) [653-Glycine][-human interleukin-1 receptor accessory protein-(1-339)-peptide (extracellular domain fragment) fusion protein with human type I interleukin-1 receptor-(5-316)-peptide (extracellular domain fragment) fusion protein with human immunoglobulin G1-(229 *C*-terminal residues)-peptide (Fc fragment)] dimer. Molecular weight is approximately 201,210 daltons. *CAS-501081-76-1. Treatment of rheumatoid arthritis, auto-inflammatory diseases, and osteoarthritis.* (Regeneron) ✧*IL-1 Trap; Interleukin-1 Trap*

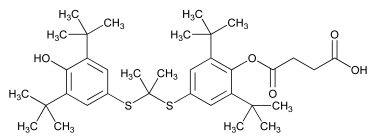
Rosabulin [*2006*] (roe″ za bue′ lin). $C_{22}H_{16}N_4O_2S$. 400.45. (1) 1-Indolizineacetamide, 3-[(4-cyanophenyl)methyl]-*N*-(3-methyl-5-isothiazolyl)-α-oxo-; (2) 2-[3-(4-Cyanobenzyl)indolizin-1-yl]-*N*-(3-methylisothiazol-5-yl)-2-oxoacetamide. *CAS-501948-05-6. Treatment of therapeutic resistant cancers.* (Synta) ✧*STA-5312*



Sevelamer Carbonate [*2006*] (se vel′ a mer). $[(C_3H_7N)_m(C_3H_5ClO)_n].xCH_2O_3$. (1) Carbonic acid, compound with (chloromethyl)oxirane polymer with 2-propen-1-amine; (2) Prop-2-en-1-amine polymer with (chloromethyl)oxirane carbonate. *CAS-845273-93-0. Control of serum phosphorus in patients with chronic kidney disease (phosphate binder).* (Genzyme) ✧*GT335-012*

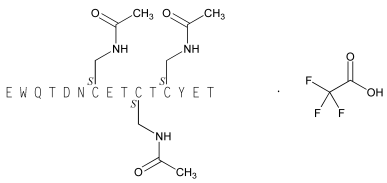


Succinobucol [*2006*] (sux in oh bue′ kol). $C_{35}H_{52}O_5S_2$. 616.91. (1) Butanedioic acid, mono[4-[[1-[[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]thio]-1-methylethyl]thio]-2,6-bis(1,1-dimethylethyl)phenyl] ester; (2) 4-[4-[[1-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]sulfanyl]-1-methylethyl]sulfanyl]-2,6-bis(1,1-dimethylethyl)phenoxy]-4-oxobutanoic acid. *CAS-216167-82-7. Reduction of cardiovascular events.* (AtheroGenics) ✧*AGI-1067*



Ticilimumab [*2006*] (tis i lim′ ue mab). $C_{6500}H_{9974}N_{1726}O_{2026}S_{52}$. (1) Immunoglobulin G2, anti-(human CTLA-4 (antigen)) (human monoclonal CP-675206 clone 11.2.1 heavy chain), disulfide with human monoclonal CP-675206 clone 11.2.1 light chain, dimer; (2) Immunoglobulin G2, anti-(human Cytotoxic T-lymphocyte protein 4 (CD 152 antigen)) (human monoclonal CP-675206 clone 11.2.1 heavy chain) disulfide with human monoclonal CP-675206 clone 11.2.1 light chain, dimer. Molecular weight is approximately 150,000 daltons. *CAS-745013-59-6*. INN. *Treatment of cancer.* (Boehringer Ingelheim) ✧*CP-675,206*

Tigapotide Triflutate [*2006*] (tye″ gah poe′ tide). $C_{82}H_{119}N_{21}O_{34}S_3.C_2HF_3O_2$. 2153.16. (1) L-Threonine, L-α-glutamyl-L-tryptophyl-L-glutaminyl-L-threonyl-L-α-aspartyl-L-asparaginyl-*S*-[(acetylamino)methyl]-L-cysteinyl-L-α-glutamyl-L-threonyl-*S*-[(acetylamino)methyl]-L-cysteinyl-L-threonyl-*S*-[(acetylamino)-methyl]-L-cysteinyl-L-tyrosyl-L-α-glutamyl-, mono(trifluoroacetate); (2) L-α-Glutamyl-L-tryptophyl-L-glutaminyl-L-threonyl-L-α-aspartyl-L-asparaginyl-*S*-[(acetylamino)methyl]-L-cysteinyl-L-α-glutamyl-L-threonyl-*S*-[(acetylamino)methyl]-L-cysteinyl-L-threonyl-*S*-[(acetylamino)methyl]-L-cysteinyl-L-tyrosyl-L-α-glutamyl-L-threonine mono(trifluoroacetate). *CAS-848084-84-4*. *Treatment of metastatic hormone refractory prostate cancer.* (Procycon) ✧*PCK3145*



Vitespen [*2006*] (vi tes′ pen). $C_{3970}H_{6275}N_{1047}O_{1302}S_{21}$. (1) gp96; (2) Glucose regulated protein 94 (grp 94); (2) Endoplasmin (human tumor rejection antigen 1). Molecular weight is approximately 90,100 daltons. *CAS-492448-75-6*. *Autologous heat shock protein immuno-stimulant for the treatment of cancer.* Oncophage (Antigenics) ✧*HSPPC-96*

DDEVDVDGTV EEDLGKSREG SRTDDEVVQR EEEAIQLDGL N*ASQIRELRE
KSEKFAFQAE VNRMMKLIIN SLYKNKEIFL RELIS*NASDA LDKIRLISLT
DENALSGNEE LTVKIKCDKE KNLLHVTDTG VGMTREELVK NLGTIAKSGT
SEFLNKMTEA QEDGQSTSEL IGQFGVGFYS AFLVADKVIV TSKHN*NDTQH
IWESDSNEFS VIADPRGNTL GRGTTITLVL KEEASDYLEL DTIKNLVKKY
SQFINFPIYV WSSKTETVEE PMEEEEAAKE EKEESDDEAA VEEEEEEKKP
KTKKVEKTVW DWELMNDIKP IWQRPSKEVE EDEYKAFYKS FSKESDDPMA
YIHFTAEGEV TFKSILFVPT SAPRGLFDEY GSKKSDYIKL YVRRVFITDD
FHDMMPKYLN FVKGVVDSDD LPLN*VSRETL QQHKLLKVIR KKLVRKTLDM
IKKIADDKYN DTFWKEFGTN IKLGVIEDHS N*RTRLAKLLR FQSSHHPTDI
TSLDQYVERM KEKQDKIYFM AGSSRKEAES SPFVERLLKK GYEVIYLTEP
VDEYCIQALP EFDGKRFQNV AKEGVKFDES EKTKESREAV EKEFEPLLNW
MKDKALKDKI EKAVVSQRLT ESPCALVASQ YGWSGNMERI MKAQAYQTGK
DISTNYYASQ KKTFEINPRH PLIRDMLRRI KEDEDDKTVL DLAVVLFETA
TLRSGYLLPD TKAYGDRIER MLRLSLNIDP DAKVEEEPEE EPEETAEDTT
EDTEQDEDEE MDVGTDEEEE TAKESTAEKD EL

* glycosylation sites

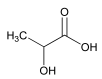
Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

Lactic Acid

Add the molecular formula, molecular weight and chemical structure to read:

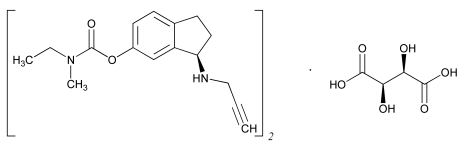
$C_3H_6O_3$. 90.08.



Ladostigil Tartrate

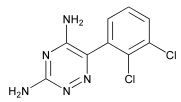
Change the chemical name and add the chemical structure to read:

(2) (3*R*)-3-(Prop-2-ynylamino)-2,3-dihydro-1*H*-inden-5-yl ethylmethylcarbamate (2*R*,3*R*)-tartrate (2:1).



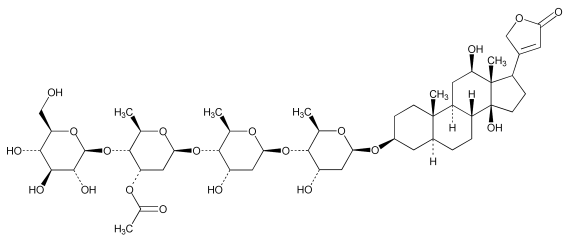
Lamotrigine

Add the chemical structure to read:



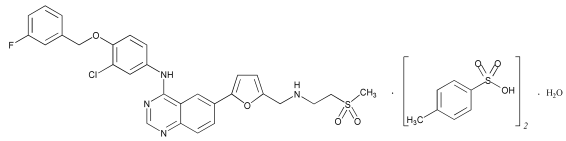
Lanatoside C

Add the chemical structure to read:



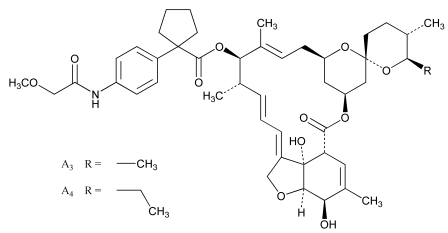
Lapatinib Ditosylate

Add the chemical structure to read:



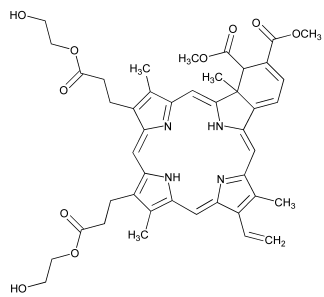
Latidectin

Add the chemical structure to read:



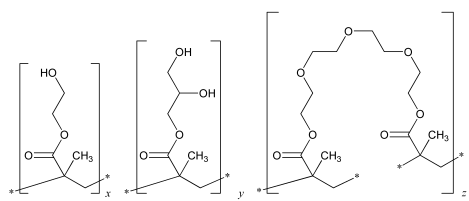
Lemuteporfin

Add the chemical structure to read:



Lenefilcon A

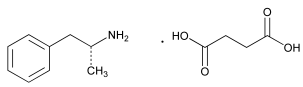
Add the chemical structure to read:



Levamfetamine Succinate

Change the chemical names and structure to read:

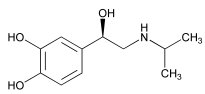
(1) Butanedioic acid, compd. with (–)-(*R*)-α-methylbenzeneethanamine (1:1); (2) (–)-(*R*)-α-Methylphenethylamine succinate (1:1).



Levisoprenaline

Change the chemical name and structure to read:

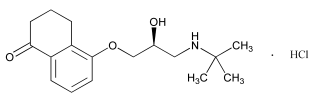
(–)-(*R*)-α-(Isopropylaminomethyl)protocatechuyl alcohol.



Levobunolol Hydrochloride

Change the chemical names and structure to read:

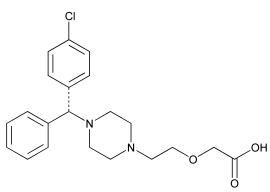
(1) 1(2*H*)-Naphthalenone, 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-, hydrochloride, (–)-(*S*); (2) (–)-(*S*)-5-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2*H*)-naphthalenone hydrochloride.



Levocetirizine

Change the chemical name and add the chemical structure to read:

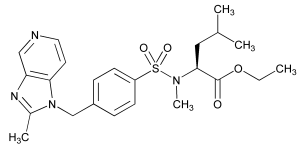
[2-[4-[(*R*)-*p*-Chloro-α-phenylbenzyl]-1-piperazinyl]ethoxy]acetic acid.



Lexipafant

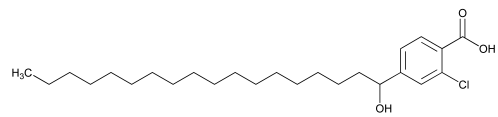
Change the chemical name and structure to read:

(1) L-Leucine, *N*-methyl-*N*-[[4-[(2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)methyl]phenyl]sulfonyl]-, ethyl ester;



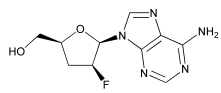
Lodelaben

Add the chemical structure to read:



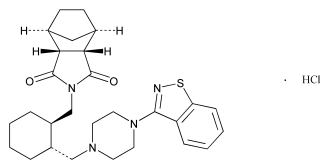
Lodenosine

Add the chemical structure to read:



Lurasidone Hydrochloride

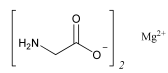
Change the chemical structure to read:



Magnesium Glycinate

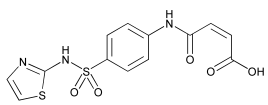
Add the CAS number and change the chemical structure to read:

CAS-14783-68-7.



Maleylsufathiazole

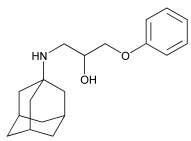
Add the chemical structure to read:



Mantabegron

Add the molecular weight and chemical structure to read:

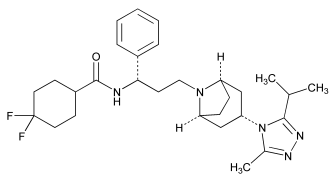
301.42.



Maraviroc

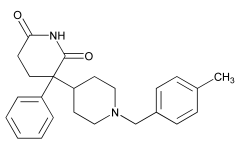
Add the molecular weight, change the chemical name, and add the chemical structure to read:

513.67. 4,4-Difluoro-*N*-[(1*S*)-3-{(1*R*,3*S*,5*S*)-3-[3-methyl-5-(propan-2-yl)-4*H*-1,2,4-triazol-4-yl]-8-azabicyclo[3.2.1]octan-8-yl}-1-phenylpropyl]cyclohexanecarboxamide.



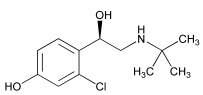
Meletimide

Change the chemical structure to read:



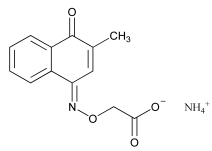
Meluadrine

Add the chemical structure to read:



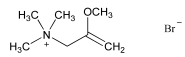
Menadoxime

Add the chemical structure to read:



Meprochol

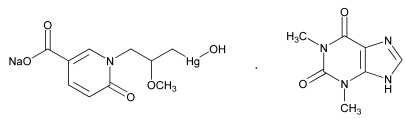
Add the chemical structure to read:



Meragidone Sodium

Add the chemical information and structure to read:

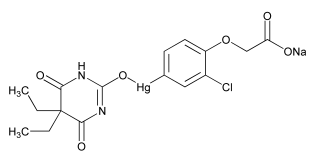
$C_{10}H_{12}HgNNaO_5 \cdot C_7H_8N_4O_2$. 629.95. (1) Mercurate(1-), (3-(5-carboxylato-1,2-dihydro-2-oxo-1-pyridinyl)-2-methoxypropyl) hydroxy-, sodium, compd. with 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione; (2) Sodium (3-(5-carboxylato-2-oxopyridin-1(2*H*)-yl)-2-methoxypropyl)(hydroxy) mercury compd. with theophylline.



Merbaphen

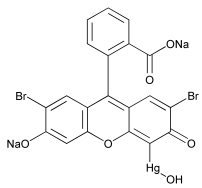
Add the chemical information and structure to read:

$C_{16}H_{16}ClHgN_2NaO_6$. 591.34. (1) Mercury(1-), (4-(carboxymethoxy)-3-chlorophenyl)(5,5-diethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrionato-*O*^{2})-, monosodium salt; (2) Sodium (4-(carboxylatomethoxy)-3-chlorophenyl)(5,5-diethyl-4,6-dioxo-1,4,5,6-tetrahydropyrimidin-2-yloxy)-mercury.



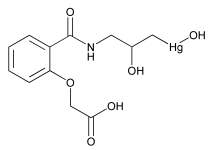
Merbromin

Add the chemical structure to read:



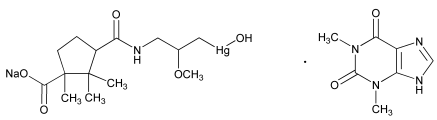
Mercuderamide

Add the chemical structure to read:



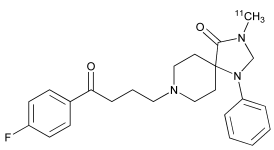
Mercurophylline

Add the chemical structure to read:



Mespiperone C 11

Add the chemical structure to read:



Synthetic Conjugated Estrogens, B

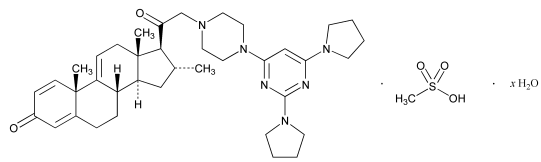
Change the chemical information to read:

Synthetic conjugated estrogens, B, contains the sodium sulfate forms of estrone, equilin, 17α-estradiol, 17α-dihydroequilin, 17β-dihydroequilin, 17α-dihydroequilenin, 17β-dihydroequilenin, equilenin, 17β-estradiol, and $\Delta^{8,9}$-dehydroestrone. The total percent label claim for the sum of estrone and equilin is 79.5%–88.0%. The individual levels for each component are the following: estrone 52.5%–61.5%, equilin 22.5%–30.5%, 17α-estradiol 2.5%–9.5%, 17α-dihydroequilin 13.5%–19.5%, 17β-dihydroequilin 0.5%–4.0%, 17α-dihydroequilenin 0.2%–3.25%, 17β-dihydroequilenin 0.2%–2.75%, equilenin 0.2%–5.5%, 17β-estradiol 0.2%–2.25%, and $\Delta^{8,9}$-dehydroestrone 0.2%–6.25%.

Tirilazad Mesylate

Change the chemical information and structure to read:

[*1993*] *Treatment of CNS trauma, stroke (lipid peroxidation inhibitor).* (Upjohn) ✧*U-74006F*



INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

[*Note—This index covers Vol. 32 No. 1, pp. 1–224; Vol. 32 No. 2, pp. 225–704; Vol. 32 No. 3, pp. 705–987; Vol. 32 No. 4, pp. 989–1388*]

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New Items at a Glance

See what's new in USP Reference Standards. For your convenient and quick reference, here's a list of Reference Standards released by USP over the past year.

This list is continuously updated with the newest Reference Standards released within the past 12 months.

Cat. No.	Description	Curr. Lot	Price
1006801	Acetone (1.5 mL/ampule; 3 ampules)	F0D028	$168
1011007	Acitretin (200 mg)	F0E266	$394
1011018	Acitretin Related Compound A (20 mg)	F0E264	$536
1011029	Acitretin Related Compound B (20 mg)	F0E265	$536
1012076	Acyclovir Related Compound A (50 mg) (AS)	F0F010	$535
1019712	Amiloride Related Compound A (30 mg) (AS)	F0E287	$526
1034909	Anecortave Acetate (200 mg)	F0E298	$168
1034910	Anecortave Acetate Related Compound A (20 mg)	F0E299	$526
1042102	L-Arabinitol (500 mg)	F0E311	$168
1065210	Berberine Chloride (50 mg)	F0E185	$281
1071202	Bicalutamide (200 mg)	F0E321	$168
1071213	Bicalutamide Related Compound A (25 mg)	F0E322	$526
1076465	Bromazepam **CIV** (100 mg) (AS)	F0F064	$224
1078201	Budesonide (200 mg)	F0E302	$168
1086301	Calcitriol (10 mg)	F0E062	$1,352
1087508	Camphor (1 g)	F0F030	$168
1496802	Parachlorophenol (500 mg)	F0E061	$168
1134346	Ciprofloxacin Related Compound A (25 mg) (AS)	F0E333	$526
1134390	Clarithromycin Identity (100 mg)	F0E141	$526
1145207	Cod Liver Oil (1 g)	F0D400	$168
1162148	Cytosine (100 mg)	F0E284	$168
1187954	2,4-Dichlorophenol (100 mg)	F0E113	$168
1241903	Erythritol (200 mg)	F0E313	$168
1249202	Escin (350 mg)	F0F088	$185
1268513	Etidronate Disodium Related Compound A (300 mg)	F0E227	$526
1270446	Fexofenadine Related Compound C (15 mg) (AS)	F0E291	$526
1273819	Flumazenil Related Compound A (20 mg)	F0E147	$675
1273820	Flumazenil Related Compound B (20 mg)	F0E148	$675
1285873	Fluticasone Propionate (100 mg)	F0F036	$832
1285884	Fluticasone Propionate Resolution Mixture (25 mg)	F0E123	$675
1285895	Fluticasone Propionate System Suitability Mixture (25 mg)	F0E122	$675
1285964	Fluvastatin Related Compound B (15 mg)	F0F017	$526
1285942	Fluvastatin for System Suitability (25 mg)	F0F016	$526
1287369	Gabapentin Related Compound E (25 mg)	F0E190	$526
1292303	Glimepiride (200 mg)	F0E228	$250
1292314	Glimepiride Related Compound A (20 mg)	F0E232	$526
1292325	Glimepiride Related Compound B (20 mg)	F0E233	$526
1292336	Glimepiride Related Compound C (20 mg)	F0E234	$526
1292347	Glimepiride Related Compound D (20 mg)	F0E235	$526
1295516	Glyburide Related Compound A (25 mg)	F0E224	$526
1313210	Hydrastine (10 mg)	F0E204	$281
1335010	Hyoscyamine Related Compound A (10 mg)	F0E250	$526
1349626	Isomalt (200 mg)	F0E263	$168
1379059	Mefloquine Hydrochloride (100 mg)	F0E165	$168
1379060	Mefloquine Related Compound A (20 mg)	F0E166	$526
1379401	Meloxicam (400 mg)	F0E158	$281
1379412	Meloxicam Related Compound A (25 mg)	F0E167	$526
1379423	Meloxicam Related Compound B (25 mg)	F0E168	$526
1379434	Meloxicam Related Compound C (30 mg)	F0E159	$526
1379445	Meloxicam Related Compound D (30 mg)	F0E160	$526
1396331	Metformin Related Compound B (25 mg)	F0F019	$526
1396342	Metformin Related Compound C (25 mg)	F0E343	$526
1424109	Methyl Alcohol (3 x 1.5 mL)	F0D015	$168
1460204	Neotame (200 mg)	F0F044	$168
1460215	Neotame Related Compound A (15 mg)	F0F045	$526
1473206	Norphenylephrine Hydrochloride (25 mg)	F0E205	$526
1478119	Ofloxacin Related Compound A (25 mg)	F0E276	$526
1478571	Ondansetron (300 mg)	F0E281	$225
1479010	Orphenadrine Related Compound A (50 mg) (AS)	F0F042	$526
1491015	Oxytetracycline Hydrochloride (200 mg) (AS)	F0E258	$168
1500353	Paroxetine System Suitability Mixture A (50 mg)	F0E150	$526
1524806	Phenol (500 mg)	F0F029	$168
1546401	Polyethylene Glycol 200 (1 g)	F0E316	$168
1546423	Polyethylene Glycol 300 (1 g)	F0E336	$168
1546445	Polyethylene Glycol 400 (1 g)	F0E344	$168
1546467	Polyethylene Glycol 600 (1 g)	F0E345	$168
1546489	Polyethylene Glycol 1000 (1 g)	F0F008	$168
1546503	Polyethylene Glycol 1500 (1 g)	F0F009	$168
1546525	Polyethylene Glycol 3000 (1 g)	F0F013	$168
1546547	Polyethylene Glycol 3350 (1 g)	F0F012	$168
1546569	Polyethylene Glycol 4000 (1 g)	F0F040	$168
1546580	Polyethylene Glycol 6000 (1 g)	F0F041	$168
1546605	Polyethylene Glycol 8000 (1 g)	F0F050	$168
1546627	Polyethylene Glycol 10000 (1 g)	F0F051	$168
1546649	Polyethylene Glycol 12000 (1 g)	F0F052	$168
1546650	Polyethylene Glycol 20000 (1 g)	F0F053	$168
1546660	Polyethylene Glycol 35000 (1 g)	F0F054	$168
1546966	Polyisobutylene (1 g)	F0E108	$168
1372402	Polyoxyl Lauryl Ether (500 mg)	F0E253	$168
1557000	Prednisolone Sodium Phosphate (100 mg)	F0E300	$168

New Items at a Glance *(Continued)*

Cat. No.	Description	Curr. Lot	Price
1598338	Ramipril Related Compound C (20 mg)	F0E157	$526
1598450	Ranitidine Resolution Mixture (20 mg)	F0E323	$1,052
1604803	Ritonavir (200 mg)	F0F049	$168
1605500	Ropivacaine Hydrochloride (200 mg)	F0E334	$168
1605512	Ropivacaine Related Compound A (25 mg)	F0E315	$526
1605523	Ropivacaine Related Compound B (50 mg)	F0E318	$526
1609013	Salicylic Acid Related Compound A (100 mg)	F0F108	$526
1612404	Sesame Oil (1 mL/ampule; 2 ampules) (AS)	F0E134	$168
1612415	Sesame Oil Related Compound A (6 mg/vial; 3 vials)	F0E131	$526
1612426	Sesame Oil Related Compound B (6 mg/vial; 3 vials)	F0E132	$526
1614363	Sodium Lauryl Sulfate (1 g) (AS)	F0D381	$168
1614670	Sodium Starch Glycolate Type B (400 mg)	F0E222	$168
1615708	Somatropin (8.63 USP Somatropin Units/vial)	F0E191	$182
1619017	Spironolactone Related Compound A (100 mg) (AS)	F0E184	$526
1642019	Sulindac Related Compound A (20 mg)	F0E314	$526
1642100	Sulisobenzone (500 mg)	F0F074	$194
1667280	Tiagabine Hydrochloride (300 mg)	F0E178	$260
1667235	Racemic Tiagabine Hydrochloride Mixture (25 mg)	F0E179	$526
1667224	Tiagabine Related Compound A (15 mg)	F0E177	$526
1667355	Tiamulin (100 mg)	F0E219	$168
1667541	Tinidazole Related Compound B (20 mg)	F0E274	$526
1672010	o-Toluenesulfonamide (200 mg)	F0E163	$263
1672020	p-Toluenesulfonamide (200 mg)	F0E162	$263
1682217	Triclosan Related Compounds Mixture A (1.2 mL/ampule; 3 ampules)	F0E292	$526
1705323	Ubidecarenone Related Compound A (15 mg)	F0E210	$526
1708718	Valproic Acid Related Compound B (50 mg) (AS)	F0E201	$526
1711428	Verapamil Related Compound D (50 mg)	F0E342	$526

New Lots in Distribution

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1012076	Acyclovir Related Compound A (50 mg) (AS) (2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-methoxy]ethyl acetate)	F0F010		1		n/f	$535
1076465	Bromazepam **CIV** (100 mg) (AS)	F0F064		1		[1812-30-2]	$224
1087508	Camphor (1 g)	F0F030	0.990 mg/mg (ai)	1		[464-49-3]	$168
1249202	Escin (350 mg)	F0F088	0.999 mg/mg (an)	1		[11072-93-8]	$185
1479010	Orphenadrine Related Compound A (50 mg) ((RS)-N,N-dimethyl-2-[(3-methylphenyl)-phenyl-methoxy]ethanamine citrate) (AS)	F0F042		1		n/f	$526
1524806	Phenol (500 mg)	F0F029	0.999 mg/mg (ai)	1		[108-95-2]	$168
1546467	Polyethylene Glycol 600 (1 g)	F0E345		1		[25322-68-3]	$168
1546489	Polyethylene Glycol 1000 (1 g)	F0F008		1		[25322-68-3]	$168
1546503	Polyethylene Glycol 1500 (1 g)	F0F009		1		[25322-68-3]	$168
1546569	Polyethylene Glycol 4000 (1 g)	F0F040		1		[25322-68-3]	$168
1546580	Polyethylene Glycol 6000 (1 g)	F0F041		1		[25322-68-3]	$168
1546605	Polyethylene Glycol 8000 (1 g)	F0F050		1		[25322-68-3]	$168
1546627	Polyethylene Glycol 10000 (1 g)	F0F051		1		[25322-68-3]	$168
1546649	Polyethylene Glycol 12000 (1 g)	F0F052		1		[25322-68-3]	$168
1546650	Polyethylene Glycol 20000 (1 g)	F0F053		1		[25322-68-3]	$168
1546660	Polyethylene Glycol 35000 (1 g)	F0F054		1		[25322-68-3]	$168
1604803	Ritonavir (200 mg)	F0F049	0.992 mg/mg (ai)	1		[155213-67-5]	$168
1609013	Salicylic Acid Related Compound A (100 mg) (4-hydroxybenzoic acid)	F0F108	0.99 mg/mg (ai)	1		[99-96-7]	$526
1642100	Sulisobenzone (500 mg)	F0F074	1.00 mg/mg (an)	1		[4065-45-6]	$194
1031401	Amoxapine (200 mg)	G1D375	1.000 mg/mg (dr)	2	G (03/07) F-1 (04/02)	[14028-44-5]	$168
1044403	Atenolol (200 mg)	I0F032	0.999 mg/mg (dr)	2	H1C320 (04/07) H (01/05) G (08/01)	[29122-68-7]	$168
1057507	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)	I0F027	1.00 mg/mg (dr)	2	H0B069 (02/07) G-4 (03/03)	[121-30-2]	$526
1078325	Bumetanide Related Compound A (10 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)	G0F031	0.99 mg/mg (ai)	2,3	F-2 (03/07) F-1 (05/00)	n/f	$526
1081501	Butamben (200 mg)	G0F059	1.000 mg/mg (dr)	2	F (01/07)	[94-25-7]	$168
1083008	2-*tert*-Butyl-4-hydroxyanisole (200 mg)	L1E348	0.996 mg/mg (ai)	2	L0C028 (03/07) K (09/03)	[88-32-4]	$168
1083100	3-*tert*-Butyl-4-hydroxyanisole (200 mg)	L0E259	0.997 mg/mg (ai)	2	K0C239(02/07) J (03/05) I-1 (09/01)	[121-00-6]	$168
1134313	Ciprofloxacin (200 mg)	H0E306	0.998 mg/mg (ai)	2,3	G-1 (02/07) G (05/01)	[85721-33-1]	$134
1134380	Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A)	G1E310		2	G (04/07) F (04/01)	n/f	$526
1138904	Clofazimine (200 mg)	F1C392	100.00%	2	F (03/07)	[2030-63-9]	$168
1171003	Denatonium Benzoate (200 mg)	I1F025	1.000 mg/mg (dr)	2	I0B129 (03/07) H (09/02)	[86398-53-0]	$168
1181302	Dextrose (500 mg)	J2E294	0.999 mg/mg (dr)	2	J-1 (04/07) J (11/02) I (08/99)	[50-99-7]	$134
1250008	Estradiol (500 mg)	M0E309	0.999 mg/mg (an)	2	L0C337 (03/07) K1B007 (07/05) K (04/03)	[50-28-2]	$168

New Lots in Distribution

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1260012	Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol)	G0E301	0.99 mg/mg (ai)	2	F0B252 (04/07)	n/f	$526
1286504	Fructose (125 mg)	I3E340	0.999 mg/mg (ai)	2	I-2 (04/07) I-1 (11/02) I (08/99)	[57-48-7]	$134
1286708	Fumaric Acid (200 mg)	H0E328	1.00 mg/mg (ai)	2	G-1 (03/07) G (04/02)	[110-17-8]	$168
1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)	J0E326	0.99 mg/mg (ai)	2	H (08/04) G-3 (03/01)	[3086-91-7]	$526
1287609	Gadopentetate Monomeglumine (500 mg)	F1F094	0.998 mg/mg (an)	2	F (12/06)	[92923-57-4]	$168
1295607	Glycerin (2 mL)	H1E032	1.00 mg/mg (ai)	2	H0C073 (03/07) G1A001 (04/04) G (12/02) F (04/99)	[56-81-5]	$168
1299007	Griseofulvin (200 mg)	I1D406	992 ug/mg (ai)	2	I (03/07) H-1 (09/02)	[126-07-8]	$168
1333003	Hydroxyzine Hydrochloride (500 mg)	J0F024	0.999 mg/mg (dr)	2	I0C385 (03/07) H (05/05)	[2192-20-3]	$168
1356665	Ketorolac Tromethamine (200 mg)	G1E331	1.000 mg/mg (dr)	2	G (04/07) F-2 (04/99)	[74103-07-4]	$168
1356654	Labetalol Hydrochloride (200 mg)	G1F090	0.998 mg/mg (dr)	2	G (02/07) F-2 (01/02) F-1 (03/01)	[32780-64-6]	$168
1358004	Leucovorin Calcium (500 mg)	K0F033	0.998 mg/mg (an)	2	J2B219 (04/07) J-1 (07/04) J (05/02)	[1492-18-8]	$173
1372005	L-Lysine Hydrochloride (200 mg)	I0E230	1.00 mg/mg (dr)	2	H (03/07) G (07/00)	[657-27-2]	$168
1441243	Metoprolol Related Compound B (50 mg) ((+/-)1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane)	G0E189		2	F0C377 (03/07)	n/f	$563
1443908	Milrinone (500 mg)	H0F083	0.999 mg/mg (an)	2	G0D340 (04/07) F0C050 (09/05)	[78415-72-2]	$281
1485191	Oxycodone **CII** (200 mg)	J0F026	0.990 mg/mg (dr)	2	I1D206 (03/07) I0B046 (08/05) H (01/03) G-1 (01/01)	[76-42-6]	$224
1492007	Palmitic Acid (500 mg)	K0F048		2	J0D329(01/07) I (12/05)	[57-10-3]	$168
1511000	Perphenazine (200 mg)	K0F018	0.998 mg/mg (dr)	2	J0B249 (04/07) I (10/03)	[58-39-9]	$168
1559006	Prednisone (250 mg)	N0E330	0.990 mg/mg (ai) (HPLC) 0.997 mg/mg (ai) (Spectrophotometric)	2	M0D211 (03/07) L1B251 (11/05) L (11/04) K-1 (01/02) K (02/00)	[53-03-2]	$168
1581504	Pseudoephedrine Sulfate (200 mg) **(List Chemical)**	H0E285	0.999 mg/mg (dr)	2	G1C135 (04/07) G (06/04) F-2 (05/02)	[7460-12-0]	$168
1623626	Sucralose (400 mg)	G1E317	0.998 mg/mg (ai)	2	G0B028 (02/07) F (04/03)	[56038-13-2]	$168
1667450	Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride)	H0F095	0.95 mg/mg (ai)	2	G (02/07)	n/f	$526
1673500	Trazodone Hydrochloride (200 mg)	G0F069	0.998 mg/mg (dr)	2	F-2 (04/07)	[25332-39-2]	$168

New Lots in Distribution

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1708707	Valproic Acid (500 mg)	L0E030	0.998 mg/mg (ai)	2	K0D224 (04/07) J1B127 (08/05) J (01/04) I-1 (11/00)	[99-66-1]	$168
1708762	Valsartan (350 mg)	G0F065	0.997 mg/mg (an)	2	F0C147 (03/07)	[137862-53-4]	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1000601	Acebutolol Hydrochloride (125 mg)	F-1				[34381-68-5]	$168
1001003	Acenocoumarol (200 mg)	G0D300			F (10/05)	[152-72-7]	$168
1001502	Acepromazine Maleate (250 mg)	F-2			F-1 (05/02)	[3598-37-6]	$168
1002505	Acesulfame Potassium (200 mg)	F0C136				[55589-62-3]	$281
1003009	Acetaminophen (400 mg)	J2C423	0.996 mg/mg (dr)		J-1 (04/06) J (05/02) I (05/99)	[103-90-2]	$134
1004001	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)	M0A029			L (06/04) K (02/00)	[103-84-4]	$81
1005004	Acetazolamide (2 g)	J1E041	0.997 mg/mg (dr)		J (02/06)	[59-66-5]	$168
1005706	Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D002	99.9% (ai)			[64-19-7]	$168
1006007	Acetohexamide (250 mg)	H			G-1 (06/99)	[968-81-0]	$168
1006506	Acetohydroxamic Acid (200 mg)	F-1			F (03/03)	[546-88-3]	$168
1006801	Acetone (1.5 mL/ampule; 3 ampules)	F0D028	0.997 mg/mg (ai)			[67-64-1]	$168
1007000	Acetophenazine Maleate (200 mg)	F-1				[5714-00-1]	$168
1008501	Acetylcholine Chloride (200 mg)				G (03/07)	[60-31-1]	$168
1009005	Acetylcysteine (200 mg)	H1B169			H (01/04)	[616-91-1]	$168
1009901	Acetyltributyl Citrate (500 mg)	G0C120			F (05/04)	[77-90-7]	$168
1009923	Acetyltriethyl Citrate (500 mg)	G0E085			F-1 (01/07) F (05/02)	[77-89-4]	$168
1011007	Acitretin (200 mg)	F0E266	0.998 mg/mg (ai)			[55079-83-9]	$394
1011018	Acitretin Related Compound A (20 mg) ((2Z,4E,6E,8E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid)	F0E264				[69427-46-9]	$536
1011029	Acitretin Related Compound B (20 mg) (ethyl (all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoate)	F0E265				[54350-48-0]	$536
1012065	Acyclovir (300 mg)	J0C149			I (06/04)	[59277-89-3]	$213
1012076	Acyclovir Related Compound A (50 mg) (AS) (2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-methoxy]ethyl acetate)	F0F010		1		n/f	$535
1012134	Ademetionine Disulfate Tosylate (500 mg)	F0D073				[97540-22-2]	$563
1012101	Adenine (200 mg)	G2D279	1.000 mg/mg (dr)		G-1 (12/05) G (06/00)	[73-24-5]	$168
1012123	Adenosine (200 mg)	G0C295			F1B058 (01/05) F (04/03)	[58-61-7]	$168
1012190	Adipic Acid (100 mg)	F0D318				[124-04-9]	$168
1012145	Agigenin (25 mg)	F				n/f	$526
1012203	Agnuside (25 mg)	F0D397	0.88 mg/mg (ai)			[11027-63-7]	$920
1012509	L-Alanine (200 mg)	G0E002	1.00 mg/mg (ai)		F-2 (08/06) F-1 (04/01)	[56-41-7]	$168
1012553	Albendazole (200 mg)	H0E240	0.996 mg/mg (dr)		G (10/06) F-1 (01/00)	[54965-21-8]	$168
1012600	Albuterol (200 mg)	I			H (12/00)	[18559-94-9]	$168
1012633	Albuterol Sulfate (200 mg)	J			I (04/00)	[51022-70-9]	$168
1012757	Alclometasone Dipropionate (300 mg)	H			G (01/00)	[66734-13-2]	$168
1012768	Alcohol (1.2 mL/ampule; 5 ampules)	F0D030				[64-17-5]	$168
1012772	Dehydrated Alcohol (1.2 mL/ampule; 5 ampules)	F0D031				[64-17-5]	$168

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1012699	Alcohol Determination–Acetonitrile (5 mL/ampule; 5 ampules)	F0C419	2% v/v (ai)			n/f	$168
1012688	Alcohol Determination–Alcohol (5 mL/ampule; 5 ampules)	F0C399	1.96% v/v (ai)			n/f	$168
1012780	Alendronate Sodium (200 mg)	G0D288	0.834 mg/mg (ai)		F0B315 (02/06)	[121268-17-5]	$168
1012906	Alfentanil Hydrochloride **CII** (500 mg)	F0B016				[70879-28-6]	$224
1012939	Allantoin (200 mg)	F0C169				[97-59-6]	$168
1012950	Alliin (25 mg)	F				[556-27-4]	$1,649
1013002	Allopurinol (250 mg)	J0C186			I-1 (01/05) I (07/02)	[315-30-0]	$168
1013024	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)	G			F-3 (05/02) F-2 (04/99)	n/f	$526
1013057	S-Allyl-L-Cysteine (25 mg)	F				n/f	$526
1014005	Alphaprodine Hydrochloride **CII** (250 mg)	F				[561-78-4]	$224
1015008	Alprazolam **CIV** (200 mg)	H1C133			H (06/05)	[28981-97-7]	$224
1016000	Alprostadil (25 mg)	H				[745-65-3]	$1,649
1017105	Altretamine (500 mg)	F				[645-05-6]	$168
1017502	Dried Aluminum Hydroxide Gel (200 mg)	F2B120			F-1 (01/04)	[21645-51-2]	$168
1017364	Aluminum Sulfate (2 g) (AS)	F0D342	55.3 % (ai)			[17927-65-0]	$168
1018505	Amantadine Hydrochloride (200 mg)	H1D207	0.998 mg/mg (ai)		H (02/06) G (04/01)	[665-66-7]	$168
1019202	Amcinonide (200 mg)	H0D346	0.995 mg/mg (ai)		G0B260 (06/06) F-1 (03/04)	[51022-69-6]	$168
1019417	Amifostine Disulfide (25 mg)	F0C152				[112901-68-5]	$526
1019508	Amikacin (300 mg)	J0E226	0.981 mg/mg (an)		I (10/06) H (08/00)	[37517-28-5]	$168
1019701	Amiloride Hydrochloride (500 mg)	H				[17440-83-4]	$168
1019712	Amiloride Related Compound A (30 mg) (AS) (Methyl 3,5-diamino-6-chloropyrazine-2-carboxylate)	F0E287				[1458-01-1]	$526
1019756	Aminobenzoate Potassium (200 mg)	F-1			F (06/01)	[138-84-1]	$168
1019767	Aminobenzoate Sodium (200 mg)	F				[55-06-6]	$168
1019803	Aminobenzoic Acid (200 mg) (p-aminobenzoic acid)	H1C083			H (10/04) G (10/00)	[150-13-0]	$168
1020008	Aminobutanol (500 mg)	G-1			G (06/99)	[96-20-8]	$421
1021000	Aminocaproic Acid (200 mg)	G0D101	0.997 mg/mg (dr)		F-4 (09/05)	[60-32-2]	$168
1022808	2-Amino-5-chlorobenzophenone (25 mg)	I			H-1 (01/03)	[719-59-5]	$526
1025205	Aminoglutethimide (200 mg)	F				[125-84-8]	$168
1025307	m-Aminoglutethimide (100 mg)	G			F (05/01)	n/f	$526
1025351	Aminohippuric Acid (200 mg)	F-1				[61-78-9]	$168
1025806	2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-d-glucose (25 mg)	F				n/f	$526
1025908	Aminopentamide Sulfate (200 mg)	F0B273				[60-46-8]	$168
1026004	m-Aminophenol (300 mg)	F				[591-27-5]	$526
1026401	Aminosalicylic Acid (125 mg)	F-1			F (03/99)	[65-49-6]	$134
1026605	3-Amino-2,4,6-triiodobenzoic Acid (50 mg)	G				[3119-15-1]	$526
1027007	5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid (50 mg)	F-1				[2280-89-9]	$526
1027302	Amiodarone Hydrochloride (200 mg)	F0D257	0.995 mg/mg (ai)			[19774-82-4]	$168
1028000	Amitraz (200 mg)	F0C042				[33089-61-1]	$168
1029002	Amitriptyline Hydrochloride (200 mg)	J0A004			I (03/03)	[549-18-8]	$168

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1029501	Amlodipine Besylate (200 mg)	F0D167	0.996 mg/mg (ai)			[111470-99-6]	$168
1029909	Ammonio Methacrylate Copolymer Type A (100 mg)	F-1			F (06/01)	[33434-24-1]	$168
1029910	Ammonio Methacrylate Copolymer Type B (100 mg)	F2C082			F-1 (06/05) F (05/00)	[33434-24-1]	$168
1029942	Ammonium Carbonate (2 g) (AS)	F0D102	33.3% NH3 (ai)			[8000-73-5]	$168
1029953	Ammonium Chloride (200 mg)	F0C134				[12125-02-9]	$168
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	100.0 % (ai)			[7783-28-0]	$168
1030001	Amobarbital **CII** (200 mg)	F-2				[57-43-2]	$224
1031004	Amodiaquine Hydrochloride (500 mg)	H0B238			G-1 (04/03)	[6398-98-7]	$168
1031401	Amoxapine (200 mg)	G1D375	1.000 mg/mg (dr)	2	G (03/07) F-1 (04/02)	[14028-44-5]	$168
1031503	Amoxicillin (200 mg)	J0C043			I (07/04)	[61336-70-7]	$168
1032007	Amphotericin B (125 mg)	J3C246	1009 ug/mg (dr)		J-2 (01/05) J-1 (07/02)	[1397-89-3]	$134
1033000	Ampicillin (200 mg)	J-1			J (12/01)	[69-53-4]	$168
1033203	Ampicillin Sodium (125 mg)	G-1			G (10/99)	[69-52-3]	$134
1033407	Ampicillin Trihydrate (200 mg)	G1D147			G (08/05)	[7177-48-2]	$168
1034002	Amprolium (200 mg)	G0C317	0.991 mg/mg (dr)		F-1 (04/05) F (04/02)	[121-25-5]	$168
1034308	Amrinone (500 mg)	G				[60719-84-8]	$168
1034320	Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyridin]-6(1H)-one)	F				[62749-46-6]	$526
1034341	Amrinone Related Compound B (100 mg) (N-(1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-yl)-2-hydroxypropanamide)	F-1			F (03/00)	n/f	$526
1034363	Amrinone Related Compound C (50 mg) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile)	F-1			F (05/00)	n/f	$526
1034909	Anecortave Acetate (200 mg)	F0E298	0.997 mg/mg (ai)			[7753-60-8]	$168
1034910	Anecortave Acetate Related Compound A (20 mg) (9(11)-dehydrocortisol)	F0E299				[10184-70-0]	$526
1036008	Anileridine Hydrochloride **CII** (250 mg)	F				[126-12-5]	$224
1036507	3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile (25 mg) (AS)	G2D383			G-1 (04/06)	[30078-48-9]	$526
1038003	Antazoline Phosphate (200 mg)	H			G-1 (04/02)	[154-68-7]	$168
1039006	Anthralin (200 mg)	I0B221			H (11/02)	[1143-38-0]	$168
1040005	Antipyrine (200 mg)	G			F-4 (09/01)	[60-80-0]	$168
1040708	Apigenin-7-glucoside (30 mg)	F				n/f	$526
1041008	Apomorphine Hydrochloride (250 mg)	H			G (01/03)	[41372-20-7]	$175
1041609	Apraclonidine Hydrochloride (100 mg)	H0B112			G (06/03)	[73218-79-8]	$518
1042000	Aprobarbital **CIII** (200 mg) (AS) **DISCONTINUED**				F-1 (02/07)	[77-02-1]	$224
1042102	L-Arabinitol (500 mg)	F0E311	1.00 mg/mg (an)			[7643-75-6]	$168
1042500	L-Arginine (200 mg)	G-1			G (09/00)	[74-79-3]	$168
1042601	Arginine Hydrochloride (125 mg)	G0B060			F-1 (05/03)	[1119-34-2]	$134
1042703	Arsanilic Acid (25 mg)	F				[98-50-0]	$168
1043003	Ascorbic Acid (1 g) (Vitamin C)	Q0B012			P (04/03)	[50-81-7]	$168
1043105	Ascorbyl Palmitate (2 g) (AS)	F0D326	0.988 mg/mg (ai)			[137-66-6]	$168
1043502	Asparagine Anhydrous (200 mg)	F0E013	1.00 mg/mg (dr)			[70-47-3]	$168
1043513	Asparagine Monohydrate (200 mg)	F0E012	1.00 mg/mg (ai)			[5794-13-8]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1043706	Aspartame (200 mg)	H1B125			H (05/03)	[22839-47-0]	$168
1043750	Aspartame Acesulfame (200 mg)	F0C137				[106372-55-8]	$168
1043728	Aspartame Related Compound A (25 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid)	I0D208	0.99 mg/mg (ai)		H (11/05) G-1 (10/99)	[5262-10-2]	$526
1043819	Aspartic Acid (100 mg)	F0B087				[6899-03-2]	$168
1044006	Aspirin (500 mg)	H			G-1 (11/02)	[50-78-2]	$168
1044301	Astemizole (200 mg)	F				[68844-77-9]	$168
1044403	Atenolol (200 mg)	I0F032	0.999 mg/mg (dr)	2	H1C320 (04/07) H (01/05) G (08/01)	[29122-68-7]	$168
1044651	Atovaquone (200 mg)	F0B190				[95233-18-4]	$168
1044662	Atovaquone Related Compound A (25 mg) (cis-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone)	F0B188				n/f	$526
1044800	Atracurium Besylate (100 mg)	F0B143				[64228-81-5]	$168
1045009	Atropine Sulfate (500 mg)	M0B098			L-2 (04/03) L-1 (06/02) L (10/00)	[5908-99-6]	$168
1045337	Avobenzone (500 mg)	G1E109	0.996 mg/mg (dr)		G0B280 (09/06) F (09/03)	[70356-09-1]	$168
1045508	Aurothioglucose (100 mg)	H0B224			G (10/03) F (12/01)	[12192-57-3]	$281
1045600	Azaerythromycin A (100 mg) (9-Deoxo-9a-aza-9a-homoerythromycin A)	G1D368			G (05/06) F-1 (02/02) F (02/99)	[76801-85-9]	$526
1045756	Azaperone (200 mg)	F				[1649-18-9]	$168
1045803	Azatadine Maleate (200 mg)	G0B300			F-1 (04/04) F (06/00)	[3978-86-7]	$168
1046001	Azathioprine (200 mg)	H			G-1 (02/00)	[446-86-6]	$168
1046056	Azithromycin (100 mg)	H0C212			G (11/04) F (06/00)	[117772-70-0]	$168
1046103	Azlocillin Sodium (200 mg)	F				[37091-65-9]	$168
1046147	Azo-aminoglutethimide (100 mg)	F				n/f	$526
1046205	Aztreonam (200 mg)	G0C077			F-1 (03/04)	[78110-38-0]	$168
1046307	Aztreonam E-Isomer (50 mg)	F1D056			F (04/05)	n/f	$526
1046409	Open Ring Aztreonam (25 mg)	G0D071			F (12/04)	[87500-74-1]	$526
1047300	Bacampicillin Hydrochloride (200 mg)	G0B053			F (11/02)	[37661-08-8]	$168
1047503	Bacitracin (1 g) (Susceptibility disk standard)	G1C254			G (07/04)	[1405-87-4]	$168
1048007	Bacitracin Zinc (200 mg)	N1E200	75.1 USP Bacitracin Units/mg (dr)		N0A024 (12/06) M-1 (11/02) M (02/00)	[1405-89-6]	$168
1048200	Baclofen (500 mg)	I				[1134-47-0]	$168
1048222	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)	H1C289			H (11/04)	n/f	$526
1048506	Beclomethasone Dipropionate (200 mg)	L0D312	0.992 mg/mg (dr)		K (02/06) J (12/00)	[5534-09-8]	$168
1048619	Benazepril Hydrochloride (125 mg)	G0E079	0.996 mg/mg (dr)		F0C250 (03/06)	[86541-74-4]	$168
1048620	Benazepril Related Compound A (15 mg) ((3R)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, monohydrochloride)	F0C252				n/f	$526

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1048630	Benazepril Related Compound B (15 mg) ((3S)-3-[[(1R)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid, monohydrochloride)	F0C256				n/f	$526
1048641	Benazepril Related Compound C (50 mg) ((3S)-3-[[(1S)-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine]-1-acetic acid)	F0C425	1.00 mg/mg (ai)			[86541-78-8]	$526
1049000	Bendroflumethiazide (200 mg)	H0C402	0.994 mg/mg (ai)		G-1 (06/05)	[73-48-3]	$168
1050009	Benoxinate Hydrochloride (200 mg)	F-2			F-1 (10/99)	[5987-82-6]	$134
1051001	Benzalkonium Chloride (5 mL of approx. 10% aqueous solution)	L0D209	Approx. 10% (w/v)		K0B151 (10/06) J (06/03)	[8001-54-5]	$168
1051500	Benzethonium Chloride (500 mg)	F0E104				[121-54-0]	$168
1054000	Benzocaine (500 mg)	J0C130			I (12/04)	[94-09-7]	$168
1055002	Benzoic Acid (300 mg)	G0D223	1.000 mg/mg (dr)		F6B173 (02/07) F-5 (03/04) F-4 (07/01)	[65-85-0]	$168
1056005	Benzonatate (1 g)	I0B003			H (01/03)	[104-31-4]	$168
1056504	1,4-Benzoquinone (200 mg)	G1B145			G (01/04) F-1 (11/01) F (09/00)	[106-51-4]	$168
1057507	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)	I0F027	1.00 mg/mg (dr)	2	H0B069 (02/07) G-4 (03/03)	[121-30-2]	$526
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272			F-1 (10/05)	[5411-22-3]	$224
1060002	Benzthiazide (200 mg)	F				[91-33-8]	$168
1061005	Benztropine Mesylate (200 mg)	I0C038			H (09/04)	[132-17-2]	$168
1061901	Benzyl Alcohol (500 mg/ampule)	G0B306			F0B106 (10/03)	[100-51-6]	$168
1062008	Benzyl Benzoate (5 g)	J0C060			I (05/04)	[120-51-4]	$168
1064003	1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride (25 mg)	F-1				n/f	$526
1065006	Bephenium Hydroxynaphthoate (500 mg)	F				[3818-50-6]	$168
1065210	Berberine Chloride (50 mg)	F0E185	0.81 mg/mg (ai)			[633-65-8]	$281
1065618	Betahistine Hydrochloride (200 mg)	F0C105				[5579-84-0]	$168
1065709	Betaine Hydrochloride (200 mg)	F-1			F (11/02)	[590-46-5]	$168
1066009	Betamethasone (200 mg)	K2C204			K-1 (10/04) K (11/02)	[378-44-9]	$168
1067001	Betamethasone Acetate (500 mg)	J0B079			I (08/03)	[987-24-6]	$168
1067307	Betamethasone Benzoate (200 mg)	F-1				[22298-29-9]	$168
1067704	Betamethasone Dipropionate (125 mg)	K0C229			J (04/04) I (03/99)	[5593-20-4]	$134
1068004	Betamethasone Sodium Phosphate (500 mg)	K0C358	0.993 mg/mg (an)		J0B043 (06/05) I-1 (02/03) I (01/01)	[151-73-5]	$168
1069007	Betamethasone Valerate (200 mg)	K0C330	0.997 mg/mg (ai)		J (07/05) I (05/00)	[2152-44-5]	$168
1069903	Betaxolol Hydrochloride (200 mg)	G			F-1 (06/00)	[63659-19-8]	$168
1070006	Betazole Hydrochloride (200 mg)	H				[138-92-1]	$168
1071009	Bethanechol Chloride (200 mg)	G1D088	1.00 mg/mg (dr)		G (03/05) F-3 (07/01)	[590-63-6]	$168
1071202	Bicalutamide (200 mg)	F0E321	0.999 mg/mg (ai)			[90357-06-5]	$168

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1071213	Bicalutamide Related Compound A (25 mg) (N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfinyl]-2-hydroxy-2-methyl-propanamide)	F0E322				n/f	$526
1071304	Bile Salts (10 g)	I0C003			H-1 (05/04) H (05/99)	[145-42-6]	$134
1071439	Positive Bioreaction (3 strips; 10 cm x 1 cm)	F0D014				n/f	$352
1071508	Biotin (200 mg)	I0D114	0.993 mg/mg (ai)		H1B019 (11/05) H (04/03)	[58-85-5]	$168
1072001	Biperiden (200 mg)	F2B080			F-1 (02/04)	[514-65-8]	$168
1073004	Biperiden Hydrochloride (200 mg)	G0E182	1.000 mg/mg (ai)		F-3 (08/06) F-2 (06/99)	[1235-82-1]	$168
1074007	Bisacodyl (125 mg)	I1B162			I (01/04) H-1 (02/99)	[603-50-9]	$134
1074700	2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine (25 mg)	F				n/f	$526
1075203	Bis(2-ethylhexyl)maleate (250 mg)	F-2			F-1 (01/01)	[142-16-5]	$526
1075509	p-Bis(di-n-propyl)carbamylbenzenesulfonamide (50 mg)	F				n/f	$526
1075531	Bismuth Citrate (100 mg)	F				[813-93-4]	$168
1075600	Bismuth Subcarbonate (1 g) (AS)	F0D324	98.4% (dr)			[5892-10-4]	$168
1075622	Bismuth Subgallate (2 g) (AS)	F0D323	54.2% Bi_2O_3 (dr)			[22650-86-8]	$168
1075644	Bismuth Subnitrate (1.5 g) (AS)	F0D388	81.7% Bi_2O_3 (dr)			[1304-85-4]	$168
1075553	Bismuth Subsalicylate (100 mg)	F1C394			F (08/05)	[14882-18-9]	$168
1075757	Bisoprolol Fumarate (200 mg)	G0D316	0.997 mg/mg (dr)		F0B038 (08/05)	[104344-23-2]	$168
1076206	Powdered Black Cohosh Extract (1.5 g)	F0D086				[84776-26-1]	$563
1076308	Bleomycin Sulfate (15 mg)	J0B213			I (01/04)	[9041-93-4]	$332
1076341	Boric Acid (1 g) (AS)	F0D036	100.0% (dr)			[10043-35-3]	$216
1076352	Bretylium Tosylate (200 mg)	F-1				[61-75-6]	$168
1076363	Brinzolamide (200 mg)	F0C034				[138890-62-7]	$168
1076374	Brinzolamide Related Compound A (50 mg) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide)	F0C033				n/f	$526
1076385	Brinzolamide Related Compound B (50 mg) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate)	F0C035				n/f	$526
1076465	Bromazepam **CIV** (100 mg) (AS)	F0F064		1		[1812-30-2]	$224
1076501	Bromocriptine Mesylate (150 mg)	I1C197			I (09/04)	[22260-51-1]	$168
1077005	Bromodiphenhydramine Hydrochloride (200 mg)	F-1				[1808-12-4]	$168
1077708	8-Bromotheophylline (400 mg)	G			F (07/02)	[10381-75-6]	$476
1078008	Brompheniramine Maleate (125 mg)	I1A036			I (01/03) H-1 (04/99)	[980-71-2]	$134
1078201	Budesonide (200 mg)	F0E302	0.997 mg/mg (ai)			[51333-22-3]	$168
1078303	Bumetanide (250 mg)	I0C111			H0B030 (05/04) G (03/03)	[28395-03-1]	$168
1078325	Bumetanide Related Compound A (10 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)	G0F031	0.99 mg/mg (ai)	2,3	F-2 (03/07) F-1 (05/00)	n/f	$526
1078336	Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid)	F-2			F-1 (01/03)	[28328-53-2]	$526

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1078507	Bupivacaine Hydrochloride (1 g)	H			G-2 (03/03) G-1 (08/02)	[14252-80-3]	$168
1078700	Buprenorphine Hydrochloride **CIII** (50 mg)	G0E026	0.995 mg/mg (ai)		F-1 (03/06) F (02/99)	[53152-21-9]	$224
1078711	Buprenorphine Related Compound A **CII** (50 mg) (21-[3-(1-propenyl)]-7alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine)	F1C076			F (04/04)	n/f	$526
1078733	Bupropion Hydrochloride (200 mg)	G0E048	0.998 mg/mg (ai)		F0C123 (02/06)	[31677-93-7]	$225
1078744	Bupropion Hydrochloride Related Compound A (15 mg) (2-(tert-butylamino)-4'-chloropropiophenone hydrochloride)	F0E082				n/f	$572
1078755	Bupropion Hydrochloride Related Compound B (15 mg) (2-(tert-butylamino)-3'-bromopropiophenone hydrochloride)	F0E011				n/f	$572
1078766	Bupropion Hydrochloride Related Compound C (40 mg) (1-(3-chlorophenyl)-2-hydroxy-1-propanone)	F0D293				n/f	$572
1078799	Bupropion Hydrochloride Related Compound F (30 mg) (1-(3-chlorophenyl)-1-hydroxy-2-propanone)	F0E076				n/f	$572
1078802	Buspirone Hydrochloride (200 mg)	H0B301			G (05/05)	[33386-08-2]	$168
1079000	Butabarbital **CIII** (200 mg)	H0C007			G (03/04)	[125-40-6]	$224
1080000	Butacaine Sulfate (600 mg)	F				[149-15-5]	$168
1081002	Butalbital **CIII** (200 mg)	H0C054			G2B077 (07/04) G-2 (06/03) G (05/02)	[77-26-9]	$224
1081501	Butamben (200 mg)	G0F059	1.000 mg/mg (dr)	2	F (01/07)	[94-25-7]	$168
1082300	Butoconazole Nitrate (200 mg)	F1B097			F (03/03)	[64872-77-1]	$168
1082504	Butorphanol Tartrate **CIV** (500 mg)	J			I (06/00)	[58786-99-5]	$224
1082708	Butylated Hydroxytoluene (500 mg) (AS)	F0D122	>99.0% (ai)			[128-37-0]	$168
1082800	Monotertiary-butyl-p-benzoquinone (100 mg) (FCC)	F				[3602-55-9]	$168
1082901	Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate (25 mg)	F-1				n/f	$526
1083008	2-*tert*-Butyl-4-hydroxyanisole (200 mg)	L1E348	0.996 mg/mg (ai)	2	L0C028 (03/07) K (09/03)	[88-32-4]	$168
1083100	3-*tert*-Butyl-4-hydroxyanisole (200 mg)	L0E259	0.997 mg/mg (ai)	2	K0C239(02/07) J (03/05) I-1 (09/01)	[121-00-6]	$168
1084000	Butylparaben (200 mg)	I0C139			H-1 (03/04) H (09/01)	[94-26-8]	$168
1085003	Caffeine (200 mg)	J1D241	0.998 mg/mg (ai)		J (02/06) I (06/02)	[58-08-2]	$168
1086006	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)	K0D372			J0B204 (11/06) I (03/04)	[58-08-2]	$100
1086108	Calcifediol (75 mg)	G1E064	0.996 mg/mg (ai) (as monohydrate)		G (07/06)	[63283-36-3]	$526
1086301	Calcitriol (10 mg)	F0E062	0.993 mg/mg (ai)			[32222-06-3]	$1,352
1086312	Calcitriol Solution (5 mL)	F0D330	0.974 ug/mL			n/f	$208
1086334	Calcium Acetate (1 g) (AS)	F0D156	100.0% (an)			[62-54-4]	$168
1086356	Calcium Ascorbate (200 mg)	F-1			F (08/01)	[5743-28-2]	$168
1086403	Calcium Carbonate (1 g) (AS)	F0D099	99.1% (dr)			[471-34-1]	$168

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1086436	Calcium Chloride (1 g) (AS)	F0D153	101.9% (ai)			[10035-04-8]	$168
1086800	Calcium Gluceptate (200 mg)	F-1			F (09/00)	[29039-00-7]	$168
1086855	Calcium Hydroxide (1 g) (AS)	F0D168	98.1% (ai)			[1305-62-0]	$168
1086888	Calcium Lactate (1 g)	F0D227				[63690-56-2]	$168
1086902	Calcium Lactobionate (200 mg)	G0B138			F-1 (01/04) F (11/01)	[110638-68-1]	$168
1086935	Calcium Levulinate (1 g) (AS)	F0E142	98.6% (dr)			[5743-49-7]	$168
1087009	Calcium Pantothenate (200 mg) (Vitamin B5)	O0C331	0.990 mg/mg (dr)		N-1 (06/05) N (06/00)	[137-08-6]	$168
1087031	Tribasic Calcium Phosphate (1 g) (AS)	F0D394	37.2 % Ca (ai)			[12167-74-7]	$168
1087202	Calcium Saccharate (200 mg)	F				[5793-89-5]	$168
1087359	Calcium Stearate (2 g) (AS)	F0D255	9.8% CaO (ai)			[1592-23-0]	$168
1087406	Calcium Sulfate (1 g) (AS)	F0D236	100.0% (dr)			[10101-41-4]	$168
1087508	Camphor (1 g)	F0F030	0.990 mg/mg (ai)	1		[464-49-3]	$168
1087701	Candelilla Wax (250 mg)	F0D123				[8006-44-8]	$168
1088001	Candicidin (200 mg)	F				[1403-17-4]	$168
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2				[13956-29-1]	$526
1090003	Cannabinol **CI** (25 mg) (AS)				F-2 (05/02)	[521-35-7]	$224
1091006	Capreomycin Sulfate (250 mg)	G			F (06/01)	[1405-37-4]	$168
1091040	Caprylic Acid (300 mg)	F0D378				[124-07-2]	$168
1091505	Caprylocaproyl Polyoxylglycerides (200 mg)	F0C312				n/f	$189
1091108	Capsaicin (100 mg)	G2D136	0.985 mg/mg (dr)		G-1 (07/05) G (03/02) F-1 (06/00) F (03/99)	[404-86-4]	$168
1091200	Captopril (200 mg)	H				[62571-86-2]	$168
1091221	Captopril Disulfide (100 mg)	G1B066			G (01/04)	[64806-05-9]	$526
1092009	Carbachol (200 mg)	G1E010	1.000 mg/mg (dr)		G (07/06)	[51-83-2]	$168
1093001	Carbamazepine (100 mg)	K0E209	0.999 mg/mg (ai)		J (11/06) I-1 (02/00)	[298-46-4]	$168
1093205	Carbarsone (200 mg)	F				[121-59-5]	$168
1093500	Carbenicillin Indanyl Sodium (300 mg)	G				[26605-69-6]	$168
1094004	Carbenicillin Monosodium Monohydrate (200 mg)	G-2				n/f	$168
1095506	Carbidopa (400 mg)	I			H (10/99)	[38821-49-7]	$168
1095517	Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)	H0B121			G (04/03)	n/f	$526
1096000	Carbinoxamine Maleate (200 mg)	H			G-1 (11/02)	[3505-38-2]	$168
1096407	Carboplatin (100 mg)	H0C240			G (07/04) F (03/00)	[41575-94-4]	$172
1096509	Carboprost Tromethamine (25 mg)	F-1			F (02/01)	[58551-69-2]	$526
1096531	Carboxymethylcellulose Calcium (1.5 g) (AS)	F0D336				[9050-04-8]	$168
1096553	Carboxymethylcellulose Sodium (1.5 g)	F0D357				[9004-32-4]	$168
1096600	Carisoprodol (1 g)	G			F-2 (05/02)	[78-44-4]	$168
1096699	Carprofen (200 mg) (AS)	F0D335				[53716-49-7]	$168
1096757	Carteolol Hydrochloride (200 mg)	F-1			F (11/00)	[51781-21-6]	$168
1096779	Casticin (25 mg)	F0D358	0.99 mg/mg (ai)			[479-91-4]	$957
1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I				[76333-53-4]	$605

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1096906	Cefaclor (400 mg)	I0E145	0.994 mg/mg HPLC (an) 1.000 mg/mg UV (an)		H (11/06)	[70356-03-5]	$168
1096917	Cefaclor, Delta-3-Isomer (30 mg)	G			F-1 (02/00)	n/f	$526
1097104	Cefadroxil (125 mg)	I1B319	935 ug/mg (ai)		I (01/05) H (04/99)	[66592-87-8]	$134
1097308	Cefamandole Lithium (200 mg)	H				n/f	$168
1097400	Cefamandole Nafate (200 mg)	H				[42540-40-9]	$168
1097501	Cefamandole Sodium (250 mg)	F				[30034-03-8]	$168
1097603	Cefazolin (400 mg)	L0C345			K (04/05) J (06/00)	[25953-19-9]	$168
1097636	Cefepime Hydrochloride (500 mg)	G0D116	860 ug/mg (an)		F0C063 (06/05)	[123171-59-5]	$168
1097647	Cefepime Hydrochloride System Suitability (25 mg)	F0C095				n/f	$526
1097658	Cefixime (500 mg)	F				[79350-37-1]	$168
1097771	Cefmenoxime Hydrochloride (350 mg)	F				[75738-58-8]	$168
1097782	Cefmetazole (200 mg)	G0E260	0.988 mg/mg (ai)		F-1 (09/06) F (04/02)	[56796-20-4]	$168
1097750	Cefonicid Sodium (1 g)	H0D105	887 ug/mg (an)		G (06/05)	[61270-78-8]	$168
1097705	Cefoperazone Dihydrate (200 mg)	H			G (12/99)	[62893-19-0]	$168
1097807	Ceforanide (200 mg)	F-1			F (07/00)	[60925-61-3]	$168
1097909	Cefotaxime Sodium (250 mg)	J0C189	901 ug/mg (ai)		I (11/04)	[64485-93-4]	$134
1097975	Cefotetan (500 mg)	H0C175			G (07/04) F (09/00)	[69712-56-7]	$168
1098005	Cefotiam Hydrochloride (325 mg)	G0B050			F (01/03)	[66309-69-1]	$168
1098107	Cefoxitin (500 mg)	J0E038	0.992 mg/mg (an)		I (05/06) H (05/00)	[35607-66-0]	$168
1098118	Cefpiramide (300 mg)	F0C203				[70797-11-4]	$168
1098027	Cefpodoxime Proxetil (350 mg)	F0C192	736 ug/mg (an)			[87239-81-4]	$168
1098049	Cefprozil (E)-Isomer (50 mg)	G0D341	872 ug/mg (ai)		F2C284 (08/05) F-1 (10/04) F (05/01)	[92676-86-3]	$526
1098050	Cefprozil (Z)-Isomer (200 mg)	H0E054	927 ug/mg (ai)		G0C037(06/06) F (12/03)	[121412-77-9]	$168
1098129	Ceftazidime, Delta-3-Isomer (15 mg)	H0E106			G (06/06) F (03/00)	n/f	$526
1098130	Ceftazidime Pentahydrate (300 mg)	H			G (12/99)	[78439-06-2]	$168
1098173	Ceftizoxime (350 mg)	I0E262	0.999 mg/mg (an)		H (12/06)	[68401-81-0]	$168
1098184	Ceftriaxone Sodium (350 mg)	G1D265	925 ug/mg (an)		G0B264 (03/06) F (08/03)	[104376-79-6]	$168
1098195	Ceftriaxone Sodium E-Isomer (25 mg)	I0C190			H (07/04) G (08/01) F-1 (02/00)	n/f	$526
1098209	Cefuroxime Sodium (200 mg)	H			G-1 (05/00)	[56238-63-2]	$168
1098220	Cefuroxime Axetil (500 mg)	G			F-1 (05/02)	[64544-07-6]	$168
1098231	Cefuroxime Axetil Delta-3-Isomers (15 mg)	H1E186			H0B160 (09/06) G (03/03)	n/f	$526
1098322	Cellaburate (350 mg) (Cellulose Acetate Butyrate)	F0D220				[9004-36-8]	$168
1098300	Cellulose Acetate (125 mg)	F-1			F (11/99)	[9004-35-7]	$134

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1098355	Cellulose Acetate Phthalate (125 mg)	F-1			F (03/99)	[9004-38-0]	$134
1098388	Microcrystalline Cellulose (1 g) (AS)	F0D362				[9004-34-6]	$168
1098402	Powdered Cellulose (1 g) (AS)	F0D364				[9004-34-6]	$168
1098708	Cephaeline Hydrobromide (200 mg)	G-1				n/f	$526
1099008	Cephalexin (400 mg)	J0D296	996 ug/mg (an)		I-2 (10/05) I-1 (03/00)	[23325-78-2]	$168
1102000	Cephalothin Sodium (200 mg)	I				[58-71-9]	$168
1102408	Cephapirin Benzathine (100 mg)	F				[97468-37-6]	$168
1102500	Cephapirin Sodium (200 mg)	I-1			I (07/02)	[24356-60-3]	$168
1102805	Cephradine (200 mg)	J			I (04/00)	[58456-86-3]	$168
1103003	Cetyl Alcohol (100 mg)	I1E065			I (07/06) H (03/99)	[36653-82-4]	$168
1103105	Cetyl Palmitate (50 mg)	F0B241				[540-10-3]	$168
1104006	Cetylpyridinium Chloride (500 mg)	J0D299	1.000 mg/mg (an)		I (10/05) H-1 (06/01) H (08/99)	[6004-24-6]	$168
1105009	Powdered Chaste Tree Extract (1.5 g)	F0C406				[91722-47-3]	$563
1106001	Chlorambucil (125 mg) (FOR U.S. SALE ONLY)	G			F-1 (02/99)	[305-03-3]	$134
1107004	Chloramphenicol (200 mg)	N1C074			N (10/04) M (03/00)	[56-75-7]	$168
1107300	Chloramphenicol Palmitate (200 mg)	G-1				[530-43-8]	$168
1107401	Chloramphenicol Palmitate Nonpolymorph A (200 mg)	F-1				[530-43-8]	$526
1107503	Chloramphenicol Palmitate Polymorph A (100 mg)	G1D219			G (10/05) F (08/99)	[530-43-8]	$526
1109000	Chlordiazepoxide **CIV** (200 mg)	I0B063			H-1 (03/03)	[58-25-3]	$224
1110009	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4				[438-41-5]	$224
1110020	Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide)	G				[963-39-3]	$526
1111001	Chlorhexidine (200 mg)	F0C306				[55-56-1]	$168
1111103	Chlorhexidine Acetate (500 mg)	G0E008	0.996 mg/mg (an)		F0C281 (02/06)	[56-95-1]	$168
1111307	Chlorhexidine Related Compounds (50 mg)	F0D017				n/f	$526
1112503	Chlorobutanol (200 mg)	G1D301			G (09/05) F-3 (12/01)	[6001-64-5]	$168
1115545	Chlorogenic Acid (50 mg)	F0C420	0.97 mg/mg (ai)			[327-97-9]	$168
1115556	beta-Chlorogenin (20 mg)	F				n/f	$526
1496802	Parachlorophenol (500 mg)	F0E061	0.99 mg/mg (ai)			[106-48-9]	$168
1117008	Chloroprocaine Hydrochloride (200 mg)	G0B285			F-3 (01/04) F-2 (03/99)	[3858-89-7]	$168
1118000	Chloroquine Phosphate (500 mg)	I			H (10/99)	[50-63-5]	$168
1121005	Chlorothiazide (200 mg)	H1E231	0.992 mg/mg HPLC (dr) 1.000 mg/mg UV (dr)		H0B161 (11/06) G (04/03)	[58-94-6]	$168
1122008	Chlorotrianisene (1 g)	F				[569-57-3]	$168
1122700	Chloroxylenol (125 mg)	F2C259			F-1 (07/04) F (10/99)	[88-04-0]	$134
1122722	Chloroxylenol Related Compound A (25 mg) (2-chloro-3,5-dimethylphenol)	G0C275			F-1 (07/04)	[5538-41-0]	$526
1123000	Chlorpheniramine Maleate (125 mg)	M0B020			L-1 (06/03)	[113-92-8]	$134

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1123102	Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) (60 Tablets)	G0B259			F (06/03)	[113-92-8]	$168
1124003	Chlorphenoxamine Hydrochloride (200 mg)	F-1				[562-09-4]	$168
1125006	Chlorpromazine Hydrochloride (200 mg)	J			I (04/99)	[69-09-0]	$168
1126009	Chlorpropamide (200 mg)	H				[94-20-2]	$168
1127001	Chlorprothixene (200 mg)	F-1				[113-59-7]	$168
1129007	Chlortetracycline Hydrochloride (200 mg)	K0C185	1008 ug/mg (ai)		J-1 (12/04) J (02/02)	[64-72-2]	$168
1130006	Chlorthalidone (200 mg)	I0C255			H-1 (11/04) H (07/99)	[77-36-1]	$168
1119309	Chlorthalidone Related Compound A (15 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid)	I0E270	0.99 mg/mg (ai)		H0D251 (12/06) G0C376 (09/05) F-3 (07/04)	n/f	$526
1130505	Chlorzoxazone (500 mg)	I			H (07/01)	[95-25-0]	$168
1130527	Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol)	G-1			G (11/00)	[95-85-2]	$526
1131009	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157			L (10/03) K (09/99)	[67-97-0]	$172
1131803	Delta-4,6-cholestadienol (30 mg)	F				[14214-69-8]	$526
1132001	Cholesteryl Caprylate (200 mg)	F				[1182-42-9]	$168
1133004	Cholestyramine Resin (500 mg)	I				[11041-12-6]	$134
1133503	Cholic Acid (2 g) (AS)	F3B159			F-2 (01/03)	[81-25-4]	$168
1133536	Choline Bitartrate (200 mg)	F0C057				[87-67-2]	$168
1133547	Choline Chloride (200 mg)	F0C058				[67-48-1]	$168
1133570	Chondroitin Sulfate Sodium (300 mg)	G0E236	1.00 mg/mg (dr)		F0B256 (09/06)	[39455-18-0]	$168
1133638	Chromium Picolinate (100 mg)	F				[14639-25-9]	$168
1134007	Chymotrypsin (300 mg)	I			H (06/01)	[9004-07-3]	$168
1134018	Ciclopirox (50 mg)	F0E086				[29342-05-0]	$168
1134030	Ciclopirox Olamine (125 mg)	H0C207			G (05/03)	[41621-49-2]	$134
1134029	Ciclopirox Related Compound A (25 mg) (3-Cyclohexyl-4,5-dihydro-5-methyl-5-isoxazolyl acetic acid)	F0E087	1.00 mg/mg (ai)			n/f	$526
1134040	Ciclopirox Related Compound B (25 mg) (6-Cyclohexyl-4-methyl-2-pyrone)	F0E088	0.99 mg/mg (ai)			[14818-35-0]	$526
1134051	Cilastatin Ammonium Salt (100 mg)	G0C334	945 ug/mg (ai)		F-1 (05/05) F (07/00)	n/f	$168
1134062	Cimetidine (200 mg)	I1C081			I (05/04)	[51481-61-9]	$168
1134073	Cimetidine Hydrochloride (200 mg)	F				[70059-30-2]	$168
1134109	Cinoxacin (200 mg)	F				[28657-80-9]	$168
1134313	Ciprofloxacin (200 mg)	H0E306	0.998 mg/mg (ai)	2,3	G-1 (02/07) G (05/01)	[85721-33-1]	$134
1134324	Ciprofloxacin Ethylenediamine Analog (25 mg)	J0A030			I (01/03) H-1 (02/99)	n/f	$526
1134335	Ciprofloxacin Hydrochloride (400 mg)	I0C265			H (02/05) G (04/00)	[86393-32-0]	$168
1134346	Ciprofloxacin Related Compound A (25 mg) (AS) (7-Chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride salt)	F0E333				n/f	$526
1134357	Cisplatin (100 mg)	H			G (03/01)	[15663-27-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1134368	Citric Acid (200 mg)	F2E269	1.000 mg/mg (dr)		F1B092 (07/06) F-1 (01/04) F (07/02)	[77-92-9]	$168
1134379	Clarithromycin (75 mg)	G0D356	977 ug/mg (ai)		F4B183 (03/06) F-3 (01/04) F-2 (09/01)	[81103-11-9]	$168
1134390	Clarithromycin Identity (100 mg)	F0E141				[81103-11-9]	$526
1134380	Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A)	G1E310		2	G (04/07) F (04/01)	n/f	$526
1134404	Clavam-2-carboxylate Potassium (1 Pellet)	H0C089			G0B225 (12/03) F (10/03)	n/f	$526
1134426	Clavulanate Lithium (200 mg)	I1C270	0.952 mg/mg (ai)		I (02/05) H (09/02)	n/f	$168
1134506	Clemastine Fumarate (250 mg)	J0C090	0.998 mg/mg (ai)		I (09/06) H (10/00)	[14976-57-9]	$168
1135000	Clidinium Bromide (2 g)	H0B115			G (03/05)	[3485-62-9]	$168
1135021	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)	I				[76201-95-1]	$526
1136002	Clindamycin Hydrochloride (200 mg)	H0E044	867 ug/mg (ai)		G4A017 (07/06) G-3 (07/03) G-2 (05/99)	[58207-19-5]	$463
1137005	Clindamycin Palmitate Hydrochloride (500 mg)	G0D334	586 ug/mg (an)		F-2 (11/05)	[25507-04-4]	$463
1138008	Clindamycin Phosphate (125 mg)	I0C165			H-3 (04/04) H-2 (07/03) H-1 (02/99)	[24729-96-2]	$232
1138201	Clioquinol (500 mg)	N0E020	0.992 mg/mg (dr)		M (03/06) L-1 (01/03)	[130-26-7]	$168
1138405	Clobetasol Propionate (200 mg)	F2C309	980 ug/mg (ai)		F-1 (03/05) F (10/01)	[25122-46-7]	$168
1138427	Clobetasol Propionate Related Compound A (50 mg) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one])	F2C417			F-1 (12/05) F (01/03)	n/f	$526
1138507	Clocortolone Pivalate (200 mg)	G				[34097-16-0]	$168
1138904	Clofazimine (200 mg)	F1C392	100.00%	2	F (03/07)	[2030-63-9]	$168
1139000	Clofibrate (1 g)	I			H (04/01)	[637-07-0]	$168
1140000	Clomiphene Citrate (500 mg)	I0E164	0.995 mg/mg (an) (HPLC) 1.000 mg/mg (an) (UV)		H (05/06) G-1 (10/99)	[50-41-9]	$168
1140101	Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine Hydrochloride)	F1B206			F (09/03)	n/f	$526
1140247	Clomipramine Hydrochloride (200 mg)	F0C075				[17321-77-6]	$168
1140305	Clonazepam **CIV** (200 mg)	H0E003	0.999 mg/mg (ai)		G1B175 (04/06) G (01/04) F-2 (01/00)	[1622-61-3]	$224
1140327	Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril)	G2B110			G-1 (01/04) G (02/99)	n/f	$526
1140338	Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone)	H			G (04/01)	[2011-66-7]	$526
1140349	Clonazepam Related Compound C (25 mg) (2-Bromo-2'-(2-chlorobenzoyl)-4'-nitroacetanilide)	F0C340				n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1140393	Clonidine (200 mg)	F0C401				[4205-90-7]	$168
1140407	Clonidine Hydrochloride (200 mg)	H0D106	1.000 mg/mg (dr)		G (05/05)	[4205-91-8]	$168
1140418	Clonidine Related Compound A (25 mg) (Acetylclonidine)	F0C373				[54707-71-0]	$526
1140429	Clonidine Related Compound B (25 mg) (2-[(E)-2,6-Dichlorophenylimino]-1-(1-{2-[(E)-2,6-dichlorophenylimino]-imidazolidin-1-yl}-ethyl)-imidazolidine)	F0C403	0.99 mg/mg (ai)			n/f	$526
1140430	Clopidogrel Bisulfate (125 mg)	F0E115	0.995 mg/mg (ai)			[120202-66-6]	$753
1140586	Clopidogrel Related Compound A (20 mg) ((S)-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetic acid, hydrochloride)	F0E117	1.18 mg/mg (bisulfate salt equivalent) (ai)			[144750-42-5]	$640
1140597	Clopidogrel Related Compound B (20 mg) (Methyl(+/-)-(o-chlorophenyl)-4,5-dihydrothieno[2,3-c]pyridine-6(7H)-acetate, hydrochloride)	F0E119	1.11 mg/mg (bisulfate salt equivalent) (ai)			[144750-52-7]	$640
1140600	Clopidogrel Related Compound C (20 mg) (methyl (-)-(R)-(o-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate, hydrogen sulfate)	F0E118	0.99 mg/mg (ai)			[120202-71-3]	$640
1140509	Clorazepate Dipotassium **CIV** (125 mg)	G0B027			F-1 (06/03) F (12/99)	[57109-90-7]	$224
1140702	Clorsulon (200 mg)	F1B084			F (01/04)	[60200-06-8]	$168
1141002	Clotrimazole (200 mg)	K0C282			J (02/05) I (05/99)	[23593-75-1]	$134
1141024	Clotrimazole Related Compound A (25 mg) ((o-chlorophenyl)diphenylmethanol)	I1D166	0.99 mg/mg (ai)		I (11/05) H (10/01) G-1 (02/99)	[66774-02-5]	$526
1141909	Cloxacillin Benzathine (200 mg)	F-1			F (03/02)	[23736-58-5]	$168
1142005	Cloxacillin Sodium (200 mg)	L0B086			K (01/04)	[7081-44-9]	$168
1142107	Clozapine (100 mg)	G0D315	1.000 mg/mg (dr)		F0C032 (11/05)	[5786-21-0]	$281
1143008	Cocaine Hydrochloride **CII** (250 mg)	I0B074			H-2 (01/04) H-1 (02/99)	[53-21-4]	$224
1145207	Cod Liver Oil (1 g)	F0D400				[8001-69-2]	$168
1143802	Codeine N-Oxide **CI** (50 mg)	G0A034			F-1 (11/02)	[3688-65-1]	$224
1144000	Codeine Phosphate **CII** (100 mg)	J0C200			I-1 (10/04) I (09/02) H-1 (01/00)	[41444-62-6]	$224
1145003	Codeine Sulfate **CII** (250 mg)	H-2			H-1 (01/02)	[6854-40-6]	$224
1146006	Colchicine (300 mg)	J			I (05/02)	[64-86-8]	$168
1146505	Colestipol Hydrochloride (200 mg)	F-1				[37296-80-3]	$168
1147009	Colistimethate Sodium (200 mg)	H1D234	0.420 mg/mg (dr)		H (09/05)	[8068-28-8]	$168
1148001	Colistin Sulfate (200 mg)	G-1			G (09/99)	[1264-72-8]	$168
1148500	Copovidone (100 mg)	F0C194				[2586-89-9]	$168
1148806	Corn Oil (1 g) (AS)	F0D181				[8001-30-7]	$168
1149004	Corticotropin (5.6 Units/vial; 5 vials)	M			L (06/99)	[9002-60-2]	$134
1150003	Cortisone Acetate (150 mg)	I				[50-04-4]	$168
1150207	Cottonseed Oil (1 g) (AS)	F0D173				[8001-29-4]	$168
1150353	Creatinine (100 mg)	F				[60-27-5]	$168
1150502	Cromolyn Sodium (500 mg)	J1E187	1.000 mg/mg (an)		J (11/06) I (06/00)	[15826-37-6]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1150513	Cromolyn Sodium Related Compound A (25 mg) (1,3-Bis-(2-acetyl-3-hydroxyphenoxy)-2-propanol) (AS)	F0E045				[16150-44-0]	$526
1150706	Crospovidone (200 mg)	G1C273			G (12/04)	[9003-39-8]	$168
1151006	Crotamiton (200 mg)	H-1			H (07/00)	[483-63-6]	$168
1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N			M-3 (08/99)	[68-19-9]	$168
1152508	Cyclacillin (200 mg)	G				[3485-14-1]	$168
1152701	Cyclandelate (200 mg)	F0C384				[456-59-7]	$168
1154004	Cyclizine Hydrochloride (200 mg)	H0D321	1.000 mg/mg (dr)		G (10/05)	[303-25-3]	$168
1154503	Cyclobenzaprine Hydrochloride (200 mg)	G0A013			F-3 (07/03)	[6202-23-9]	$168
1154558	Alpha Cyclodextrin (50 mg)	F-1			F (10/00)	[10016-20-3]	$168
1154569	Beta Cyclodextrin (250 mg)	G			F-1 (12/02)	[7585-39-9]	$168
1154707	Cyclomethicone 4 (200 mg)	F-2			F-1 (06/02)	[69430-24-6]	$168
1154809	Cyclomethicone 5 (200 mg)	G0D052			F-2 (07/05) F-1 (09/99)	[69430-24-6]	$168
1154900	Cyclomethicone 6 (200 mg)	F2B024			F-1 (03/03)	[69430-24-6]	$168
1156000	Cyclopentolate Hydrochloride (300 mg)	I0C424	0.999 mg/mg (dr)		H (03/05) G (04/00)	[5870-29-1]	$168
1157002	Cyclophosphamide (500 mg) (FOR U.S. SALE ONLY)	J1B200			J (02/05)	[6055-19-2]	$134
1157501	2-Cyclopropylmethylamino-5-chlorobenzophenone (50 mg)	F				n/f	$526
1158005	Cycloserine (200 mg)	G				[68-41-7]	$168
1158504	Cyclosporine (50 mg)	H-1			H (11/02) G-2 (03/00)	[59865-13-3]	$518
1158650	Cyclosporine Resolution Mixture (25 mg)	F				[108027-45-8] (U)	$445
1159008	Cyclothiazide (200 mg)	F-1				[2259-96-3]	$168
1161000	Cyproheptadine Hydrochloride (500 mg)	G			F-4 (11/02)	[41354-29-4]	$168
1161509	L-Cysteine Hydrochloride (200 mg)	H			G (05/00)	[7048-04-6]	$168
1162002	Cytarabine (250 mg)	G-2			G-1 (07/00)	[147-94-4]	$168
1162148	Cytosine (100 mg)	F0E284	1.00 mg/mg (dr)			[71-30-7]	$168
1162308	Dacarbazine (125 mg)	H			G (01/99)	[4342-03-4]	$134
1162320	Dacarbazine Related Compound A (50 mg) (5-aminoimidazole-4-carboxamide Hydrochloride)	H0C052			G (03/04) F (03/00)	[72-40-2]	$526
1162330	Dacarbazine Related Compound B (50 mg) (2-azahypoxanthine)	G0C325			F-1 (03/05) F (12/01)	[63907-29-9]	$649
1162400	Dactinomycin (50 mg)	I				[50-76-0]	$462
1162501	Danazol (200 mg)	H			G (10/00)	[17230-88-5]	$168
1164008	Dapsone (125 mg)	H0D260	0.998 mg/mg (dr)		G-3 (02/06) G-2 (08/99)	[80-08-0]	$134
1164700	Daunorubicin Hydrochloride (200 mg)	L0B307			K (11/03) J (08/00)	[23541-50-6]	$518
1165000	Decamethonium Bromide (250 mg)	F				[541-22-0]	$168
1166003	Deferoxamine Mesylate (500 mg)	I				[138-14-7]	$168
1166309	Dehydroacetic Acid (200 mg)	F				[520-45-6]	$168
1166400	Dehydrocarteolol Hydrochloride (100 mg)	F				n/f	$526
1166502	Dehydrocholic Acid (200 mg)	F-1			F (03/04)	[81-23-2]	$168
1169001	Demecarium Bromide (250 mg)	F				[56-94-0]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1170000	Demeclocycline Hydrochloride (200 mg)	H1C036			H (08/04)G-1 (08/01)	[64-73-3]	$168
1046089	N-Demethylazithromycin (15 mg)	F0E068	0.92 mg/mg (ai)			n/f	$526
1171003	Denatonium Benzoate (200 mg)	I1F025	1.000 mg/mg (dr)	2	I0B129 (03/07) H (09/02)	[86398-53-0]	$168
1171251	2-Deoxy-D-Glucose (100 mg) (AS)	F0E006				[154-17-6]	$177
1171706	Desacetyl Diltiazem Hydrochloride (50 mg)	J0C143	1.00 mg/mg (ai)		I (07/05) H (08/00)	[23515-45-9]	$526
1171900	Desflurane (0.5 mL)	F0C187				[57041-67-5]	$168
1171910	Desflurane Related Compound A (0.1 mL) (bis-(1,2,2,2-tetrafluoroethyl) ether)	F0C031				n/f	$526
1172006	Desipramine Hydrochloride (125 mg)	I0E283	1.000 mg/mg (dr)		H-1 (11/06) H (10/99)	[58-28-6]	$134
1173009	Deslanoside (100 mg)	H-1				[17598-65-1]	$168
1173235	Desogestrel (50 mg)	G0C390			F0B282 (11/04)	[54024-22-5]	$168
1173246	Desogestrel Related Compound A (15 mg) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17alpha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer)	F0B279				n/f	$526
1173257	Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel)				F0B284 (03/07)	n/f	$526
1173268	Desogestrel Related Compound C (25 mg) (3-Keto-desogestrel)	F0B281				[54048-10-1]	$526
1046078	Desosaminylazithromycin (15 mg)	F0E067	0.99 mg/mg (ai)			n/f	$526
1173508	Desoximetasone (200 mg)	H0B036			G (01/04)	[382-67-2]	$168
1174001	Desoxycorticosterone Acetate (200 mg)	J0C014			I (01/04) H (05/00)	[56-47-3]	$168
1175004	Desoxycorticosterone Pivalate (125 mg)	H0C276			G (01/04)	[808-48-0]	$134
1176007	Dexamethasone (125 mg)	J				[50-02-2]	$134
1176506	Dexamethasone Acetate (200 mg)	H0E339	0.996 mg/mg (dr)		G (12/06) F-1 (06/99)	[1177-87-3]	$168
1177000	Dexamethasone Phosphate (200 mg)	K0E275	0.996 mg/mg (dr)		J1B070 (01/07) J (08/03) I (03/00)	[312-93-6]	$168
1178002	Dexbrompheniramine Maleate (200 mg)	J			I (03/03)	[2391-03-9]	$168
1179005	Dexchlorpheniramine Maleate (300 mg)	H0D199	0.999 mg/mg (ai)		G1A025 (11/05) G (12/02)	[2438-32-6]	$168
1179504	Dexpanthenol (500 mg)	J0C293			I (08/04) H (02/02)	[81-13-0]	$173
1179628	Dextran 1 (50 mg)	F0D297				[9004-54-0]	$173
1179708	Dextran 40 (50 mg)	F0C247				[9004-54-0]	$168
1179741	Dextran 70 (50 mg)	F0C260				[9004-54-0]	$168
1179854	Dextran 4 Calibration (100 mg)	F0C002				[9004-54-0]	$168
1179865	Dextran 10 Calibration (100 mg)	F0C010				[9004-54-0]	$168
1179876	Dextran 40 Calibration (100 mg)	F0C011				[9004-54-0]	$168
1179720	Dextran 40 System Suitability (200 mg)	F0B181				[9004-54-0]	$168
1179887	Dextran 70 Calibration (100 mg)	F0C013				[9004-54-0]	$168
1179763	Dextran 70 System Suitability (200 mg)	F0B182				[9004-54-0]	$168
1179898	Dextran 250 Calibration (100 mg)	F0C039				[9004-54-0]	$168
1179650	Dextran T-10 (200 mg)	F0D238	1.000 mg/mg (dr)			[9004-54-0]	$168
1179800	Dextran Vo Marker (100 mg)	F0B242				[9004-54-0]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1180004	Dextroamphetamine Sulfate **CII** (500 mg)	I0C311	1.000 mg/mg (dr)		H (05/05) G (08/03) F-6 (12/99)	[51-63-8]	$234
1180503	Dextromethorphan (2 g)	H			G (06/00)	[125-71-3]	$526
1181007	Dextromethorphan Hydrobromide (500 mg)	J0B167			I (07/03)	[6700-34-1]	$168
1181302	Dextrose (500 mg)	J2E294	0.999 mg/mg (dr)	2	J-1 (04/07) J (11/02) I (08/99)	[50-99-7]	$134
1181506	Diacetylated Monoglycerides (200 mg)	G				[68990-54-5]	$168
1182000	Diacetylfluorescein (200 mg)	H			G (01/02)	[596-09-8]	$168
1183002	Diacetylmorphine Hydrochloride **CI** (25 mg) (AS) (Heroin Hydrochloride)	J			I-1 (10/99)	[1502-95-0]	$224
1184005	Diatrizoic Acid (100 mg)	H0E084			G (04/06)	[50978-11-5]	$168
1184027	Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid)	I			H (02/00)	[1713-07-1]	$526
1185008	Diazepam **CIV** (100 mg)	I1C364	0.999 mg/mg (ai)		I (02/06) H (12/01)	[439-14-5]	$224
1185020	Diazepam Related Compound A (25 mg) (2-Methyl-amino-5-chlorobenzophenone)	I			H-1 (11/02) H (04/00)	[1022-13-5]	$526
1023403	Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril)	I1C102			I (12/04) H (04/01)	[5220-02-0]	$526
1186000	Diazoxide (200 mg)	G1C017			G (12/03)	[364-98-7]	$168
1187003	Dibucaine Hydrochloride (200 mg)	I			H-2 (01/03)	[61-12-1]	$168
1187080	Dibutyl Phthalate (200 mg)	F0D125				[84-74-2]	$168
1187091	Dibutyl Sebacate (1 mL) (AS)	F0D128	99.2% (ai)			[109-43-3]	$168
1187207	Dichloralphenazone **CIV** (200 mg)	F0B010				[480-30-8]	$224
1187954	2,4-Dichlorophenol (100 mg)	F0E113	0.99 mg/mg (ai)			[120-83-2]	$168
1188006	Dichlorphenamide (200 mg)	G-1				[120-97-8]	$168
1188301	Dichlorvos (150 mg) (2,2-dichlorovinyl dimethyl phosphate) (AS)	F0D141				[62-73-7]	$173
1188800	Diclofenac Sodium (200 mg)	H0B150			G-1 (03/04) G (05/01)	[15307-79-6]	$168
1188811	Diclofenac Related Compound A (50 mg) (N-(2,6-dichlorophenyl)indolin-2-one)	I0D337	1.00 mg/mg (ai)		H (06/06) G (05/02)	[15362-40-0]	$530
1189009	Dicloxacillin Sodium (500 mg)	J0C182			I0B142 (09/04) H (05/03)	[13412-64-1]	$168
1190008	Dicumarol (200 mg)	G				[66-76-2]	$168
1191000	Dicyclomine Hydrochloride (125 mg)	H			G (03/99)	[67-92-5]	$134
1192003	Dienestrol (125 mg)	I				[84-17-3]	$134
1192808	Diethanolamine (3 mL)	F0D118				[111-42-2]	$168
1193006	Diethylcarbamazine Citrate (200 mg)	G-1				[1642-54-2]	$168
1193301	Diethylene Glycol Monoethyl Ether (0.5 mL/ampule)	G0C159			F0B095 (09/06)	[111-90-0]	$168
1193505	Diethyl Phthalate (200 mg)	G			F-1 (03/00)	[84-66-2]	$168
1194009	Diethylpropion Hydrochloride **CIV** (200 mg)	H				[134-80-5]	$224
1195001	Diethylstilbestrol (200 mg)	K5B291			K-4 (05/04)	[56-53-1]	$168
1197007	Diethyltoluamide (3 g)	H1D076	0.981 mg/mg (an)		H (11/06)	[134-62-3]	$134
1197302	Diflorasone Diacetate (200 mg)	G			F-1 (03/00)	[33564-31-7]	$168
1197506	Diflunisal (200 mg)	G				[22494-42-4]	$168
1198000	Digitalis (3 g)	F				[8031-42-3]	$168
1199002	Digitoxin (200 mg)	M				[71-63-6]	$168

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1200000	Digoxin (250 mg)	O0B096			N-1 (04/03)	[20830-75-5]	$168
1200600	Dihydrocapsaicin (25 mg)	G0C071			F-1 (12/03) F (01/00)	[19408-84-5]	$281
1200804	Dihydrocodeine Bitartrate **CII** (200 mg)	I0D205	0.997 mg/mg (dr)		H (09/05) G (03/01)	[5965-13-9]	$224
1201002	17alpha-Dihydroequilin (50 mg)	I0C277			H (07/04)	[6639-99-2]	$225
1202005	Dihydroergotamine Mesylate (250 mg) **(List Chemical)**	J0B085			I (03/03)	[6190-39-2]	$168
1203008	Dihydrostreptomycin Sulfate (200 mg)	J				[5490-27-7]	$168
1204000	Dihydrotachysterol (30 mg/ampule; 4 ampules)	J0D250	0.996 mg/mg (ai)		I (06/05)	[67-96-9]	$168
1204102	Dihydroxyacetone (250 mg)	F				[96-26-4]	$168
1204805	Diloxanide Furoate (200 mg)	F0C026				[3736-81-0]	$168
1205003	Diltiazem Hydrochloride (200 mg)	I				[33286-22-5]	$168
1206006	Dimenhydrinate (100 mg)	J0B055			I (06/03)	[523-87-5]	$168
1208001	Dimethisoquin Hydrochloride (2 g)	G				[2773-92-4]	$168
1210105	N-(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS)	F				[41992-23-8]	$168
1211006	Dimethyl Sulfoxide (3 g)	H0D273	0.999 mg/mg (ai)		G0C198 (10/06) F-3 (07/04) F-2 (05/02)	[67-68-5]	$225
1213001	Dinoprost Tromethamine (50 mg)	F				[38562-01-5]	$1,649
1213103	Dinoprostone (50 mg)	F0C030				[363-24-6]	$1,649
1214004	Dioxybenzone (150 mg)	F1B277			F (10/03)	[131-53-3]	$168
1217909	Diphenhydramine Citrate (125 mg)	H1C350	1.000 mg/mg (dr)		H0B128 (08/06) G (04/03)	[88637-37-0]	$134
1218005	Diphenhydramine Hydrochloride (200 mg)	J0B013			I (07/03)	[147-24-0]	$168
1219008	Diphenoxylate Hydrochloride **CII** (200 mg)	I1D339	0.998 mg/mg (dr)		I (08/06) H (03/02)	[3810-80-8]	$224
1220302	Dipivefrin Hydrochloride (200 mg)	I			H (06/99)	[64019-93-8]	$168
1220506	Dipyridamole (200 mg)	H			G-1 (01/99)	[58-32-2]	$168
1220700	Dirithromycin (200 mg)	F				[62013-04-1]	$168
1221000	Disodium Guanylate (300 mg) (FCC)	F-1				[5550-12-9]	$168
1222002	Disodium Inosinate (500 mg) (FCC)	F				[4691-65-0]	$168
1222501	Disopyramide Phosphate (200 mg)	H-1			H (03/02)	[22059-60-5]	$168
1223005	2,4-Disulfamyl-5-trifluoromethylaniline (125 mg)	G				[654-62-6]	$526
1224008	Disulfiram (200 mg)	F-3			F-2 (07/02)	[97-77-8]	$168
1224507	Dobutamine Hydrochloride (600 mg)	H-1			H (01/00)	[49745-95-1]	$168
1224700	Docusate Calcium (500 mg)	H0B044			G-1 (07/02)	[128-49-4]	$168
1224802	Docusate Sodium (500 mg)	K0D134	0.988mg/mg (an)		J (09/05) I-1 (05/02)	[577-11-7]	$168
1224904	Docusate Potassium (100 mg)	F-1			F (11/99)	[7491-09-0]	$168
1224959	Dolasetron Mesylate (200 mg)	F0C319				[115956-13-3]	$168
1224960	Dolasetron Mesylate Related Compound A (25 mg) (Hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one hydrochloride)	F0C321				n/f	$526
1225204	Dopamine Hydrochloride (200 mg)	G			F-5 (05/02)	[62-31-7]	$168
1225281	Dorzolamide Hydrochloride (200 mg)	G0E278	0.998 mg/mg (ai)		F0C040 (11/06)	[130693-82-2]	$168
1225292	Dorzolamide Hydrochloride Related Compound A (20 mg) ((4R,6R)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide, monohydrochloride)	G0E029			F0C068 (12/05)	n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1225000	Doxapram Hydrochloride (200 mg)	F4C053			F-3 (07/04)	[7081-53-0]	$168
1225419	Doxazosin Mesylate (200 mg)	G0E173	0.997 mg/mg (ai)		F0C079 (08/06)	[77883-43-3]	$168
1225500	Doxepin Hydrochloride (500 mg)	I				[1229-29-4]	$168
1225703	Doxorubicin Hydrochloride (50 mg)	K			J (06/02)	[25316-40-9]	$518
1226003	Doxycycline Hyclate (200 mg)	J0E174	859 ug/mg (ai) (chromatographic) 864 ug/mg (ai) (spectroscopic)		I (09/06) H (01/00)	[24390-14-5]	$168
1227006	Doxylamine Succinate (300 mg)	I0B266			H (01/04)	[562-10-7]	$168
1229001	Droperidol (250 mg)	I0C029			H-1 (01/05) H (04/99)	[548-73-2]	$168
1230000	Dyclonine Hydrochloride (200 mg)	G				[536-43-6]	$168
1231003	Dydrogesterone (200 mg)	I0B114			H (01/04)	[152-62-5]	$168
1231502	Dyphylline (200 mg)	G-2			G-1 (11/02)	[479-18-5]	$168
1231728	Powdered Echinacea Purpurea Extract (1 g)	F0D018				[90028-20-9]	$563
1231706	Powdered Echinacea Angustifolia Extract (1 g)	F0D019				[84696-11-7]	$563
1231808	Econazole Nitrate (200 mg)	G1C346	1.00 mg/mg (ai)		G (07/05)	[68797-31-9]	$168
1232006	Edetate Calcium Disodium (200 mg)	H0B272			G-3 (11/04) G-2 (11/99)	[23411-34-9]	$168
1233009	Edetate Disodium (200 mg)	I0D405			H (06/06) G-2 (04/02)	[6381-92-6]	$168
1233508	Edetic Acid (200 mg)	F-1				[60-00-4]	$168
1234001	Edrophonium Chloride (200 mg)	H			G (08/99)	[116-38-1]	$168
1234704	Powdered Eleuthero Extract (1.5 g)	F0C291				[84696-12-5]	$563
1234668	Eleutheroside B (15 mg) (Syringin)	F0E056	95% (ai)			[118-34-3]	$884
1234680	Eleutheroside E (15 mg) (Syringaresinol diglucoside)	F0E057	98% (ai)			[96038-87-8]	$884
1234806	Emedastine Difumarate (100 mg)	F0C059				[87233-62-3]	$168
1235004	Emetine Hydrochloride (300 mg)	H0B201			G (05/03)	[316-42-7]	$168
1235274	Enalaprilat (300 mg)	J0C268			I (11/04) H (03/01) G (08/99)	[84680-54-6]	$134
1235300	Enalapril Maleate (200 mg)	J1C267	0.992 mg/mg (ai)		J (05/05) I (06/01)	[76095-16-4]	$168
1235503	Endotoxin (10,000 USP Endotoxin Units)	G3E069			G2B274 (06/06) G-1 (12/03) G (06/99)	n/f	$168
1235809	Enflurane (1 mL)	G-1			G (02/01)	[13838-16-9]	$168
1235900	Enrofloxacin (200 mg) (AS)	F0E094				[93106-60-6]	$168
1236007	Ephedrine Sulfate (200 mg) **(List Chemical)**	H-2			H-1 (11/02)	[134-72-5]	$168
1236506	4-Epianhydrotetracycline Hydrochloride (50 mg)	J0C041			I-1 (12/03) I (06/00)	[4465-65-0]	$526
1236801	Epilactose (200 mg)	H0E049	1.00 mg/mg (dr)		G (08/06) F-1 (06/00)	[50468-56-9]	$526
1237000	Epinephrine Bitartrate (200 mg)	O				[51-42-3]	$168
1237509	Epitetracycline Hydrochloride (200 mg) (AS)	G0E261			F (12/06)	[23313-80-6]	$526
1238002	Equilin (25 mg)	I1B290			I (11/04) H-1 (05/00)	[474-86-2]	$225
1239005	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275			O (02/04) N (12/99)	[50-14-6]	$182
1239504	Ergoloid Mesylates (300 mg)	I			H-1 (01/00)	[8067-24-1]	$168
1240004	Ergonovine Maleate (100 mg) **(List Chemical)**	N			M-1 (07/02)	[129-51-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1241007	Ergosterol (50 mg)	H				[57-87-4]	$168
1241506	Ergotamine Tartrate (150 mg) **(List Chemical)**	I0B174			H (01/04)	[379-79-3]	$168
1241550	Ergotaminine (100 mg) **(List Chemical)**	G0B177			F-1 (06/04)	[639-81-6]	$168
1241903	Erythritol (200 mg)	F0E313				[149-32-6]	$168
1242000	Erythromycin (250 mg)	M1E251	96.7% Erythromycin A 978 ug/mg (ai) (microbial)		M (02/07) L (08/99)	[114-07-8]	$168
1242010	Erythromycin B (150 mg)	G1C080			G (11/04) F-1 (09/01) F (05/01)	[527-75-3]	$168
1242021	Erythromycin C (50 mg)	F-3			F-2 (01/03) F-1 (02/02) F (02/99)	n/f	$526
1242032	Erythromycin Related Compound N (50 mg) (N-Demethylerythromycin A)	F2A023			F-1 (06/04) F (09/99)	n/f	$526
1243002	Erythromycin Estolate (200 mg)	H			G (01/03)	[3521-62-8]	$168
1245008	Erythromycin Ethylsuccinate (200 mg)	H			G-1 (06/01)	[1264-62-6]	$168
1246000	Erythromycin Gluceptate (200 mg)	H			G (07/03)	[23067-13-2]	$168
1247003	Erythromycin Lactobionate (200 mg)	H-1			H (01/02)	[3847-29-8]	$168
1248006	Erythromycin Stearate (200 mg)	H0B187			G-1 (05/03)	[643-22-1]	$168
1249009	Erythrosine Sodium (100 mg)	F				[49746-10-3]	$168
1249202	Escin (350 mg)	F0F088	0.999 mg/mg (an)	1		[11072-93-8]	$185
1250008	Estradiol (500 mg)	M0E309	0.999 mg/mg (an)	2	L0C337 (03/07) K1B007 (07/05) K (04/03)	[50-28-2]	$168
1251000	Estradiol Benzoate (250 mg) (AS)	H0C332			G-1 (01/06)	[50-50-0]	$168
1252003	Estradiol Cypionate (200 mg)	G-1			G (02/00)	[313-06-4]	$168
1254009	Estradiol Valerate (100 mg)	L1D286	0.996 mg/mg (ai)		L (04/06) K (05/02)	[979-32-8]	$168
1254508	Estriol (100 mg)	J			I-1 (06/01)	[50-27-1]	$168
1255001	Estrone (200 mg)	K1B099			K (07/03) J-1 (07/00)	[53-16-7]	$168
1255500	Estropipate (500 mg)	J0B262			I (12/03) H (09/01)	[7280-37-7]	$168
1256004	Ethacrynic Acid (200 mg)	F				[58-54-8]	$168
1257007	Ethambutol Hydrochloride (200 mg)	H			G (08/02)	[1070-11-7]	$168
1258305	Ethchlorvynol **CIV** (0.7 ml)	F0B011				[113-18-8]	$224
1260001	Ethinyl Estradiol (150 mg)	Q0C162			P1B193 (11/04) P0B052 (01/04) P (03/03) O (08/99)	[57-63-6]	$168
1260012	Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol)	G0E301	0.99 mg/mg (ai)	2	F0B252 (04/07)	n/f	$526
1261004	Ethionamide (200 mg)	H0B148			G (03/03)	[536-33-4]	$168
1262801	Ethopabate (125 mg)	F				[59-06-3]	$168
1262823	Ethopabate Related Compound A (25 mg) (Methyl-4-acetamido-2-hydroxybenzoate)	F				n/f	$526
1263000	Ethopropazine Hydrochloride (300 mg)	G				[1094-08-2]	$168
1264002	Ethosuximide (125 mg)	H			G-2 (11/01) G-1 (05/99)	[77-67-8]	$134
1264501	Ethotoin (200 mg)	F				[86-35-1]	$168
1265005	Ethoxzolamide (200 mg)	F				[452-35-7]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1265504	Ethylcellulose (1 g)	H-1			H (06/99)	[9004-57-3]	$168
1266008	Ethyl Maltol (1 g) (FCC)	H				[4940-11-8]	$168
1266507	Ethylnorepinephrine Hydrochloride (200 mg)	F				[3198-07-0]	$168
1267000	Ethylparaben (200 mg)	I0A016			H (01/04)	[120-47-8]	$168
1267500	Ethyl Vanillin (200 mg)	F2B134			F-1 (04/04)	[121-32-4]	$168
1268003	Ethynodiol Diacetate (200 mg)	I0A033			H-1 (01/03) H (04/01)	[297-76-7]	$168
1268502	Etidronate Disodium (200 mg)	G			F-2 (02/03)	[7414-83-7]	$168
1268513	Etidronate Disodium Related Compound A (300 mg) (Sodium phosphite dibasic pentahydrate)	F0E227	1.00 mg/mg (an)			[13517-23-2]	$526
1268604	Etidronic Acid Monohydrate (1 g)	G			F-1 (05/99)	[2809-21-4]	$168
1268706	Etodolac (400 mg)	G			F (10/01)	[41340-25-4]	$168
1268728	Etodolac Related Compound A (25 mg) ((+/-)-8-ethyl-1-methyl-1,3,4,9-tetrahydropyrano [3,4-b]-indole-1-acetic acid)	F-1			F (05/02)	[109518-50-5]	$526
1268808	Etoposide (300 mg)	H0C315			G (11/04)	[33419-42-0]	$134
1268852	Etoposide Resolution Mixture (30 mg)	F0B209				[33419-42-0]	$526
1268965	Eugenol (500 mg) (AS)	F0D303				[97-53-0]	$168
1269200	Famotidine (125 mg)	I0E063	0.997 mg/mg (dr)		H-1 (06/06) H (11/02) G (03/99)	[76824-35-6]	$134
1269389	Felodipine (200 mg)	G0D065	0.999 mg/mg (ai)		F-1 (04/05) F (09/02)	[72509-76-3]	$168
1269390	Felodipine Related Compound A (100 mg) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate)	F0B207				[96302-71-7]	$526
1269403	Fenbendazole (100 mg)	F				[43210-67-9]	$526
1269414	Fenbendazole Related Compound A (30 mg) (Methyl (1H-benzimidazole-2-yl)carbamate)	F0D009	0.99 mg/mg (ai)			[10605-21-7]	$526
1269425	Fenbendazole Related Compound B (30 mg) (Methyl [5(6)-chlorobenzimidazole-2-yl]carbamate)	F0D008	0.99 mg/mg (ai)			n/f	$526
1269458	Fenoldopam Mesylate (200 mg)	F0C125				[67227-57-0]	$168
1269469	Fenoldopam Related Compound A (20 mg) (N-Methyl-6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1H-3-benzazepine-7,8-diol hydrochloride)	F0C124				n/f	$526
1269470	Fenoldopam Related Compound B (20 mg) (1H-3-Benzazapine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate)	F0C126				n/f	$526
1269505	Fenoprofen Calcium (500 mg)	G-1				[53746-45-5]	$168
1269550	Fenoprofen Sodium (500 mg)	G			F-1 (05/02)	[66424-46-2]	$168
1270355	Ferrous Sulfate (1.5 g) (AS)	F0D196	101.0% (ai)			[7782-63-0]	$168
1270005	Fentanyl Citrate **CII** (100 mg)	K0C264			J2B227 (11/04) J-1 (09/03) J (05/02) I (06/00)	[990-73-8]	$260
1270377	Fexofenadine Hydrochloride (200 mg)	F1E289	0.996 mg/mg (ai)		F0D244 (02/07)	[138452-21-8]	$168
1270388	Fexofenadine Related Compound A (25 mg) (4-[1-oxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-alpha,alpha-dimethyl benzeneacetic acid)	F0D245	0.99 mg/mg (ai)			n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1270399	Fexofenadine Related Compound B (25 mg) (3-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]butyl]-alpha,alpha-dimethyl benzeneacetic acid hydrochloride)	F0D246				n/f	$526
1270446	Fexofenadine Related Compound C (15 mg) ((+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene) (AS)	F0E291				n/f	$526
1270402	Finasteride (200 mg)	F1E139	0.997 mg/mg (ai)		F (07/06)	[98319-26-7]	$168
1270800	Flecainide Acetate (200 mg)	F2A022			F-1 (02/05) F (06/03)	[54143-56-5]	$168
1270821	Flecainide Related Compound A (75 mg) (3-[2,5-bis(2,2,2-trifluoroethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride)	F				n/f	$526
1271008	Floxuridine (250 mg)	F-2			F-1 (08/01)	[50-91-9]	$168
1271700	Fluconazole (200 mg)	F0D262	1.00 mg/mg (ai)			[86386-73-4]	$168
1271711	Fluconazole Related Compound A (10 mg) (2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D080	0.95 mg/mg (ai)			n/f	$526
1271722	Fluconazole Related Compound B (10 mg) (2-(4-fluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-propan-2-ol)	F0D081	0.92 mg/mg (ai)			[81886-51-3]	$526
1271733	Fluconazole Related Compound C (10 mg) (1,1'-(1,3-phenylene)di(1H-1,2,4-triazole))	F0D082	0.98 mg/mg (ai)			n/f	$526
1272000	Flucytosine (200 mg)	G0E151	1.000 mg/mg (dr)		F (06/05)	[2022-85-7]	$168
1272204	Fludarabine Phosphate (300 mg)				F0C374 (04/07)	[75607-67-9]	$168
1272907	Fludeoxyglucose (100 mg)	F0E100				[29702-43-0]	$208
1272918	Fludeoxyglucose Related Compound A (15 mg) (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane)	F0D119	1.00 mg/mg (ai)			[23978-09-8]	$578
1273003	Fludrocortisone Acetate (250 mg)	H			G (08/01)	[514-36-3]	$168
1273808	Flumazenil (200 mg)	F0C305				[78755-81-4]	$843
1273819	Flumazenil Related Compound A (20 mg) (8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazol-[1,5-alpha][1,4]benzodiazepine-3-carboxylic acid)	F0E147				n/f	$675
1273820	Flumazenil Related Compound B (20 mg) (Ethyl 8-hydroxy-5,6-dihydro-5-methyl-6-oxo-4H-imidazol-[1,5-alpha][1,4]benzodiazepine-3-carboxylate)	F0E148				n/f	$675
1274006	Flumethasone Pivalate (200 mg)	I			H (01/02)	[2002-29-1]	$168
1274505	Flunisolide (200 mg)	I			H (01/01)	[77326-96-6]	$168
1274607	Flunixin Meglumine (300 mg)	H0E241	1.000 mg/mg (dr)		G (11/06) F-1 (04/02) F (09/99)	[42461-84-7]	$168
1275009	Fluocinolone Acetonide (100 mg)	J1E014	0.993 mg/mg (dr)		J (03/06) I (11/99)	[67-73-2]	$168
1276001	Fluocinonide (100 mg)	I				[356-12-7]	$168
1277004	Fluorescein (200 mg)	G0B171			F-1 (02/03)	[2321-07-5]	$168
1277252	Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz)	J0C294			I (08/04) H (04/99)	n/f	$495
1277274	Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz)	G0D270			F (06/05)	n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1277300	Fluoride Dentifrice: Sodium Monofluorophosphate-Calcium Carbonate (4.6 oz)	G				n/f	$526
1277354	Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz)	G				n/f	$526
1277401	Fluoride Dentifrice: Sodium Monofluorophosphate (1000 ppm)/Silica (5.25 oz)	G-1			G (08/99)	n/f	$526
1277423	Fluoride Dentifrice: Sodium Monofluorophosphate (1500 ppm)/Silica (5.25 oz)	F-1			F (07/99)	n/f	$526
1277456	Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz)	H0B105			G (11/02)	n/f	$526
1278007	Fluorometholone (200 mg)	I0B184			H-1 (11/02)	[426-13-1]	$168
1278109	Fluorometholone Acetate (200 mg)	F				[3801-06-7]	$168
1278302	Fluoroquinolonic Acid (50 mg)	H0C140			G (01/05) F-1 (12/99)	[86393-33-1]	$526
1279000	Fluorouracil (250 mg)	H2D190	1.000 mg/mg (dr)		H-1 (09/05) H (01/02)	[51-21-8]	$168
1279804	Fluoxetine Hydrochloride (200 mg)	F2C132			F-1 (02/05) F (11/99)	[59333-67-4]	$168
1279815	Fluoxetine Related Compound A (15 mg) (N-methyl-3-phenyl-3-[(alpha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride)	H0C131			G (06/04) F-1 (05/01) F (06/00)	n/f	$526
1279826	Fluoxetine Related Compound B (5 mL of a 0.01N HCl solution, approx. 2 mg/mL) (N-methyl-3-phenylpropylamine)	G0D023	approx. 2 mg/mL (ai)		F3C085 (05/05) F-2 (06/04) F-1 (09/02) F (09/00)	[23580-89-4]	$526
1279837	Fluoxetine Related Compound C (15 mg) (N-Methyl-N-[3-phenyl-3-(4-trifluoromethyl-phenoxy)-propyl]-succinamic acid)	F0C352				n/f	$526
1280009	Fluoxymesterone **CIII** (200 mg)	G-2			G-1 (04/00)	[76-43-7]	$224
1280803	Fluphenazine Decanoate Dihydrochloride (500 mg)	G			F-1 (10/01)	n/f	$172
1281001	Fluphenazine Enanthate Dihydrochloride (125 mg)	H			G (02/99)	[3105-68-8]	$134
1282004	Fluphenazine Hydrochloride (125 mg)	H				[146-56-5]	$134
1284000	Flurandrenolide (100 mg)	I0B245			H (09/03)	[1524-88-5]	$168
1285002	Flurazepam Hydrochloride **CIV** (200 mg)	J0C365	0.996 mg/mg (ai)		I (09/03)	[1172-18-5]	$224
1285308	Flurazepam Related Compound C (50 mg) (5-chloro-2-(2-diethylaminoethylamino)-2'-fluorobenzophenone Hydrochloride)	I0D361	1.00 mg/mg (ai)		H-1 (40/06)	n/f	$526
1285603	Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one)	I0C092			H (01/04)	[2886-65-9]	$526
1285750	Flurbiprofen (200 mg)	H0D349	0.994 mg/mg (ai)		G (01/06)	[5104-49-4]	$168
1285760	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)	H			G (03/01)	n/f	$526
1285807	Flurbiprofen Sodium (200 mg)	F				[56767-76-1]	$168
1285851	Flutamide (200 mg)	H0B278			G (11/04) F-1 (06/00)	[13311-84-7]	$168
1285862	o-Flutamide (50 mg)	F-1			F (01/00)	n/f	$526
1285873	Fluticasone Propionate (100 mg)	F0F036	0.989 mg/mg (ai)			[80474-14-2]	$832
1285884	Fluticasone Propionate Resolution Mixture (25 mg)	F0E123				n/f	$675

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1285895	Fluticasone Propionate System Suitability Mixture (25 mg) (Fluticasone Propionate and Fluticasone Propionate Related Compounds B, C and D)	F0E122				n/f	$675
1285964	Fluvastatin Related Compound B (15 mg) ([R*,S*-E]-(+/-)-7-[3-(4-fluorophenyl)-1-methylethyl-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1, dimethylethyl ester)	F0F017				[129332-29-2]	$526
1285942	Fluvastatin for System Suitability (25 mg) (Fluvastatin sodium and fluvastatin sodium antiisomer ([R*,R*-E]-(+/-)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt))	F0F016				n/f	$526
1285909	Fluvoxamine Maleate (200 mg)	F0E016	0.996 mg/mg (dr)			[61718-82-9]	$463
1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P			O (07/00)	[59-30-3]	$168
1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176			H-1 (04/04) H (01/00)	[1492-18-8]	$168
1286060	Formononetin (50 mg)	F0C196				[485-72-3]	$563
1286300	10-Formylfolic Acid (25 mg)	F2B226			F-1 (01/04)	[134-05-4]	$526
1286366	Fosphenytoin Sodium (250 mg)	G0E124	0.999 mg/mg (an)		F0C156 (07/06)	[92134-98-0]	$168
1286504	Fructose (125 mg)	I3E340	0.999 mg/mg (ai)	2	I-2 (04/07) I-1 (11/02) I (08/99)	[57-48-7]	$134
1286606	L-Fucose (200 mg) (AS)	F0E007				[2438-80-4]	$177
1286708	Fumaric Acid (200 mg)	H0E328	1.00 mg/mg (ai)	2	G-1 (03/07) G (04/02)	[110-17-8]	$168
1286800	Furazolidone (200 mg)	G-2			G-1 (01/01)	[67-45-8]	$168
1287008	Furosemide (125 mg)	J1B131			J (10/03)	[54-31-9]	$134
1287020	Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid)	J			I (08/02)	n/f	$526
1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)	J0E326	0.99 mg/mg (ai)	2	H (08/04) G-3 (03/01)	[3086-91-7]	$526
1287303	Gabapentin (250 mg)	G0E005	0.999 mg/mg (ai)		F (03/06)	[60142-96-3]	$168
1287325	Gabapentin Related Compound A (50 mg) (3,3-pentamethylene-5-butyrolactam)	G0E125	1.00mg/mg (ai)		F1D263 (07/06) F (10/05)	[64744-50-9]	$526
1287369	Gabapentin Related Compound E (25 mg) (Carboxymethyl-cyclohexanecarboxylic acid)	F0E190	0.99 mg/mg (ai)			n/f	$526
1287507	Gadodiamide (500 mg)	F				[131410-48-5]	$168
1287518	Gadodiamide Related Compound A (50 mg) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide)	F				n/f	$526
1287529	Gadodiamide Related Compound B (50 mg) (gadolinium disodium diethylenetriamine pentaacetic acid)	F				n/f	$526
1287609	Gadopentetate Monomeglumine (500 mg)	F1F094	0.998 mg/mg (an)	2	F (12/06)	[92923-57-4]	$168
1287631	Gadoteridol (500 mg)	F				[120066-54-8]	$168
1287642	Gadoteridol Related Compound A (50 mg) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid)	F0A002				[120041-08-9]	$526
1287653	Gadoteridol Related Compound B (50 mg) (1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt)	F0B198				[112188-16-6]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1287664	Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetradecane-4,7-diacetic acid)	F0B199				[220182-19-4]	$526
1287675	Gadoversetamide (200 mg)	F0C172				[131069-91-5]	$168
1287686	Gadoversetamide Related Compound A (200 mg) (Hydrogen[8,11,14-tris(carboxymethyl)-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(4-)]gadolinium)	F0C173				n/f	$526
1287711	Galactitol (500 mg)	F0D376	0.99 mg/mg (ai)			[608-66-2]	$168
1287700	Galactose (200 mg)	F-4			F-3 (05/01)	[59-23-4]	$526
1288000	Gallamine Triethiodide (200 mg)	F				[65-29-2]	$168
1288306	Ganciclovir (200 mg)	F0C287				[82410-32-0]	$394
1288317	Ganciclovir Related Compound A (15 mg) ((RS)-2-Amino-9-(2,3-dihydroxy-propoxymethyl)-1,9-dihydro-purin-6-one)	F0C288				n/f	$675
1288463	Gemcitabine Hydrochloride (200 mg)	F0D037	0.997 mg/mg (ai)			[122111-03-9]	$168
1288500	Gemfibrozil (200 mg)	H				[25812-30-0]	$168
1288510	Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-dimethyl-4-(propene-1-yl)phenoxy]valeric acid)	G0D369	0.99 mg/mg (ai)		F0C101 (10/05)	n/f	$526
1289003	Gentamicin Sulfate (200 mg)	M0D314	697 ug/mg (dr)		L0C279 (08/04) K (12/04) J-1 (04/00)	[1405-41-0]	$168
1290002	Gentian Violet (650 mg)	G0E112	1.000 mg/mg (an)		F (08/06)	[548-62-9]	$168
1291005	Gibberellic Acid (200 mg) (FCC)	G			F (04/01)	[77-06-5]	$168
1291504	Powdered Ginger (500 mg)	F				n/f	$281
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289				[50647-08-0]	$563
1292008	Gitoxin (50 mg)	G			F-3 (07/00)	[4562-36-1]	$526
1292303	Glimepiride (200 mg)	F0E228	0.994 mg/mg (ai)			[93479-79-1]	$260
1292314	Glimepiride Related Compound A (20 mg) (glimepiride cis-isomer)	F0E232				n/f	$526
1292325	Glimepiride Related Compound B (20 mg) (glimepiride sulfonamide)	F0E233				[119018-29-0]	$526
1292336	Glimepiride Related Compound C (20 mg) (Glimepiride urethane)	F0E234				[119018-30-3]	$526
1292347	Glimepiride Related Compound D (20 mg) (Glimepiride-3-isomer)	F0E235				n/f	$526
1292507	Glipizide (125 mg)	G1C174			G (07/04)	[29094-61-9]	$134
1292609	Glipizide Related Compound A (25 mg) (N-{2-[(4-aminosulfonyl)phenyl]ethyl}-5-methyl-pyrazinecarboxamide)	G-1			G (04/99)	n/f	$526
1294207	Glucosamine Hydrochloride (200 mg)	F0C363				[66-84-2]	$168
1294976	Glutamic Acid (200 mg)	F0C069				[56-86-0]	$168
1294808	Glutamine (100 mg)	F0B244				[56-85-9]	$168
1294848	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F				n/f	$730
1295006	Glutethimide **CII** (500 mg)	F				[77-21-4]	$224
1295505	Glyburide (200 mg)	G1C347	0.990 mg/mg (dr)		G (04/06) F-2 (11/02)	[10238-21-8]	$168
1295516	Glyburide Related Compound A (25 mg) (5-chloro-2-methoxy-N-[2-(4-sulfamoylphenyl)ethyl]benzamide)	F0E224				[16673-34-0]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1295607	Glycerin (2 mL)	H1E032	1.00 mg/mg (ai)	2	H0C073 (03/07) G1A001 (04/04) G (12/02) F (04/99)	[56-81-5]	$168
1295709	Glyceryl Behenate (200 mg)	F3B113			F-2 (03/03)	[18641-57-1]	$168
1295800	Glycine (200 mg)	G0E099	0.999 mg/mg (dr)		F-3 (05/06) F-2 (02/00)	[56-40-6]	$168
1296009	Glycopyrrolate (200 mg)	H0B304			G (05/04)	[596-51-0]	$168
1295888	Glycyrrhizic Acid (25 mg)	F0C006				[1405-86-3]	$526
1297001	Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package)	H			G (07/00)	[9002-61-3]	$1,082
1298004	Gramicidin (200 mg)	I			H-1 (07/02)	[1405-97-6]	$168
1299007	Griseofulvin (200 mg)	I1D406	992 ug/mg (ai)	2	I (03/07) H-1 (09/02)	[126-07-8]	$168
1299200	Griseofulvin Permeability Diameter (2 g)	J0C380			I0C138 (10/04) H (08/03)	[126-07-8]	$168
1300004	Guaiacol (1 g)	K			J (04/00)	[90-05-1]	$168
1301007	Guaifenesin (200 mg)	I1C098	0.993 mg/mg (dr)		I (11/05) H (09/02)	[93-14-1]	$168
1301404	Guanabenz Acetate (200 mg)	G			F-1 (06/00)	[23256-50-0]	$168
1301608	Guanadrel Sulfate (200 mg)	F-1				[22195-34-2]	$168
1301801	Guanethidine Monosulfate (200 mg)	F				[645-43-2]	$168
1302000	Guanethidine Sulfate (500 mg)	G-1				[60-02-6]	$168
1302101	Guanfacine Hydrochloride (125 mg)	G0B123			F-1 (02/03) F (11/99)	[29110-48-3]	$134
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224			F (12/04)	[23092-17-3]	$224
1302509	Halcinonide (300 mg)	F				[3093-35-4]	$168
1303002	Haloperidol (200 mg)	I			H-1 (05/02)	[52-86-8]	$168
1303013	Haloperidol Related Compound A (15 mg) (4,4'-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone)	K0C362			J (12/04)	[67987-08-0]	$526
1303308	Haloprogin (200 mg)	F				[777-11-7]	$168
1303501	Halothane (1 mL)	G0D068			F-1 (03/05)	[151-67-7]	$168
1304005	Heparin Sodium (10 x 1 mL)	K-5			K-4 (08/03) K-3 (02/99)	[9041-08-1]	$168
1305008	Hexachlorophene (500 mg)	I			H-2 (01/01)	[70-30-4]	$168
1305507	2E, 4E-Hexadienoic Acid Isobutylamide (25 mg)	F0C353	1.00 mg/mg (ai)			[82240-09-3]	$584
1307003	Hexobarbital **CIII** (500 mg)	F				[56-29-1]	$224
1308006	Hexylcaine Hydrochloride (1 g)	F-1				[532-76-3]	$168
1308200	Hexylene Glycol (125 mg)	G			F-2 (04/02) F-1 (04/99)	[107-41-5]	$168
1308307	Hexylresorcinol (200 mg)	F				[136-77-6]	$168
1308505	L-Histidine (200 mg)	G0A018			F-2 (01/03) F-1 (04/00)	[71-00-1]	$168
1309009	Histamine Dihydrochloride (250 mg)	M0C280			L (07/04)	[56-92-8]	$168
1310008	Homatropine Hydrobromide (200 mg)	H2C049			H-1(02/05) H (08/02)	[51-56-9]	$168
1311000	Homatropine Methylbromide (250 mg)	J			I-1 (06/01)	[80-49-9]	$168
1311306	Homopolymer Polypropylene (3 Strips)	F0C096				[9003-07-0]	$168
1311408	Homosalate (500 mg)	H0D322	0.994 mg/mg (ai)		G0D072 (09/06) F0B102 (04/05)	[118-56-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1313006	Hydralazine Hydrochloride (200 mg)	K1E183	0.998 mg/mg (dr)		K (10/06) J-1 (09/02)	[304-20-1]	$168
1313210	Hydrastine (10 mg)	F0E204	0.99 mg/mg (ai)			[118-08-1]	$281
1314009	Hydrochlorothiazide (200 mg)	I			H (05/02)	[58-93-5]	$168
1315001	Hydrocodone Bitartrate **CII** (250 mg)	L0E176	0.997 mg/mg (dr)		K0C217 (11/06) J0A026 (01/05) I-1 (12/02) I (07/02) H-2 (11/99)	[34195-34-1]	$224
1315012	Hydrocodone Bitartrate Related Compound A **CII** (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl)	F0C214				[847-86-9]	$555
1316004	Hydrocortisone (200 mg)	M1C110			M (10/04) L (09/00)	[50-23-7]	$168
1317007	Hydrocortisone Acetate (200 mg)	K			J (10/99)	[50-03-3]	$168
1317302	Hydrocortisone Butyrate (200 mg)	H				[13609-67-1]	$168
1318000	Hydrocortisone Cypionate (200 mg)	F				[508-99-6]	$168
1319002	Hydrocortisone Hemisuccinate (200 mg)	I0D343	0.998 mg/mg (dr)		H (03/06) G-3 (03/02) G-2 (08/99)	[83784-20-7]	$168
1320001	Hydrocortisone Phosphate Triethylamine (200 mg)	F-1				n/f	$168
1321004	Hydrocortisone Valerate (200 mg)	F-1			F (07/02)	[57524-89-7]	$168
1322007	Hydroflumethiazide (200 mg)	F-2				[135-09-1]	$168
1323000	Hydromorphone Hydrochloride **CII** (50 mg)	J0C372			I (01/05) H-2 (03/01)	[71-68-1]	$224
1324002	Hydroquinone (500 mg)	H0C249			G-1 (10/04) G (11/01) F-4 (02/99)	[123-31-9]	$168
1325005	Hydroxyamphetamine Hydrobromide (200 mg)	G			F (06/01)	[306-21-8]	$168
1327000	Hydroxychloroquine Sulfate (200 mg)	J0B297			I (05/04)	[747-36-4]	$168
1329006	Hydroxyprogesterone Caproate (200 mg)	H				[630-56-8]	$168
1329709	Hydroxypropyl Betadex (200 mg)	F0B295				[128446-35-5]	$168
1329800	Hydroxypropyl Cellulose (200 mg)	F-1				[9004-64-2]	$168
1332000	Hydroxyurea (200 mg)	H			G (01/00)	[127-07-1]	$168
1333003	Hydroxyzine Hydrochloride (500 mg)	J0F024	0.999 mg/mg (dr)	2	I0C385 (03/07) H (05/05)	[2192-20-3]	$168
1333058	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)	H1E248			H (09/06)	[303-26-4]	$526
1334006	Hydroxyzine Pamoate (500 mg)	H0C016			G-1 (07/03)	[10246-75-0]	$168
1335009	Hyoscyamine Sulfate (125 mg)	H0C193			G2A007 (09/04) G-1 (08/02) G (10/99)	[6835-16-1]	$134
1335010	Hyoscyamine Related Compound A (10 mg) (Norhyoscyamine Sulfate)	F0E250				[537-29-1]	$526
1335202	Hyperoside (50 mg)	F				[482-36-0]	$925
1330005	Hypromellose (250 mg) (Hydroxypropyl Methylcellulose)	H0C387			G-1 (11/04) G (02/02)	[9004-65-3]	$168
1335279	Hypromellose Acetate Succinate (100 mg)	F0D275				[71138-97-1]	$168
1335304	Hypromellose Phthalate (100 mg)	F-1			F (12/00)	[9050-31-1]	$168
1335508	Ibuprofen (750 mg)	J1E043	0.999 mg/mg (ai)		J (08/06) I (06/02)	[15687-27-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1335701	Idarubicin Hydrochloride (50 mg)	I0D309	955 ug/mg (ai)		H0C061 (11/05) G (11/03) F (06/00)	[57852-57-0]	$518
1336001	Idoxuridine (250 mg)	H1B230			H (07/04)	[54-42-2]	$168
1336205	Ifosfamide (500 mg)	G1C371	1.000 mg/mg (an)		G (03/06) F-1 (11/00) F (02/99)	[3778-73-2]	$168
1336500	Imidazole (200 mg)	G2E031	1.00 mg/mg (ai)		G1B132 (10/06) G (01/04)	[288-32-4]	$526
1336806	Imidurea (200 mg)	H			G (10/99)	[39236-46-9]	$168
1337004	Iminodibenzyl (25 mg)	I0C253			H (11/04)	[494-19-9]	$526
1337809	Imipenem Monohydrate (100 mg)	H0E040	0.929 mg/mg (ai)		G1C296 (05/06) G (01/05) F (01/01)	[74431-23-5]	$168
1338007	Imipramine Hydrochloride (200 mg)	I			H (09/01)	[113-52-0]	$168
1338801	Indapamide (250 mg)	H1E103	0.998 mg/mg (dr)		H (07/06) G (07/02)	[26807-65-8]	$168
1338812	Indapamide Related Compound A (50 mg) (4-Chloro-N-(2-methyl-indol-1-yl)-3-sulfamoylbenzamide) (AS)	F0E052				[63968-75-2]	$526
1339000	Indigotindisulfonate Sodium (500 mg)	H1B153			H (06/03)	[860-22-0]	$168
1339178	Indinavir (100 mg)	F0D308	0.971 mg/mg (ai)			[180683-37-8]	$168
1339189	Indinavir System Suitability (100 mg)	F0D352				[180683-37-8]	$526
1340009	Indocyanine Green (200 mg)	I0B045			H (09/01)	[3599-32-4]	$168
1341001	Indomethacin (200 mg)	J0B165			I (01/04) H (05/99)	[53-86-1]	$168
1342004	Insulin (100 mg)	H				[9004-10-8]	$168
1342106	Insulin Human (100 mg)	I0C383	26.6 USP Insulin Human Units/mg (ai)		H1A031 (07/05) H (11/02) G (04/00)	[11061-68-0]	$168
1342321	Insulin Lispro (5.97 mg)	F0E140	172 USP Insulin Lispro Units/vial			[133107-64-9]	$168
1342208	Insulin (Beef) (100 mg)	F				[11070-73-8]	$168
1342300	Insulin (Pork) (100 mg)	F				[12584-58-6]	$168
1342503	Iocetamic Acid (200 mg)	F				[16034-77-8]	$168
1343007	Iodipamide (200 mg)	G				[606-17-7]	$168
1343517	Iodixanol (200 mg)	F0B240				[92339-11-2]	$168
1343540	Iodixanol Related Compound C (25 mg) (5-Acetyl[3-[[3,5-bis[[(2,3-dihydroxypropyl)amino]-carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B236				n/f	$526
1343550	Iodixanol Related Compound D (50 mg) (5-[Acetyl(2-hydroxy-3-methylpropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B231				[89797-00-2]	$526
1343561	Iodixanol Related Compound E (25 mg) (5-[[3-[[3-[[(2,3-Dihydoxypropyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimino)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B229				n/f	$526
1344305	o-Iodohippuric Acid (100 mg)	F				[147-58-0]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1344509	Iodoquinol (100 mg)	I0D285			H (07/06) G (07/02)	[83-73-8]	$168
1344600	Iohexol (100 mg)	F-1			F (01/99)	[66108-95-0]	$134
1344622	Iohexol Related Compound A (100 mg) (5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F-1			F (10/01)	n/f	$526
1344644	Iohexol Related Compound B (50 mg) (5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F-1			F (01/04)	[76801-93-9]	$526
1344666	Iohexol Related Compound C (100 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide)	F-1			F (09/03)	n/f	$526
1344702	Iopamidol (200 mg)	G				[60166-93-0]	$168
1344724	Iopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoiso-phthalamide)	G				[60166-98-5]	$526
1344735	Iopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide)	F				n/f	$526
1344804	Iopromide (400 mg)	F				[73334-07-3]	$168
1344826	Iopromide Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide)	F				n/f	$526
1344837	Iopromide Related Compound B (50 mg) (5-(Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide)	F				n/f	$526
1345002	Iothalamic Acid (200 mg)	G				[2276-90-6]	$168
1345104	Ioversol (200 mg)	F				[87771-40-2]	$168
1345115	Ioversol Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide)	F				[76801-93-9]	$526
1345126	Ioversol Related Compound B (50 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide)	F				n/f	$526
1345159	Ioxaglic Acid (100 mg)	F				[59017-64-0]	$168
1345206	Ioxilan (400 mg)	F				[107793-72-6]	$168
1345228	Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2-hydroxyethyl)carbamoyl benzoic acid)	F				[22871-58-5]	$526
1346005	Ipodate Calcium (200 mg)	F-1			F (06/06)	[1151-11-7]	$168
1347008	Ipodate Sodium (200 mg)	F-1				[1221-56-3]	$168
1347755	Isoamyl Methoxycinnamate (750 mg/ampule)	F0B017				[71617-10-2]	$168
1348000	Isocarboxazid (200 mg)	F-1				[59-63-2]	$168
1348500	Isoetharine Hydrochloride (250 mg)	F-2				[2576-92-3]	$168
1348907	Isoflupredone Acetate (200 mg)	F0C109				[338-98-7]	$168
1349003	Isoflurane (1 mL)	H1C199			H (12/04)	[26675-46-7]	$168
1349014	Isoflurane Related Compound A (0.1 mL) (1-Chloro-2,2,2-trifluoroethyl chlorodifluoromethyl ether)	F0C232				n/f	$526
1349025	Isoflurane Related Compound B (0.1 mL) (2,2,2-Trifluoroethyldifluoromethyl ether)	F0C233				n/f	$526
1349502	L-Isoleucine (200 mg)	F-2			F-1 (09/02)	[73-32-5]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1349604	Isomalathion (50 mg)	G0D311	0.97 mg/mg (ai)		F1B107 (11/05) F (01/03)	[3344-12-5]	$526
1349626	Isomalt (200 mg)	F0E263	0.511 mg/mg 1,6-GPS; 0.453 mg/mg 1,1-GPM (ai)			[64519-82-0]	$168
1349659	Isometheptene Mucate (200 mg)	F				[7492-31-1]	$168
1349706	Isoniazid (200 mg)	H				[54-85-3]	$168
1350002	Isopropamide Iodide (200 mg)	F-2				[71-81-8]	$168
1350308	Isopropyl Alcohol (1.5 mL/ampule; 3 ampules) (AS)	F0D261	99.9% (ai)			[67-63-0]	$168
1350400	Isopropyl Myristate (500 mg)	J0D247			I1C183 (06/06) I (01/05)	[110-27-0]	$168
1350603	Isopropyl Palmitate (500 mg)	I			H (10/99)	[142-91-6]	$168
1351005	Isoproterenol Hydrochloride (125 mg)	K				[51-30-9]	$134
1352008	Isosorbide (75% solution, 1 g)	I			H-2 (10/00)	[652-67-5]	$168
1353000	Diluted Isosorbide Dinitrate (500 mg of 25% mixture with mannitol)	I2E153	25.1 % (ai)		I-1 (08/06) I (10/99)	[87-33-2]	$168
1353500	Isotretinoin (200 mg)	I1E066	0.998 mg/mg (ai)		I (08/06) H (10/00)	[4759-48-2]	$168
1354003	Isoxsuprine Hydrochloride (200 mg)	F-3				[579-56-6]	$168
1354207	Isradipine (200 mg)	H0E252	0.995 mg/mg (dr)		G0B054 (01/07) F (05/03)	[75695-93-1]	$168
1354218	Isradipine Related Compound A (25 mg) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinedicarboxylate)	F1D243			F (02/06)	n/f	$526
1354309	Ivermectin (200 mg)	G0D408	0.906 mg/mg (ai)		F0B196 (02/06)	[70288-86-7]	$168
1355006	Kanamycin Sulfate (200 mg)	J			I (06/99)	[25389-94-0]	$168
1355709	Powdered Kava Extract (1 g)	F0C161				n/f	$281
1355753	Kawain (200 mg)	F0C160				[500-64-1]	$225
1356009	Ketamine Hydrochloride **CIII** (250 mg)	H0E091	0.998 mg/mg (ai)		G-2 (06/06) G-1 (07/00)	[1867-66-9]	$224
1356020	Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol)	F0C118				[6740-87-0]	$526
1356508	Ketoconazole (200 mg)	G4B179			G-3 (01/04) G-2 (06/01) G-1 (01/99)	[65277-42-1]	$168
1356632	Ketoprofen (200 mg)	H0B216			G (07/04) F-2 (05/99)	[22071-15-4]	$168
1356643	Ketoprofen Related Compound A (25 mg) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) (AS)	H0E028			G (11/05)	[107257-20-5]	$526
1356665	Ketorolac Tromethamine (200 mg)	G1E331	1.000 mg/mg (dr)	2	G (04/07) F-2 (04/99)	[74103-07-4]	$168
1356654	Labetalol Hydrochloride (200 mg)	G1F090	0.998 mg/mg (dr)	2	G (02/07) F-2 (01/02) F-1 (03/01)	[32780-64-6]	$168
1356698	Lactase (200 mg)	F0D032	105,000 USP units/g (ai)			[9031-11-2]	$168
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	88.5% (ai)			[50-21-5]	$168
1356676	Anhydrous Lactose (100 mg)	G1C004			G (12/04) F (06/01)	[63-42-3]	$168
1356687	Lactitol (500 mg)	G0E254	0.997 mg/mg (an)		F0B005 (09/06)	[81025-04-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1356701	Lactose Monohydrate (500 mg)	H0C151			G-1 (07/05) G (08/02)	[5989-81-1]	$168
1356803	Lactulose (1 g)	H			G-1 (08/00)	[4618-18-2]	$168
1356836	Lamivudine (200 mg)	F0C361				[134678-17-4]	$168
1356847	Lamivudine Resolution Mixture A (10 mg)	F0D024				[134678-17-4]	$526
1356880	Lanolin (20 g)	F				[8006-54-0]	$168
1356905	Lanolin Alcohols (5 g)	G0C421	1.00 mg/mg (ai)		F (11/04)	[8027-33-6]	$168
1356916	Lansoprazole (150 mg)	G0D307	0.995 mg/mg (ai)		F0B310 (10/05)	[103577-45-3]	$168
1356927	Lansoprazole Related Compound A (25 mg) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]-methyl]sulfonyl]benzimidazole)	F0B311				n/f	$526
1356950	Lauroyl Polyoxylglycerides (500 mg)	F1E144			F0D020 (08/06)	n/f	$168
1356971	Letrozole (200 mg)	F0B170				[112809-51-5]	$168
1356982	Letrozole Related Compound A (25 mg) (4,4'-(1H-1,3,4-triazol-1-ylmethylene)dibenzonitrile)	G0D298			F0B168 (10/05)	n/f	$526
1357001	L-Leucine (200 mg)	H0B237			G-1 (04/04) G (08/00)	[61-90-5]	$168
1358004	Leucovorin Calcium (500 mg)	K0F033	0.998 mg/mg (an)	2	J2B219 (04/07) J-1 (07/04) J (05/02)	[1492-18-8]	$173
1358503	Leuprolide Acetate (200 mg)	F0C430	0.907 mg/mg (an,fb)			[74381-53-6]	$1,649
1359302	Levamisole Hydrochloride (125 mg)	F2C122			F-1 (05/04)	[16595-80-5]	$134
1359506	Levmetamfetamine **CII** (75 mg)	F1C113	98% (ai)		F(08/05)	[33817-09-3]	$224
1359801	Levobunolol Hydrochloride (200 mg)	H0E047	0.999 mg/mg (dr)		G (04/06)	[27912-14-7]	$168
1359903	Levocarnitine (400 mg)	G0B197			F-2 (06/03) F-1 (12/00)	[541-15-1]	$168
1359925	Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride)	F-1			F (08/01)	[6538-82-5]	$526
1361009	Levodopa (200 mg)	I			H (09/00)	[59-92-7]	$168
1361010	Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)-alanine)	K			J (01/03) I (06/00)	[27244-64-0]	$526
1420006	Levodopa Related Compound B (50 mg) (3-Methoxytyrosine)	I0C300			H (07/04)		$526
1362500	Levonordefrin (200 mg)	F-1				[829-74-3]	$168
1363004	Levopropoxyphene Napsylate (300 mg)	G				[55557-30-7]	$168
1364007	Levorphanol Tartrate **CII** (500 mg)	I0D138	1.000 mg/mg (an)		H (07/05) G (03/01)	[5985-38-6]	$224
1365000	Levothyroxine (500 mg)	L0D226	0.994 mg/mg (dr)		K (12/06) J (10/00)	[51-48-9]	$168
1366002	Lidocaine (250 mg)	L				[137-58-6]	$168
1367005	Lincomycin Hydrochloride (200 mg)	H2B130			H-1 (01/04)	[7179-49-9]	$168
1367504	Lindane (200 mg)	F-2				[58-89-9]	$168
1367708	Linoleoyl Polyoxylglycerides (100 mg)	F0C283				n/f	$168
1368008	Liothyronine (250 mg)	M0D338	0.993 mg/mg (dr)		L1C262 (12/05) L (08/04) K (08/01)	[6893-02-3]	$168
1368609	Lisinopril (300 mg)	I1C045			I (11/04) H (09/01) G (10/99)	[83915-83-7]	$168
1369000	Lithium Carbonate (300 mg)	G0B031			F-2 (01/03) F-1 (01/01)	[554-13-2]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1370000	Loperamide Hydrochloride (200 mg)	H0C202			G-2 (09/04) G-1 (02/03)	[34552-83-5]	$168
1370203	Loracarbef (200 mg)	F				[121961-22-6]	$168
1370225	Loracarbef L-Isomer (25 mg)	F				n/f	$526
1370270	Loratadine (200 mg)	G0D344	0.999 mg/mg (ai)		F0C414 (12/05)	[79794-75-5]	$281
1370280	Loratadine Related Compound A (15 mg) (8-Chloro-6,11-dihydro-11(4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b] pyridine)	F0D229				[100643-71-8]	$526
1370291	Loratadine Related Compound B (15 mg) (8-Chloro-6,11-dihydro-11(N-methyl-4-piperidinylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine)	F0D230				n/f	$526
1370305	Lorazepam **CIV** (200 mg)	I1D404	0.998 mg/mg (ai)		I0C048 (06/06) H0B023 (06/04)	[846-49-1]	$224
1370327	Lorazepam Related Compound A (25 mg) (7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-acetoxy-2H-1,4-benzodiazepin-2-one)	G			F-1 (06/01)	[2848-96-6]	$526
1370338	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)	G			F-2 (01/04)	[2958-36-3]	$526
1370349	Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde)	H			G (01/03) F-3 (01/02)	n/f	$526
1370350	Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid)	G0A014			F-2 (01/04)	[54643-79-7]	$526
1370360	Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol)	H0D254	0.98 mg/mg (ai)		G (02/06) F-3 (07/02) F-2 (04/99)	n/f	$526
1370462	Losartan Potassium (250 mg)	F0D287	0.998 mg/mg (ai)			[124750-99-8]	$168
1370600	Lovastatin (125 mg)	H2C012			H1B067 (01/04) H (08/03)	[75330-75-5]	$134
1370611	Lovastatin Related Compound A (10 mg) (dihydro-lovastatin)	H0D274			G0C326 (11/05) F0B235 (09/04)	n/f	$526
1370702	Loxapine Succinate (125 mg)	H0C094	0.998 mg/mg (dr)		G0B026 (11/05) F-2 (06/03) F-1 (07/01) F (03/99)	[27833-64-3]	$134
1370804	Lutein (1 mL)	F0D291	0.056 mg/mg in corn oil (ai)			[127-40-2]	$919
1370906	Lynestrenol (20 mg)	F0B314				[52-76-6]	$219
1371002	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) (AS) (LSD)	I				[50-37-3]	$584
1371501	L-Lysine Acetate (200 mg)	F1C027			F (11/04)	[57282-49-2]	$168
1372005	L-Lysine Hydrochloride (200 mg)	I0E230	1.00 mg/mg (dr)	2	H (03/07) G (07/00)	[657-27-2]	$168
1373008	Mafenide Acetate (400 mg)	F1D216	0.999 mg/mg (an)		F (07/05)	[13009-99-9]	$168
1286209	Mafenide Related Compound A (50 mg) (4-Formylbenzenesulfonamide)	G0C351	1.00 mg/mg (dr)		F (08/05)	n/f	$526
1374000	Magaldrate (200 mg)	F-1				[74978-16-8]	$168
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	41.8% MgO (ai)			[546-93-0]	$168
1374248	Magnesium Chloride (1 g) (AS)	F0D157	100.3% (ai)			[7791-18-6]	$168
1374260	Magnesium Hydroxide (1 g) (AS)	F0D158	98.5% (dr)			[1309-42-8]	$168
1374292	Magnesium Phosphate (2 g) (AS)	F0E107	99.8% (ig)			[7757-87-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1374306	Magnesium Salicylate (200 mg)	F2B081			F-1 (01/04)	[18917-95-8]	$168
1374340	Magnesium Stearate (5 g) (AS)	F0D214	65% Stearate 29% Palmitate 4.8% Mg (ai)			[577-04-0]	$168
1374361	Magnesium Sulfate (1 g) (AS)	F0D160	99.8% (ig)			[10034-99-8]	$168
1374408	Malathion (500 mg)	G0D143	0.993 mg/mg (ai)		F-1 (11/05) F (08/01)	[121-75-5]	$168
1374500	Maleic Acid (300 mg)	G			F-2 (12/00)	[110-16-7]	$526
1374601	Malic Acid (200 mg)	G0B158			F-1 (04/03)	[6915-15-7]	$168
1374907	Maltitol (200 mg)	G			F-1 (12/99)	[585-88-6]	$168
1375003	Maltol (4 g) (FCC)	G			F-1 (12/99)	[118-71-8]	$168
1375025	Maltose Monohydrate (500 mg)	F0E035	0.947 mg/mg (ai)			[6363-53-7]	$168
1375058	Mandelic Acid (500 mg)	F				[90-64-2]	$168
1375069	Mangafodipir Trisodium (200 mg)	F0D272	0.996 mg/mg (an)			[140678-14-4]	$168
1375070	Mangafodipir Related Compound A (15 mg) (manganese (II) dipyridoxyl monophosphate sodium salt)	F0D266				n/f	$526
1375080	Mangafodipir Related Compound B (15 mg) (manganese (II) dipyridoxyl diphosphate mono-overalkylated sodium salt)	F0D267				n/f	$526
1375091	Mangafodipir Related Compound C (15 mg) (manganese (III) dipyridoxyl diphosphate sodium salt)	F0D283				n/f	$526
1375127	Manganese Chloride (1 g) (AS)	F0D150	99.6% (dr)			[13446-34-9]	$168
1375149	Manganese Sulfate (1 g) (AS)	F0D151	99.8% (ai)			[10034-96-5]	$168
1375105	Mannitol (200 mg)	I0B212			H (03/04)	[69-65-8]	$168
1375207	Maprotiline Hydrochloride (200 mg)	H			G (07/02)	[10347-81-6]	$168
1375309	Mazindol **CIV** (350 mg)	H			G (02/03)	[22232-71-9]	$224
1375502	Mebendazole (200 mg)	G1C195			G (11/04)	[31431-39-7]	$168
1375706	Mebrofenin (100 mg)	F				[78266-06-5]	$168
1376006	Mecamylamine Hydrochloride (200 mg)	F-2				[826-39-1]	$168
1376505	Mechlorethamine Hydrochloride (100 mg) (FOR U.S. SALE ONLY)	F-1			F (09/00)	[55-86-7]	$168
1377009	Meclizine Hydrochloride (500 mg)	I-1				[31884-77-2]	$168
1377508	Meclocycline Sulfosalicylate (300 mg)				G (03/07)	[73816-42-9]	$168
1377803	Meclofenamate Sodium (500 mg)	H				[6385-02-0]	$168
1378001	Medroxyprogesterone Acetate (200 mg)	I0D013	0.995 mg/mg (ai)		H-2 (09/05) H-1 (04/03)	[71-58-9]	$168
1378012	Medroxyprogesterone Acetate Related Compound A (25 mg) (4,5-beta-Dihydromedroxyprogesterone acetate)	F0C427	1.00 mg/mg (ai)			n/f	$541
1379004	Medrysone (500 mg)	F				[2668-66-8]	$168
1379605	Mefenamic Acid (200 mg)	G0C025			F3A032 (08/04) F-2 (01/03)	[61-68-7]	$168
1379059	Mefloquine Hydrochloride (100 mg)	F0E165				[51773-92-3]	$168
1379060	Mefloquine Related Compound A (20 mg) (threo-mefloquine)	F0E166				n/f	$526
1379106	Megestrol Acetate (500 mg)	I			H (05/00)	[595-33-5]	$168
1379140	Meglumine (500 mg) (AS)	F0D385	99.5% (dr)			[6284-40-8]	$168
1380105	Melatonin (100 mg) (AS)	F0E027	0.999 mg/mg (dr)			[73-31-4]	$179
1379254	Melengestrol Acetate (125 mg)	F0D304	0.993 mg/mg (ai)			[2919-66-6]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1379265	Melengestrol Acetate Related Compound A (25 mg) (17-hydroxy-16-methylenepregna-4-ene-3,20-dione 17-acetate)	F0D305	1.00 mg/mg (ai)			n/f	$526
1379276	Melengestrol Acetate Related Compound B (25 mg) (6,16-dimethylene-17-hydroxypregna-4-ene-3,20-dione 17-acetate)	F0D306	0.98 mg/mg (ai)			n/f	$526
1379401	Meloxicam (400 mg)	F0E158	0.999 mg/mg (ai)			[71125-38-7]	$281
1379412	Meloxicam Related Compound A (25 mg) (4-Hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylic acid ethyl ester 1,1-dioxide)	F0E167				[24683-26-9]	$526
1379423	Meloxicam Related Compound B (25 mg) (2-Amino-5-methyl-thiazole)	F0E168	1.00 mg/mg (ai)			[7305-71-7]	$526
1379434	Meloxicam Related Compound C (30 mg) (Isopropyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide)	F0E159	0.99 mg/mg (ai)			n/f	$526
1379445	Meloxicam Related Compound D (30 mg) (4-Methoxy-2-methyl-(5-methyl-1,3-thiazol-2yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide)	F0E160	1.00 mg/mg (ai)			n/f	$526
1379300	Melphalan Hydrochloride (100 mg) (FOR U.S. SALE ONLY)	H0B296	0.975 mg/mg (ai)		G (01/05)	[3223-07-2]	$168
	Melting Point Standards - See Cross Reference Section						
1381006	Menadione (200 mg) (Vitamin K3)	H-3			H-2 (02/00)	[58-27-5]	$168
1381709	Menthol (250 mg)	I0B049			H (04/03)	[2216-51-5]	$168
1381742	Menthyl Anthranilate (500 mg/ampule)	F0B103				[134-09-8]	$168
1382009	Mepenzolate Bromide (200 mg)	F				[76-90-4]	$168
1383001	Meperidine Hydrochloride **CII** (200 mg)	I			H-1 (12/99)	[50-13-5]	$224
1385007	Mephenytoin (250 mg)	G				[50-12-4]	$168
1386000	Mephobarbital **CIV** (250 mg)	G			F (01/01)	[115-38-8]	$224
1387002	Mepivacaine Hydrochloride (200 mg)	H			G-4 (02/99)	[1722-62-9]	$168
1388005	Meprednisone (200 mg)				G (03/07)	[1247-42-3]	$168
1389008	Meprobamate **CIV** (200 mg)	G-1			G (03/02)	[57-53-4]	$224
1390007	Meprylcaine Hydrochloride (200 mg)	F				[956-03-6]	$168
1391000	3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt (75 mg)	G				n/f	$526
1392002	Mercaptopurine (500 mg)	I2C263			I-1 (10/04) I (07/02) H (12/99)	[6112-76-1]	$168
1392454	Meropenem (300 mg)	F0C201				[119478-56-7]	$197
1392705	Mesalamine (200 mg)	H0C341			G1B001 (06/05) G (01/03) F-1 (03/00)	[89-57-6]	$168
1393005	Mesoridazine Besylate (250 mg)	J0C117			I-1 (12/04)	[32672-69-8]	$168
1394008	Mestranol (200 mg)	K0C065			J (07/04) I-1 (09/99)	[72-33-3]	$168
1395500	Metaproterenol Sulfate (200 mg)	F-3				[5874-97-5]	$168
1396003	Metaraminol Bitartrate (200 mg)	F-3				[33402-03-8]	$168
1396309	Metformin Hydrochloride (200 mg)	H0E136	1.00 mg/mg (ai)		G0D271 (07/06) F0C209 (08/05)	[1115-70-4]	$197
1396310	Metformin Related Compound A (50 mg) (1-Cyanoguanidine)	F0C210				[461-58-5]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1396331	Metformin Related Compound B (25 mg) (1-Methylbiguanide hydrochloride)	F0F019				[1674-62-0]	$526
1396342	Metformin Related Compound C (25 mg) (N,N-Dimethyl-[1,3,5]triazine-2,4,6-triamine)	F0E343				[1985-46-2]	$526
1396364	Methacholine Chloride (500 mg) (AS)	F0D222	100.0% (dr)			[62-51-1]	$182
1396400	Methacrylic Acid Copolymer Type A (200 mg)	G0B140			F-2 (04/03)	n/f	$168
1396502	Methacrylic Acid Copolymer Type B (200 mg)	G0B141			F-2 (04/03)	n/f	$168
1396604	Methacrylic Acid Copolymer Type C (100 mg)	G1B088			G (08/03)	n/f	$134
1397006	Methacycline Hydrochloride (200 mg)	I0C348	903 ug/mg (ai)		H (10/05) G (04/01)	[3963-95-9]	$168
1398009	Methadone Hydrochloride **CII** (200 mg)	I0B163			H-1 (08/03)	[1095-90-5]	$224
1399001	Methamphetamine Hydrochloride **CII** (125 mg)	I				[51-57-0]	$224
1401001	Methantheline Bromide (200 mg)	F-1				[53-46-3]	$168
1402004	Methapyrilene Fumarate (200 mg)	F-1				[33032-12-1]	$168
1404000	Methaqualone **CI** (500 mg)	F-1				[72-44-6]	$224
1405002	Metharbital **CIII** (200 mg)	F-2			F-1 (07/99)	[50-11-3]	$224
1406005	Methazolamide (500 mg)	H0B239			G-1 (05/04)	[554-57-4]	$168
1407008	Methdilazine (200 mg)	F-1				[1982-37-2]	$168
1408000	Methdilazine Hydrochloride (200 mg)	G				[1229-35-2]	$168
1409003	Methenamine (500 mg)	H0C047			G (05/04)	[100-97-0]	$168
1409502	Methenamine Hippurate (200 mg)	F				[5714-73-8]	$168
1409604	Methenamine Mandelate (200 mg)	G0C304			F-2 (01/05) F-1 (11/00)	[587-23-5]	$168
1410002	Methicillin Sodium (500 mg) (AS)	J0C333			I1B186 (11/04) I (03/03) H (03/00)	[7246-14-2]	$168
1411005	Methimazole (200 mg)	G			F (02/01)	[60-56-0]	$168
1411504	L-Methionine (200 mg)	G1D398	1.00 mg/mg (ai)		G (08/06) F-2 (11/99)	[63-68-3]	$168
1412008	Methocarbamol (200 mg)	H2B029			H-1 (03/04)	[532-03-6]	$168
1413000	Methohexital **CIV** (500 mg)	G0D252	1.000 mg/mg (an)		F-2 (08/05)	[18652-93-2]	$224
1414003	Methotrexate (500 mg)	I1D108	0.999 mg/mg (an)		I (01/06)	[59-05-2]	$168
1415006	Methotrimeprazine (125 mg)	F-2			F-1 (05/99)	[60-99-1]	$134
1416009	Methoxamine Hydrochloride (200 mg)	F				[61-16-5]	$168
1417001	Methoxsalen (500 mg)	H				[298-81-7]	$168
1418004	Methoxyflurane (1 mL)	G				[76-38-0]	$168
1419007	Methoxyphenamine Hydrochloride (250 mg)	F				[5588-10-3]	$168
1421009	Methscopolamine Bromide (200 mg)	G1D004	0.999 mg/mg (dr)		G (02/05)	[155-41-9]	$168
1422001	Methsuximide (500 mg)	F-2			F-1 (08/99)	[77-41-8]	$168
1424007	Methyclothiazide (200 mg)	G				[135-07-9]	$168
1424018	Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide)	G			F-2 (12/00)	n/f	$526
1424109	Methyl Alcohol (3 x 1.5 mL)	F0D015	0.999 mg/mg (ai)			[67-56-1]	$168
1424211	Methylbenzethonium Chloride (500 mg)	F0E101				[25155-18-4]	$177
1424222	Methyl Benzylidene Camphor (200 mg)	F0B118				[36861-47-9]	$168
1424233	Methyl Caprate (300 mg)	G0D087			F (04/06)	[110-42-9]	$168
1424244	Methyl Caproate (300 mg)	F				[106-70-7]	$168
1424255	Methyl Caprylate (300 mg)	G0D064	1.00 mg/mg (ai)		F (07/05)	[111-11-5]	$168
1424506	Methylcellulose (1 g) (AS)	G0B222			F-2 (05/03)	[9004-67-5]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) (AS) (STP)	F				[15589-00-1]	$224
1426002	Methyldopa (500 mg)	I1E059	0.999 mg/mg (an)		I (02/06)	[41372-08-1]	$168
1427005	Methyldopate Hydrochloride (200 mg)	G-2				[2508-79-4]	$168
1428008	Methylene Blue (250 mg)	H0D163	1.000 mg/mg (dr) (Colorimetric) 0.90 mg/mg (dr) (TLC)		G (08/05)	[7220-79-3]	$168
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) (AS) (MDA)	F-1				[6292-91-7]	$224
1430000	Methylergonovine Maleate (50 mg) **(List Chemical)**	J			I (05/02)	[57432-61-8]	$168
1430305	Methyl Laurate (500 mg)	G0C356	0.998 mg/mg (ai)		F (03/05)	[111-82-0]	$168
1430327	Methyl Linoleate (5 x 50 mg)	G0D107	0.99 mg/mg (ai)		F (07/06)	[112-63-0]	$168
1430349	Methyl Linolenate (5 x 50 mg)				F (09/06)	[301-00-8]	$168
1430509	3-O-Methylmethyldopa (50 mg)	G-1				n/f	$526
1431002	Methyl 5-methyl-3-isoxazolecarboxylate (25 mg)	F-1			F (01/01)	n/f	$526
1431501	Methyl Myristate (300 mg)	G0C357	0.998 mg/mg (ai)		F (03/05)	[124-10-7]	$168
1431556	Methyl Oleate (500 mg)	G0C148			F (04/04)	[112-62-9]	$168
1431603	Methyl Palmitate (300 mg)	G0E329	1.00 mg/mg (ai)		F(02/07)	[112-39-0]	$168
1431625	Methyl Palmitoleate (300 mg)	F				n/f	$168
1432005	Methylparaben (125 mg)	K0C382	0.999 mg/mg (dr)		J-1 (10/05) J (03/03))	[99-76-3]	$134
1433008	Methylphenidate Hydrochloride **CII** (125 mg)	I1C241			I (04/05) H (05/01)	[298-59-9]	$179
1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)	F0C368	0.5 mg/mL (ai)			n/f	$605
1434022	Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride)	G			F-2 (10/99)	n/f	$526
1435003	Methylprednisolone (200 mg)	I0E170	0.995 mg/mg (dr)		H (07/06)	[83-43-2]	$168
1436006	Methylprednisolone Acetate (200 mg)	H0D148	0.995 mg/mg (ai)		G-2 (05/05) G-1 (02/00)	[53-36-1]	$168
1437009	Methylprednisolone Hemisuccinate (200 mg)	I0C146			H (07/04)	[2921-57-5]	$168
1437450	Methyl Salicylate (2 mL) (AS)	F0D070	99.1 % (ai)			[119-36-8]	$168
1437508	Methyl Stearate (300 mg)	G0E290	1.0 mg/mg (ai)		F (11/06)	[112-61-8]	$168
1438001	Methyltestosterone **CIII** (200 mg)	J1E324	0.996 mg/mg (dr)		J (02/07) I (11/01)	[58-18-4]	$224
1440003	Methysergide Maleate (350 mg)	H1F038	0.997 mg/mg (dr)		H (12/06)	[129-49-7]	$260
1440808	Metoclopramide Hydrochloride (500 mg)	H0D121	0.999 mg/mg (an)		G (06/05) F-2 (06/99)	[54143-57-6]	$168
1441006	Metocurine Iodide (300 mg)	G				[7601-55-0]	$168
1441200	Metolazone (200 mg)	G0B246			F-1 (05/03)	[17560-51-9]	$168
1441287	Metoprolol Fumarate (200 mg)	F				[119637-66-0]	$168
1441232	Metoprolol Related Compound A (20 mg) ((+/-)1-(ethylamino)-3-[4-(2-methoxyethyl)phenoxy]-propan-2-ol)	F0C343				n/f	$563
1441243	Metoprolol Related Compound B (50 mg) ((+/-)1-chloro-2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]-propane)	G0E189		2	F0C377 (03/07)	n/f	$563

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1441254	Metoprolol Related Compound C (20 mg) ((+/-)4-[2-Hydroxy-3-(1-methylethyl)aminopropoxy]-benzaldehyde)	F0C344				n/f	$563
1441265	Metoprolol Related Compound D (50 mg) ((+/-)N,N-bis-[2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl](1-methylethyl)amine hydrochloride)	G0E188			F0C378 (12/06)	n/f	$563
1441298	Metoprolol Succinate (200 mg)	F0C415	0.998 mg/mg (ai)			[98418-47-4]	$168
1441301	Metoprolol Tartrate (200 mg)	H1B059			H (01/04) G-1 (11/99)	[56392-17-7]	$168
1441505	Metrizamide (500 mg)	F				[31112-62-6]	$168
1442009	Metronidazole (100 mg)	J0C316	1.000 mg/mg (dr)		I (07/05)	[443-48-1]	$168
1443001	Metyrapone (200 mg)	H			G (06/01)	[54-36-4]	$168
1443205	Metyrosine (200 mg)	F				[672-87-7]	$168
1443250	Mexiletine Hydrochloride (200 mg)	F3E098	0.999 mg/mg (dr)		F-2 (02/06) F-1 (09/02)	[5370-01-4]	$168
1443307	Mezlocillin Sodium (350 mg)	G				[59798-30-0]	$168
1443409	Miconazole (200 mg)	G-1			G (07/02)	[22916-47-8]	$168
1443500	Miconazole Nitrate (200 mg)	J0D011	0.997 mg/mg (dr)		I (06/06) H (06/99)	[22832-87-7]	$168
1443850	Powdered Milk Thistle Extract (250 mg)	F0B321				[84604-20-6]	$281
1443908	Milrinone (500 mg)	H0F083	0.999 mg/mg (an)	2	G0D340 (04/07) F0C050 (09/05)	[78415-72-2]	$281
1443919	Milrinone Related Compound A (50 mg) (1,6-Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide)	F0C051				[80047-24-1]	$526
1444004	Minocycline Hydrochloride (200 mg)	I0C178			H-3 (04/04) H-2 (07/02)	[13614-98-7]	$168
1444208	Minoxidil (125 mg)	H1C168			H (03/04) G (05/99)	[38304-91-5]	$134
1444279	Mirtazapine (350 mg)	F0D155	0.999 mg/mg (an)			[61337-67-5]	$865
1444707	Mitomycin (50 mg)	K			J (07/01)	[50-07-7]	$518
1445007	Mitotane (500 mg)	G0C044			F (07/04)	[53-19-0]	$168
1445200	Mitoxantrone Hydrochloride (400 mg)	I0D174	0.990 mg/mg (an)		H (05/05) G (03/01)	[70476-82-3]	$539
1445211	Mitoxantrone System Suitability Mixture (0.3 mg)	F0D010				n/f	$541
1445404	Modafinil **CIV** (200 mg)	F0D351	0.997 mg/mg (ai)			[68693-11-8]	$270
1445459	Molindone Hydrochloride (500 mg)	F				[15622-65-8]	$168
1445470	Mometasone Furoate (200 mg)	H0E009	0.998 mg/mg (dr)		G0B073 (01/07) F-1 (04/03) F (02/01)	[83919-23-7]	$168
1445481	Monensin Sodium (200 mg)	F0B293				[22373-78-0]	$168
1445506	Monobenzone (200 mg)	F				[103-16-2]	$168
1445925	Monoethanolamine (1 mL)	F0D149				[141-43-5]	$168
1445801	Mono- and Di-acetylated Monoglycerides (200 mg)	F				[68990-54-5]	$168
1446000	Monoglycerides (125 mg)	H1D232	0.963 mg/mg (ai)		H (11/05)	[68990-53-4]	$134
1446600	Monosodium Glutamate (1 g) (AS)	F0D387	99.7% (ai)			[6106-04-3]	$168
1446804	Monostearyl Maleate (100 mg)	G			F-2 (04/00)	[2424-62-6]	$526
1446906	Morantel Tartrate (100 mg)	F0D295	0.997 mg/mg (ai)			[26155-31-7]	$168
1446950	Moricizine Hydrochloride (250 mg)	F1D057	0.999 mg/mg (an)		F (03/05)	[29560-58-5]	$422
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G				[6009-81-0]	$224

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1448005	Morphine Sulfate **CII** (500 mg)	N0E161	0.999 mg/mg (an)		M0D016 (09/06) L0B056 (04/05) K (06/03) J-1 (07/00)	[6211-15-0]	$359
1448504	Moxalactam Disodium (500 mg)	F-1				[64953-12-4]	$168
1448901	Mupirocin (50 mg)	F2C158			F-1 (12/04) F (03/02)	[12650-69-0]	$168
1448923	Mupirocin Lithium (100 mg)	H0C176	926 ug/mg (ai)		G (03/05) F (02/01)	[73346-79-9]	$168
1448990	Myristic Acid (200 mg)	F0E120				[544-63-8]	$168
1449008	Myristyl Alcohol (1 g)	G			F (02/02)	[112-72-1]	$168
1449518	Nabumetone (200 mg)	F0C072				[42924-53-8]	$168
1449530	Nabumetone Related Compound A (15 mg) (1-(6-Methoxy-2-naphthyl)-but-1-en-3-one)	F0D165				n/f	$526
1449700	Nadolol (200 mg)	G0C308	0.995 mg/mg (ai)		F-3 (04/05) F-2 (04/02)	[42200-33-9]	$168
1450007	Nafcillin Sodium (200 mg)	H				[7177-50-6]	$168
1450404	Naftifine Hydrochloride (200 mg)	F				[65473-14-5]	$168
1451000	Nalidixic Acid (200 mg)	G				[389-08-2]	$168
1452002	Nalorphine Hydrochloride **CIII** (250 mg)	I				[57-29-4]	$224
1453005	Naloxone (125 mg)	M0D085	0.999 mg/mg (dr)		L0B124 (09/06) K-1 (12/02) K (07/01)	[465-65-6]	$134
1453504	Naltrexone (200 mg)	H0C150			G1B039 (03/04) G (02/03)	[16590-41-3]	$168
1453526	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride)	F				n/f	$526
1454008	Nandrolone **CIII** (50 mg)	F4D144	1.00 mg/mg (ai)		F-3 (04/05)	[434-22-0]	$605
1455000	Nandrolone Decanoate **CIII** (250 mg)	J0D218	0.999 mg/mg (dr)		I (06/06)	[360-70-3]	$224
1456003	Nandrolone Phenpropionate **CIII** (250 mg)	H				[62-90-8]	$224
1457006	Naphazoline Hydrochloride (200 mg)	L0E207	0.989 mg/mg (dr)		K (02/07)	[550-99-2]	$168
1457301	Naproxen (200 mg)	I-1			I (03/03) H-1 (01/01)	[22204-53-1]	$168
1457403	Naproxen Sodium (200 mg)	J0C379	0.999 mg/mg (dr)		I (07/05)	[26159-34-2]	$168
1457469	Naratriptan Hydrochloride (125 mg)	F0C360	0.998 mg/mg (ai)			[143388-64-1]	$225
1457505	Natamycin (200 mg)	J0D180	0.917 mg/mg (ai)		I (06/05) H (11/99)	[7681-93-8]	$168
1458009	Neomycin Sulfate (200 mg)	L3E135	782 ug/mg (dr)		L-2 (01/07) L-1 (09/01) L (02/99)	[1405-10-3]	$168
1459001	Neostigmine Bromide (200 mg)	G				[114-80-7]	$168
1460000	Neostigmine Methylsulfate (200 mg)	I			H (07/00)	[51-60-5]	$168
1460204	Neotame (200 mg)	F0F044	0.954 mg/mg (ai)			[165450-17-9]	$168
1460215	Neotame Related Compound A (15 mg) (N-[N-(3,3-dimethylbutyl)-L-alpha-aspartyl]-L-phenylalanine)	F0F045	1.00 mg/mg (ai)			n/f	$526
1460500	Netilmicin Sulfate (500 mg)	I0C388	653 ug/mg (dr)		H (01/05) G (05/02)	[56391-57-2]	$168
1460703	Nevirapine Anhydrous (100 mg)	F0D159	0.997 mg/mg (ai)			[129618-40-2]	$168
1460714	Nevirapine Hemihydrate (100 mg)	F0D034				n/f	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1460725	Nevirapine Related Compound A (15 mg) (5,11-Dihydro-6H-11-ethyl-4-methyl-dipyrido[3,2-b2',3'-e][1,4]diazepin-6-one)	F0D035				n/f	$526
1460736	Nevirapine Related Compound B (15 mg) (5,11-Dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one)	F0D033				n/f	$526
1461003	Niacin (200 mg)	I0E295	0.998 mg/mg (ai)		H2C121 (02/07) H-1 (01/05)	[59-67-6]	$168
1462006	Niacinamide (500 mg) (Vitamin B3)	N0E024	0.999 mg/mg (dr)		M-1 (04/06) M (02/01)	[98-92-0]	$168
1463304	Nicotine Bitartrate Dihydrate (500 mg)	G1C070			G (05/05) F (05/99)	[6019-06-3]	$168
1463508	Nifedipine (125 mg)	K0D401	0.998 mg/mg (ai)		J0B243 (03/06) I-1 (04/04)	[21829-25-4]	$134
1463600	Nifedipine Nitrophenylpyridine Analog (25 mg)	K			J (04/01)	n/f	$526
1463701	Nifedipine Nitrosophenylpyridine Analog (25 mg)	K			J (07/02)	n/f	$526
1464001	Nitrofurantoin (500 mg)	J			I-1 (11/02)	[67-20-9]	$168
1021703	Nitrofurantoin Related Compound A (25 mg) (N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine)	F2E037	0.98 mg/mg (ai)		F-1 (08/06)	n/f	$526
1465004	Nitrofurazone (200 mg)	I0E149	0.995 mg/mg (ai)		H-1 (11/06) H (09/01)	[59-87-0]	$168
1465503	Nitrofurfural Diacetate (100 mg)	G0D066	0.99 mg/mg (ai)		F-1 (12/04)	[92-55-7]	$526
1466007	Nitrofurazone Related Compound A (500 mg) (5-Nitro-2-furfuraldazine)	H0B100			G (07/03)	n/f	$526
1466506	Diluted Nitroglycerin (5 ampules, approx. 200 mg of a 0.948% solution in propylene glycol each)	G				[55-63-0]	$168
1467804	Nizatidine (200 mg)	G			F-1 (06/00)	[76963-41-2]	$168
1467950	Nonoxynol 9 (0.5 mL)	H-1			H (03/02)	[26027-38-3]	$168
1468002	Nonoxynol 10 (200 mg)	F				[26027-38-3]	$168
1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)	H1B035			H (03/03) G (03/00)	[1088-11-5]	$605
1468501	Norepinephrine Bitartrate (125 mg)	I0C381			H (04/05)	[69815-49-2]	$134
1469005	Norethindrone (200 mg)	K0C307	0.998 mg/mg (ai)		J1B065 (09/05) J-1 (05/03) J (07/02) I-1 (03/01)	[68-22-4]	$168
1470004	Norethindrone Acetate (100 mg)	J1E102	0.997mg/mg (dr)		J0B072 (09/06) I (04/03) H (06/99)	[51-98-9]	$168
1471007	Norethynodrel (200 mg)	G				[68-23-5]	$168
1471506	Norfloxacin (200 mg)	H1D317	0.995 mg/mg (dr)		H (12/06) G (04/01)	[70458-96-7]	$168
1471914	Norgestimate (200 mg)	F0C086				[35189-28-7]	$168
1472000	Norgestrel (125 mg)	J0C269			I (07/04) H (05/99)	[6533-00-2]	$134
1473002	Noroxymorphone Hydrochloride **CII** (50 mg)	H1C177			H (11/04)	n/f	$605
1473206	Norphenylephrine Hydrochloride (25 mg)	F0E205				[15308-34-6]	$526
1474005	Nortriptyline Hydrochloride (200 mg)	I1D054	1.000 mg/mg (dr)		I (05/05) H (04/00)	[894-71-3]	$168
1474504	Noscapine (500 mg)	G				[128-62-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1475008	Novobiocin (200 mg)	H0D327	1012 ug/mg (dr)		G-2 (05/05)	[303-81-1]	$168
1476000	Nylidrin Hydrochloride (200 mg)	F-2				[849-55-8]	$168
1477003	Nystatin (200 mg)	O0D177	5751 Nystatin units/mg (dr)		N1B004 (09/05) N (01/03)	[1400-61-9]	$168
1477900	Octinoxate (500 mg) (Octyl Methoxycinnamate)	H0D213	0.987 mg/mg (ai)		G0C024 (09/05) F0B032 (12/03)	[5466-77-3]	$168
1477943	Octisalate (400 mg) (Octyl Salicylate)	G0D278	0.995 mg/mg (ai)		F0B091 (12/05)	[118-60-5]	$168
1477411	Octocrylene (500 mg)	G0C211			F0B104 (05/04)	[6197-30-4]	$168
1477502	Octoxynol 9 (200 mg)	G			F-2 (07/00)	[9002-93-1]	$168
1477808	Octyldodecanol (200 mg)	H0D059			G (03/06) F-1 (07/99)	[5333-42-6]	$168
1478108	Ofloxacin (200 mg)	G0E180	0.999 mg/mg (ai)		F-2 (07/06) F-1 (08/02)	[82419-36-1]	$168
1478119	Ofloxacin Related Compound A (25 mg) ((RS)-9-fluoro-2,3-dihydro-3-methyl-7-oxo-10-(piperazin-1-yl)-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid)	F0E276				[82419-52-1]	$526
1478130	Oleic Acid (1 g)	F0E001				[112-80-1]	$168
1478152	Oleoyl Polyoxylglycerides (100 mg)	F0C313				n/f	$168
1478254	Olive Oil (1 g) (AS)	F0D175				[8001-25-0]	$168
1478505	Omeprazole (200 mg)	H1B211			H (05/04) G-1 (04/02) G (09/01)	[73590-58-6]	$168
1478516	Omeprazole Related Compound A (15 mg) (Omeprazole Sulfone) (AS)	F0D363				[88546-55-8]	$526
1478571	Ondansetron (300 mg)	F0E281	0.999 mg/mg (an)			[99614-02-5]	$225
1478582	Ondansetron Hydrochloride (300 mg)	G0D154	0.993 mg/mg (an)		F0C222 (05/05)	[103639-04-9]	$225
1478593	Ondansetron Related Compound A (50 mg) (3[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4H-carbazol-4-one hydrochloride)	F0C191				[119812-29-2]	$526
1478618	Ondansetron Related Compound C (50 mg) (1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one)	F0C251				[27397-31-1]	$526
1478629	Ondansetron Related Compound D (50 mg) (1,2,3,9-Tetrahydro-9-methyl-3-methylene-4H-carbazol-4-one)	F0C226				n/f	$526
1478630	Ondansetron Resolution Mixture (50 mg)	F0D242				n/f	$526
1479009	Orphenadrine Citrate (200 mg)	G			F-4 (05/02)	[4682-36-4]	$168
1479010	Orphenadrine Related Compound A (50 mg) ((RS)-N,N-dimethyl-2-[(3-methylphenyl)-phenylmethoxy]ethanamine citrate) (AS)	F0F042		1		n/f	$526
1481000	Oxacillin Sodium (200 mg)	J			I (03/02)	[7240-38-2]	$168
1482003	Oxandrolone **CIII** (50 mg)	H0E223	0.994 mg/mg (ai)		G0B220 (08/06) F-4 (07/03)	[53-39-4]	$224
1482207	Oxaprozin (200 mg)	F0C115				[21256-18-8]	$168
1483006	Oxazepam **CIV** (200 mg)	H0D259	1.000 mg/mg (dr)		G-1 (08/05) G (12/00)	[604-75-1]	$224
1483301	Oxfendazole (200 mg)	F0C128				[53716-50-0]	$168
1483505	Oxprenolol Hydrochloride (200 mg)	I0C344			H (02/05)	[6452-73-9]	$168
1484009	Oxtriphylline (500 mg)	G				[4499-40-5]	$168
1485001	Oxybenzone (150 mg)	H0B263			G (11/03) F-2 (12/99)	[131-57-7]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1485103	Oxybutynin Chloride (200 mg)	H0E080	0.998 mg/mg (dr)		G-1 (05/06) G (11/02)	[1508-65-2]	$168
1485114	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)	H0E169	1.00 mg/mg (dr)		G (07/06) F-2 (01/00)	[4335-77-7]	$526
1485125	Oxybutynin Related Compound B (20 mg) (Cyclohexyl mandelic acid methyl ester)	F0D061				[10399-13-0]	$526
1485136	Oxybutynin Related Compound C (20 mg) (4-(Ethylmethylamino)but-2-ynyl(+/-)-2-cyclohexyl-2-hydroxy-2-phenylacetate hydrochloride)	F0D062				n/f	$526
1485191	Oxycodone **CII** (200 mg)	J0F026	0.990 mg/mg (dr)	2	I1D206 (03/07) I0B046 (08/05) H (01/03) G-1 (01/01)	[76-42-6]	$224
1486004	Oxymetazoline Hydrochloride (200 mg)	J0C206			I (03/05)	[2315-02-8]	$168
1487007	Oxymetholone **CIII** (200 mg)	G1B247			G (10/03)	[434-07-1]	$224
1488000	Oxymorphone **CII** (500 mg)	H0B214			G (03/03)	[76-41-5]	$224
1490103	Oxyquinoline Sulfate (200 mg)	F-1			F (07/02)	[134-31-6]	$168
1491004	Oxytetracycline (200 mg)	J0C084	913 ug/mg (ai)		I-1 (10/04)	[6153-64-6]	$168
1491015	Oxytetracycline Hydrochloride (200 mg) (AS)	F0E258				[2058-46-0]	$168
1491300	Oxytocin (5 vials, 46 USP units per vial)	F				[50-56-6]	$168
1491332	Paclitaxel (200 mg)	G0E018	0.989 mg/mg (ai)		F0C180 (04/06)	[33069-62-4]	$1,631
1491343	Paclitaxel Related Compound A (20 mg) (Cephalomannine)	F0C179				[71610-00-9]	$815
1491354	Paclitaxel Related Compound B (20 mg) (10-Deacetyl-7-epipaclitaxel)	G0E019	0.98 mg/mg (ai)		F0C181 (03/06)	nf	$815
1491503	Padimate O (300 mg)	H0B154			G (04/03)	[21245-02-3]	$168
1492040	Palm Oil (1 g) (AS)	F0D179				[8002-75-3]	$168
1492007	Palmitic Acid (500 mg)	K0F048		2	J0D329(01/07) I (12/05)	[57-10-3]	$168
1493000	Pamoic Acid (250 mg)	G-4			G-3 (01/03)	[130-85-8]	$168
1494057	Pancreatin Amylase and Protease (2 g)	I1E218	174 USP Units of amylase activity/mg 124 USP Units of protease activity/mg		I (09/06) H (10/00)	[8049-47-6]	$168
1494079	Pancreatin Lipase (2 g)	I1E327	21.2 USP Units of Lipase Activity/mg (ai)	6	I (05/06) H-1 (03/01)	[8049-47-6]	$168
1494217	Pancuronium Bromide (200 mg)	F0D377	0.99 mg/mg (an)			[15500-66-0]	$303
1494501	Panthenol, Racemic (200 mg)	G			F-1 (02/00)	[16485-10-2]	$168
1494807	Pantolactone (500 mg)	F				[599-04-2]	$526
1495005	Papain (1 g)	I0C389	6700 USP units/mg (ai)		H (06/04) G (12/01)	[9001-73-4]	$168
1496008	Papaverine Hydrochloride (200 mg)	H				[61-25-6]	$168
1497000	Paramethadione (500 mg)	G				[115-67-3]	$168
1498003	Paramethasone Acetate (200 mg)	G			F-1 (05/01)	[1597-82-6]	$168
1498706	Parbendazole (200 mg)	F				[14255-87-9]	$168
1499006	Pargyline Hydrochloride (200 mg)	F-1				[306-07-0]	$168
1500003	Paromomycin Sulfate (125 mg)	G			F-3 (01/01)	[1263-89-4]	$168
1500218	Paroxetine Hydrochloride (350 mg)	G0D003	0.972 mg/mg (ai)		F0B288 (09/04)	[110429-35-1]	$168
1500230	Paroxetine Related Compound B (10 mg) (trans-4-phenyl-3-[(3,4-methylenedioxy)phenoxymethyl]piperidine hydrochloride)	G0D137	0.92 mg/mg (ai)		F0B189 (10/05)	n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1500240	Paroxetine Related Compound C (15 mg) ((+)-trans-Paroxetine hydrochloride)	G0D053	0.96 mg/mg (ai)		F0B192 (05/05)	[130855-30-0]	$526
1500251	Paroxetine Related Compound D (10 mg) (AS) (cis-Paroxetine hydrochloride)	G0E096			F0C228 (12/06)	n/f	$526
1500262	Paroxetine Related Compound E Mixture (25 mg) (1-Methyl-4-(p-fluorophenyl)-1,2,3,6-tetrahydropyridine in Paroxetine Hydrochloride Matrix)	F1F028	0.86 ng/mg (ai)		F0D225 (11/06)	n/f	$526
1500273	Paroxetine Related Compound F (10 mg) (trans(-)-1-Methyl-3-[(1,3-benzodioxol-5-yloxy)-methyl]-4-(4-fluorophenyl)piperidine)	F0D237	1.00 mg/mg (ai)			n/f	$526
1500284	Paroxetine Related Compound G (0.4 mg) ((+/-)trans-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4''-fluorophenyl-4'-phenyl)piperidine hydrochloride)	G0E121	0.4 mg in ~1.5 mg povidone		F0D110 (12/06)	n/f	$526
1500353	Paroxetine System Suitability Mixture A (50 mg)	F0E150				n/f	$526
1500400	Parthenolide (25 mg)	F				[20554-84-1]	$168
1500502	Particle Count Set (2 blanks and 2 suspensions)	J0D067			I (12/05) H (09/02)	n/f	$526
1500557	Peanut Oil (1 g) (AS)	F0D171				[8002-03-7]	$168
1500808	Penbutolol Sulfate (200 mg)	F				[38363-32-5]	$168
1501006	Penicillamine (200 mg)	H1B164			H (01/04)	[52-67-5]	$168
1501108	Penicillamine Disulfide (100 mg)	H			G (07/00)	[20902-45-8]	$526
1502009	Penicillin G Benzathine (200 mg)	J1D164			J (04/06)	[41372-02-5]	$168
1502508	Penicillin G Potassium (200 mg)	J0C349	89.3%/1595 USP Penicillin G units/mg (ai)		I (07/05) H (02/99)	[113-98-4]	$168
1502552	Penicillin G Procaine (200 mg)	G0C271			F-1 (08/04) F (03/99)	[6130-64-9]	$168
1502701	Penicillin G Sodium (150 mg)	L4C366			L-3 (08/06) L-2 (09/01)	[69-57-8]	$168
1504489	Penicillin V (200 mg)	F1C318			F (08/05)	[87-08-1]	$168
1504503	Penicillin V Potassium (200 mg)	H0C213			G-1 (06/04) G (06/00)	[132-98-9]	$168
1505007	Pentazocine **CIV** (500 mg)	I0C418	0.998 mg/mg (dr)		H (01/05) G-1 (11/00)	[359-83-1]	$224
1505506	Pentetic Acid (100 mg)	F-1			F (09/01)	[67-43-6]	$168
1507002	Pentobarbital **CII** (200 mg)	I0D359	0.997 mg/mg (ai)		H3C144 (12/04) H-2 (07/04) H-1 (08/02)	[76-74-4]	$224
1508901	Pentoxifylline (200 mg)	F1D350	0.999 mg/mg (dr)		F0B202 (12/05)	[6493-05-6]	$168
1510007	Pepsin (5 g)	F-2				[9001-75-6]	$168
1510801	Perflubron (0.5 mL)	G0C103			F (04/04)	[423-55-2]	$168
1510845	Pergolide Mesylate (200 mg)	F1C225			F (07/04)	[66104-23-2]	$210
1510867	Pergolide Sulfoxide (50 mg)	F0B014				[72822-01-6]	$210
1511000	Perphenazine (200 mg)	K0F018	0.998 mg/mg (dr)	2	J0B249 (04/07) I (10/03)	[58-39-9]	$168
1511203	Perphenazine Sulfoxide (100 mg)	G-1			G (07/02)	[10078-25-8]	$526
1512002	Phenacemide (250 mg)	F				[63-98-9]	$168
1513005	Phenacetin (500 mg)	H-1			H (09/00)	[62-44-2]	$168
1514008	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)	H3A009			H-2 (02/03) H-1 (06/01)	[62-44-2]	$100
1515000	Phenazopyridine Hydrochloride (200 mg)	H0C426	0.998 mg/mg (dr)		G-4 (12/04)	[136-40-3]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025			G (12/02)	[956-90-1]	$224
1516502	Phendimetrazine Tartrate **CIII** (350 mg)	G			F (01/01)	[50-58-8]	$224
1517006	Phenelzine Sulfate (200 mg)	G			F-1 (04/02)	[156-51-4]	$168
1517301	D-Phenethicillin Potassium (200 mg)	F				n/f	$526
1517607	L-Phenethicillin Potassium (200 mg)	F				n/f	$168
1520000	Phenformin Hydrochloride (200 mg)	G				[834-28-6]	$168
1522006	Phenindione (250 mg)	F				[83-12-5]	$168
1522301	Pheniramine Maleate (100 mg)	F1C342			F (08/04)	[132-20-7]	$168
1523009	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2				[1707-14-8]	$224
1524001	Phenobarbital **CIV** (200 mg)	J				[50-06-6]	$224
1524806	Phenol (500 mg)	F0F029	0.999 mg/mg (ai)	1		[108-95-2]	$168
1524908	Phenolphthalein (250 mg)	F-3				[77-09-8]	$168
1525004	Phenolsulfonphthalein (100 mg)	F-2				[143-74-8]	$168
1525707	Phenothiazine (500 mg) (AS)	F0D231	0.994 mg/mg (dr)			[92-84-2]	$168
1526007	Phenoxybenzamine Hydrochloride (250 mg)	G				[63-92-3]	$168
1526200	Phenoxyethanol (500 mg) (2-Phenoxyethanol)	F0D069	0.998 mg/mg (ai)			[122-99-6]	$168
1528002	Phensuximide (500 mg)	G			F-1 (03/01)	[86-34-0]	$168
1528501	Phentermine Hydrochloride **CIV** (200 mg)	H0B309			G (08/03)	[1197-21-3]	$224
1529005	Phentolamine Hydrochloride (300 mg)	F				[73-05-2]	$168
1530004	Phentolamine Mesylate (200 mg)	I				[65-28-1]	$168
1530503	L-Phenylalanine (200 mg)	H			G (02/02)	[63-91-2]	$168
1530809	Phenylbenzimidazole Sulfonic Acid (200 mg)	F				[27503-81-7]	$168
1531007	Phenylbutazone (250 mg)	J0A008			I-1 (02/03)	[50-33-9]	$168
1533002	Phenylephrine Hydrochloride (125 mg)	K1C290			K (03/05) J (02/99)	[61-76-7]	$134
1533250	Phenylethyl Alcohol (1 mL)	F0D395				[60-12-8]	$168
1533308	5-Phenylhydantoin (100 mg)	F				[89-24-7]	$526
1533851	Phenylpropanediol (100 mg)	F				n/f	$526
1533909	Phenylpropanolamine Bitartrate (100 mg) **(List Chemical)**	F				[67244-90-0]	$168
1534005	Phenylpropanolamine Hydrochloride (250 mg) **(List Chemical)**	J			I (02/02)	[154-41-6]	$168
1534402	Phenyltoloxamine Citrate (100 mg)	F0E127				[1176-08-5]	$168
1534413	Phenyltoloxamine Related Compound A (50 mg) (2-(2-benzylphenoxy)ethylmethylamine hydrochloride)	F0E128				n/f	$526
1535008	Phenytoin (200 mg)	J0E090	0.999 mg/mg (ai)		I2B233 (05/06) I-1 (03/04) I (04/01)	[57-41-0]	$168
1535507	Phenytoin Sodium (200 mg)	H1E335	1.000 mg/mg (dr) (UV)		H (02/07) G (05/99)	[630-93-3]	$168
1535019	Phenytoin Related Compound A (50 mg) (2,2-Diphenylglycine)	F0C155				[3060-50-2]	$526
1535020	Phenytoin Related Compound B (50 mg) (alpha-((aminocarbonyl)amino)-alpha-phenyl benzeneacetic acid)	F0C157				[6802-95-5]	$526
1535700	Phosphated Riboflavin (100 mg)	G1B286			G (07/04)	[6184-17-4]	$134
1535802	Phosphoric Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D026	86.8% (ai)			[7664-38-2]	$168
1537003	Physostigmine Salicylate (200 mg)	H-1			H (06/00)	[57-64-7]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1538006	Phytonadione (500 mg) (Vitamin K1)	N0B303			M-1 (07/04) M (09/01)	[84-80-0]	$168
1538505	Pilocarpine (300 mg)	F				[92-13-7]	$168
1538902	Pilocarpine Hydrochloride (200 mg)	I0D055	0.998 mg/mg (dr)		H (09/05)	[54-71-7]	$168
1539009	Pilocarpine Nitrate (200 mg)	I1E138	0.991 mg/mg (dr)		I (11/06)	[148-72-1]	$168
1539508	Pimozide (200 mg)	G				[2062-78-4]	$168
1539701	Pindolol (200 mg)	I0B210			H-1 (12/04)	[13523-86-9]	$168
1541000	Piperacetazine (250 mg)	F				[3819-00-9]	$168
1541500	Piperacillin (500 mg)	H				[66258-76-2]	$168
1541703	Piperazine Adipate (200 mg)	F				[142-88-1]	$168
1541805	Piperazine Citrate (200 mg)	F				[144-29-6]	$168
1541907	Piperazine Dihydrochloride (200 mg)	F				[142-64-3]	$168
1542003	Piperazine Phosphate (200 mg)	F				[14538-56-8]	$168
1543006	Piperidolate Hydrochloride (200 mg)	F				[129-77-1]	$168
1544508	Piroxicam (200 mg)	H1D038	0.998 mg/mg (ai)		H (07/05) G (01/99)	[36322-90-4]	$168
1545205	Plicamycin (50 mg)	H			G (04/00)	[18378-89-7]	$518
1545409	Polacrilex Resin (100 mg)	F1D233			F (05/06)	n/f	$168
1545500	Polacrilin Potassium (200 mg)	F-2			F-1 (09/00)	n/f	$168
1546106	Poloxalene (500 mg)	F0C009				[9003-11-6]	$168
1546300	Polydimethylsiloxane (500 mg)	H0C020			G-5 (05/04) G-4 (06/01)	[9016-00-6]	$168
1546707	Polyethylene, High Density (3 strips)	G1D115			G (06/05) F-1 (04/01)	[9002-88-4]	$168
1546809	Low-Density Polyethylene (3 strips)	H0E114			G1B166 (10/06) G (06/04) F-2 (12/99)	[9002-88-4]	$168
1546401	Polyethylene Glycol 200 (1 g)	F0E316				[25322-68-3]	$168
1546423	Polyethylene Glycol 300 (1 g)	F0E336				[25322-68-3]	$168
1546445	Polyethylene Glycol 400 (1 g)	F0E344				[25322-68-3]	$168
1546467	Polyethylene Glycol 600 (1 g)	F0E345		1		[25322-68-3]	$168
1546489	Polyethylene Glycol 1000 (1 g)	F0F008		1		[25322-68-3]	$168
1546503	Polyethylene Glycol 1500 (1 g)	F0F009		1		[25322-68-3]	$168
1546525	Polyethylene Glycol 3000 (1 g)	F0F013				[25322-68-3]	$168
1546547	Polyethylene Glycol 3350 (1 g)	F0F012				[25322-68-3]	$168
1546569	Polyethylene Glycol 4000 (1 g)	F0F040		1		[25322-68-3]	$168
1546580	Polyethylene Glycol 6000 (1 g)	F0F041		1		[25322-68-3]	$168
1546605	Polyethylene Glycol 8000 (1 g)	F0F050		1		[25322-68-3]	$168
1546627	Polyethylene Glycol 10000 (1 g)	F0F051		1		[25322-68-3]	$168
1546649	Polyethylene Glycol 12000 (1 g)	F0F052		1		[25322-68-3]	$168
1546650	Polyethylene Glycol 20000 (1 g)	F0F053		1		[25322-68-3]	$168
1546660	Polyethylene Glycol 35000 (1 g)	F0F054		1		[25322-68-3]	$168
1546853	Polyethylene Oxide (100 mg)	F-1				[25322-68-3]	$168
1546900	Polyethylene Terephthalate (PET) (3 Strips)	F				[25038-59-9]	$168
1546922	Polyethylene Terephthalate G (PETG) (3 Strips)	F				[25640-14-6]	$168
1546966	Polyisobutylene (1 g)	F0E108				[9003-27-4]	$168
1547007	Polymyxin B Sulfate (200 mg)	K			J-1 (09/99)	[1405-20-5]	$168
1547200	Polyoxyl 35 Castor Oil (1 g)	F0E116				[61791-12-6]	$168
1547801	Polyoxyl 20 Cetostearyl Ether (100 mg)	F0C292				[9004-95-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1372402	Polyoxyl Lauryl Ether (500 mg)	F0E253				[9002-92-0]	$168
1547903	Polyoxyl 40 Stearate (200 mg)	F-2			F-1 (05/00)	[9004-99-3]	$168
1547404	Polyoxyl 50 Stearate (200 mg)	F				[9004-99-3]	$168
1547346	Polyoxyl 2 Stearyl Ether (1 g) (AS)	F0D353				[9005-00-9]	$168
1372606	Polyoxyl 10 Stearyl Ether (1 g)	F0D354				[9005-00-9]	$168
1547368	Polyoxyl 20 Stearyl Ether (1 g) (AS)	F0D355				[9005-00-9]	$168
1547925	Polysorbate 20 (2 g) (AS)	F0D130				[9005-64-5]	$168
1547936	Polysorbate 40 (2 g) (AS)	F0D204				[9005-66-7]	$168
1547947	Polysorbate 60 (2 g) (AS)	F0D131				[9005-67-8]	$168
1547969	Polysorbate 80 (2 g) (AS)	F0D132				[9005-65-6]	$168
1548000	Polythiazide (200 mg)	F-1				[346-18-9]	$168
1549807	Potassium Acetate (500 mg) (AS)	F0E083	99.7% (dr)			[127-08-2]	$168
1548101	Potassium Benzoate (1 g) (AS)	F0D161	0.999 mg/mg (an)			[582-25-2]	$168
1548134	Potassium Bicarbonate (1 g) (AS)	F0D074	99.9% (dr)			[298-14-6]	$168
1549840	Potassium Bitartrate (3 g) (AS)	F0D384	99.9% (dr(			[868-14-4]	$168
1548167	Potassium Carbonate (1 g) (AS)	F0D075	99.8% (dr)			[584-08-7]	$168
1548190	Potassium Chloride (1 g) (AS)	F0D127	100.0% (dr)			[7447-40-7]	$168
1548225	Potassium Citrate (1 g) (AS)	F0D201	100.0% (dr)			[6100-05-6]	$168
1550001	Potassium Gluconate (200 mg)	H0C064			G (06/04)	[299-27-4]	$168
1551004	Potassium Guaiacolsulfonate (500 mg)	J0B292			I-1 (07/03) I (11/00)	[78247-49-1]	$168
1548280	Potassium Iodide (1 g) (AS)	F0D078	100.0% (dr)			[7681-11-0]	$168
1548349	Potassium Nitrate (5 g) (AS)	F0D325	100.0% (ai)			[7757-79-1]	$168
1551128	Dibasic Potassium Phosphate (5 g) (AS)	F0D281	99.7% (dr)			[7758-11-4]	$168
1551139	Monobasic Potassium Phosphate (5 g) (AS)	F0D313	100.0% (dr)			[7778-77-0]	$168
1551140	Potassium Sodium Tartrate (2 g) (AS)	F0D380	99.8% (an)			[6381-59-5]	$168
1548407	Potassium Sorbate (1 g) (AS)	F0D264	99.6% (dr)			[24634-61-5]	$168
1551150	Potassium Sucrose Octasulfate (300 mg)	I0B283			H0B119 (04/04) G-1 (04/03) G (02/01)	[76578-81-9]	$168
1551300	Potassium Trichloroammineplatinate (20 mg)	I0D022	0.84 mg/mg (dr)		H0B149 (12/04) G-1 (01/03) G (07/99)	[13820-91-2]	$526
1551503	Povidone (100 mg)	F-1			F (11/01)	[9003-39-8]	$168
1553000	Pralidoxime Chloride (200 mg)	G-2			G-1 (03/01) G (08/99)	[51-15-0]	$168
1554002	Pramoxine Hydrochloride (500 mg)	I1D197	0.998 mg/mg (dr)		I (10/05) H (11/02)	[637-58-1]	$168
1554501	Prazepam **CIV** (500 mg)	G0C066			F-1 (11/02)	[2955-38-6]	$224
1554603	Praziquantel (200 mg)	G			F-3 (07/02) F-2 (09/00)	[55268-74-1]	$168
1554658	Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a]isoquinolin-4-one)	F-1				n/f	$526
1554669	Praziquantel Related Compound B (50 mg) (2-(cyclohexylcarbonyl)-2,3,6,7-tetrahydro-4H-pyrazino [2,1-alpha]isoquinolin-4-one)	G0E039	0.98 mg/mg (dr)		F-2 (12/05) F-1 (06/00)	n/f	$526
1554670	Praziquantel Related Compound C (50 mg) (2-(N-formylhexahydrohippuroyl)-1,2,3,4-tetrahydroisoquinolin-1-one)	F-2			F-1 (06/00)	n/f	$526
1554705	Prazosin Hydrochloride (500 mg)	H0B254			G-1 (02/05) G (02/01)	[19237-84-4]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1555005	Prednisolone (200 mg)	N0D212	1.000 mg/mg (dr)		M (02/06) L-1 (04/02)	[50-24-8]	$168
1556008	Prednisolone Acetate (200 mg)	J			I-1 (02/02)	[52-21-1]	$168
1556507	Prednisolone Hemisuccinate (125 mg)	H-1			H (02/99)	[2920-86-7]	$134
1557000	Prednisolone Sodium Phosphate (100 mg)	F0E300				[125-02-0]	$168
1558003	Prednisolone Tebutate (200 mg)	F				[7681-14-3]	$168
1559006	Prednisone (250 mg)	N0E330	0.990 mg/mg (ai) (HPLC) 0.997 mg/mg (ai) (Spectrophotometric)	2	M0D211 (03/07) L1B251 (11/05) L (11/04) K-1 (01/02) K (02/00)	[53-03-2]	$168
1559505	Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets)	O0C056			N (06/04) M (09/02) L (11/00)	[53-03-2]	$194
1560990	Prilocaine (200 mg)	F0E073				[721-50-6]	$168
1561008	Prilocaine Hydrochloride (200 mg)	F3B215			F-2 (03/04)	[1786-81-8]	$168
1561019	Prilocaine Related Compound A (100 mg) (o-toluidine hydrochloride)	F0E074	1.00 mg/mg (ai)			[636-21-5]	$526
1561020	Prilocaine Related Compound B (50 mg) ((RS)-N-(4-methylphenyl)-2-(propylamino)propanamide)	F0E075				n/f	$526
1561507	Primaquine Phosphate (200 mg)	F-1				[63-45-6]	$168
1562000	Primidone (200 mg)	H0D399	1.000 mg/mg (dr)		G (07/06) F-6 (04/99)	[125-33-7]	$168
1563003	Probenecid (200 mg)	I0A011			H-1 (03/03)	[57-66-9]	$168
1563309	Probucol (200 mg)	G			F-1 (01/02)	[23288-49-5]	$168
1563320	Probucol Related Compound A (25 mg) (2,2',6,6'-tetra-*tert*-butyldiphenoquinone)	F-2			F-1 (11/04)	n/f	$526
1563331	Probucol Related Compound B (25 mg) (4,4'-dithio-bis(2,6-di-*tert*-butylphenol))	F-2			F-1 (08/03)	n/f	$526
1563342	Probucol Related Compound C (25 mg) (4-[(3,5-di-*tert*-butyl-2-hydroxyphenylthio)isopropylidenethio]-2,6-di-*tert*-butylphenol)	F-2			F-1 (05/00)	n/f	$526
1563502	Procainamide Hydrochloride (200 mg)	H1B117			H (04/03)	[614-39-1]	$168
1564006	Procaine Hydrochloride (200 mg)	I0E089	0.998 mg/mg (dr)		H (12/06)	[51-05-8]	$168
1565009	Procarbazine Hydrochloride (200 mg)	F				[366-70-1]	$168
1566001	Prochlorperazine Maleate (200 mg)	H-1				[84-02-6]	$168
1567004	Procyclidine Hydrochloride (200 mg)	G				[1508-76-5]	$168
1568007	Progesterone (200 mg)	I0D373	0.998 mg/mg (ai)		H6C088(03/06) H-5 (11/04) H-4 (07/02)	[57-83-0]	$134
1568506	L-Proline (200 mg)	G0D146	1.00 mg/mg (dr)		F-2 (09/05) F-1 (01/02)	[147-85-3]	$168
1569000	Promazine Hydrochloride (200 mg)	H0B261			G (10/03)	[53-60-1]	$168
1570009	Promethazine Hydrochloride (500 mg)	K			J-1 (10/00)	[58-33-3]	$168
1570304	Propafenone Hydrochloride (200 mg)	G1C184			G (12/04) F-1 (01/01)	[34183-22-7]	$168
1570508	Propantheline Bromide (200 mg)	I0A019			H (11/02)	[50-34-0]	$168
1329505	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)	G0B258			F-1 (12/03)	n/f	$526
1571001	Proparacaine Hydrochloride (200 mg)	G				[5875-06-9]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1572208	Propionic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D029	99.8 % w/w (ai)			[79-09-4]	$168
1572503	Propofol (200 mg)	F0D379	0.999 mg/mg (ai)			[2078-54-8]	$168
1572536	Propofol Related Compound A (25 mg) (3,3'-5,5'-Tetraisopropyldiphenol)	F0E060	1.00 mg/mg (ai)			n/f	$526
1572547	Propofol Related Compound B (50 mg) (2,6-diisopropylbenzoquinone)	F0D239	0.99 mg/mg (ai)			n/f	$526
1572558	Propofol Related Compound C (50 mg) (2,6-diisopropylphenyl isopropylether)	F0D240				n/f	$526
1572525	Propofol Resolution Mixture (100 mg) (Propofol, 2,6-diisopropylphenyl isopropylether, and 2-isopropyl-6-n-propylphenol)	F0D193				n/f	$526
1573007	Propoxycaine Hydrochloride (200 mg)	F				[550-83-4]	$168
1574000	Propoxyphene Hydrochloride **CII** (1 g)	L0C285			K (09/04)	[1639-60-7]	$224
1575002	Propoxyphene Napsylate **CII** (1 g)	H1C323	0.993 mg/mg (an)		H (05/05)	[26570-10-5]	$224
1575206	Propoxyphene Related Compound A (50 mg) (alpha-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride)	G6D124	0.99 mg/mg (ai)		G-5 (01/06)	n/f	$526
1008002	Propoxyphene Related Compound B (50 mg) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane)	H0D012	0.94 mg/mg (ai)		G-3 (05/05)	n/f	$526
1576005	Propranolol Hydrochloride (200 mg)	I0C170			H-1 (12/04) H (09/01)	[318-98-9]	$168
1576504	Propylene Carbonate (200 mg)	F				[108-32-7]	$168
1576708	Propylene Glycol (1 mL)	I0C022			H (03/04) G (02/99)	[57-55-6]	$168
1576800	Propyl Gallate (200 mg)	G2D203	1.000 mg/mg (dr)		G-1 (10/05) G (01/03)	[121-79-9]	$168
1577008	Propylparaben (200 mg)	J0D402	1.000 mg/mg (ai)		I (08/06) H (02/00)	[94-13-3]	$168
1578000	Propylthiouracil (200 mg)	G			F-1 (01/00)	[51-52-5]	$168
1578500	Prostaglandin A1 (25 mg)	H0B108			G (04/03)	[14152-28-4]	$572
1578554	Prostaglandin B1 (25 mg) ((13E,15S)-15-Hydroxy-9-oxoprosta-8(12),13-dien-1-oic Acid)	F0E022	1.00 mg/mg (ai)			[1345-51-2]	$1,352
1580002	Protriptyline Hydrochloride (200 mg)	G0E034	0.999 mg/mg (dr)		F-1 (12/05)	[1225-55-4]	$168
1581005	Pseudoephedrine Hydrochloride (125 mg) **(List Chemical)**	J1B203			J (01/04) I (05/02)	[345-78-8]	$134
1581504	Pseudoephedrine Sulfate (200 mg) **(List Chemical)**	H0E285	0.999 mg/mg (dr)	2	G1C135 (04/07) G (06/04) F-2 (05/02)	[7460-12-0]	$168
1584003	Pyrantel Pamoate (1 g)	I			H-1 (04/00)	[22204-24-6]	$168
1585006	Pyrazinamide (200 mg)	G			F-2 (02/00)	[98-96-4]	$168
1586009	Pyridostigmine Bromide (200 mg)	I0C324	0.999 mg/mg (dr)		H (01/05)	[101-26-8]	$168
1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P			O-1 (04/00)	[58-56-0]	$168
1588004	Pyrilamine Maleate (200 mg)	I0B276			H (12/03)	[59-33-6]	$168
1589007	Pyrimethamine (200 mg)	H			G (07/02)	[58-14-0]	$168
1592001	Pyrvinium Pamoate (500 mg)	G				[3546-41-6]	$168
1592205	Quazepam **CIV** (200 mg)	F				[36735-22-5]	$224
1592227	Quazepam Related Compound A (30 mg) (7-Chloro-1-(2,2,2-trifluoroethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one)	F				n/f	$526
1592409	Quercetin (500 mg)	G0D407	1.000 mg/mg (an)		F0B015	[6151-25-3]	$168
1593004	Quinacrine Hydrochloride (200 mg)	F-1				[6151-30-0]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1593412	Quinapril Related Compound A (50 mg) (Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate)	F0C114				[103733-49-9]	$526
1593423	Quinapril Related Compound B (50 mg) (3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-,[3S-[2[R*(R*)],3R*]]-)	F0C116				[82768-85-2]	$526
1594007	Quinethazone (1.5 g)	G				[73-49-4]	$168
1594506	Quinic Acid (200 mg)	F				[77-95-2]	$168
1595000	Quinidine Gluconate (200 mg)	H1A028			H (04/03)	[7054-25-3]	$168
1595509	Quinidine Sulfate (500 mg)	H-1			H (12/99)	[6591-63-5]	$168
1596807	Quinine Hydrochloride Dihydrate (1 g)	F0C108				[6119-47-7]	$168
1597005	Quinine Sulfate (500 mg)	I0E071	0.984 mg/mg (an) (HPLC) 1.000 mg/mg (an) (Spectrophotometric)		H (06/06)	[6119-70-6]	$168
1597504	Quininone (50 mg)	H0B034			G-1 (03/04)	[84-31-1]	$526
1598008	3-Quinuclidinyl Benzilate (25 mg) (FOR U.S. SALE ONLY)	H			G (11/01)	[6581-06-2]	$557
1598303	Ramipril (200 mg)	G0D345	0.998 mg/mg (ai)		F0C099 (11/05)	[87333-19-5]	$168
1598314	Ramipril Related Compound A (20 mg) ((2S,3aS,6aS)-1-[(S)2-[[(S)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[b]pyrrole-2-carboxylic acid)	F0C100				[91224-69-0]	$526
1598338	Ramipril Related Compound C (20 mg) (Hexahydroramipril Hydrochloride)	F0E157				n/f	$526
1598347	Ramipril Related Compound D (20 mg) (Ramipril Diketopiperazine)	F0E036				n/f	$526
1598405	Ranitidine Hydrochloride (200 mg)	H0B268			G (01/04)	[66357-59-3]	$168
1598507	Ranitidine Related Compound A (50 mg) (5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate)	H1B137			H (01/04) G (01/01)	[91224-69-0]	$526
1598609	Ranitidine Related Compound B (50 mg) (N,N'-bis[2-[[[5-[(dimethylamino)methyl]-2-furanyl]-methyl]thio]ethyl]-2-nitro-1,1-ethenediamine)	G1D347			G (03/06) F-4 (04/02)	[72126-78-4]	$526
1598700	Ranitidine Related Compound C (50 mg) (N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]-sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine)	I1B136			I (01/04) H (05/01)	[73851-70-4]	$526
1598450	Ranitidine Resolution Mixture (20 mg)	F0E323				n/f	$1,052
1599000	Rauwolfia Serpentina (15 g)	G				[8063-17-0]	$168
1599500	Powdered Red Clover Extract (500 mg)	F0C188				n/f	$281
1600813	Repaglinide (200 mg)	G0D276	0.999 mg/mg (ai)		F0B265 (02/06)	[135062-02-1]	$168
1600824	Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N-acetyl-L-glutamate salt)	F0B267				n/f	$526
1600835	Repaglinide Related Compound B (50 mg) (3-Ethoxy-4-ethoxycarbonyl-phenylacetic acid)	F0B269				[99469-99-5]	$526
1600846	Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl] benzoic acid)	F0B271				[107362-12-9]	$526
1601000	Reserpine (200 mg)	O0C106			N (06/03)	[50-55-5]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1601102	Residual Solvents Mixture - Class 1 (1.2 mL/ampule; 3 ampules)	F0C407				n/f	$168
1601146	Residual Solvent Class 1 - Benzene (1.2 mL/ampule; 3 ampules)	F0C408	10.1 mg/mL (ai)			n/f	$168
1601168	Residual Solvent Class 1 - Carbon Tetrachloride (1.2 mL/ampule; 3 ampules)	F0C409	19.7 mg/mL (ai)			n/f	$168
1601180	Residual Solvent Class 1 - 1,2-Dichloroethane (1.2 mL/ampule; 3 ampules)	F0C412	25.1 mg/mL (ai)			n/f	$168
1601204	Residual Solvent Class 1 - 1,1-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0C411	37.9 mg/mL (ai)			n/f	$168
1601226	Residual Solvent Class 1 - 1,1,1-Trichloroethane (1.2 mL/ampule; 3 ampules)	F0C410	49.1 mg/mL (ai)			n/f	$168
1601281	Residual Solvents Class 2 - Mixture A (1.2 mL/ampule; 3 ampules)	F0D051				n/f	$168
1601292	Residual Solvents Class 2 - Mixture B (1.2 mL/ampule; 3 ampules)	F0D248				n/f	$168
1601306	Residual Solvent Class 2 - Mixture C (1.2 mL/ampule; 3 ampules)	F0D182				n/f	$168
1601340	Residual Solvent Class 2 - Acetonitrile (1.2 mL/ampule; 3 ampules)	F0D049	2.00 mg/mL (ai)			n/f	$168
1601361	Residual Solvent Class 2 - Chlorobenzene (1.2 mL/ampule; 3 ampules)	F0D048	1.81 mg/mL (ai)			n/f	$168
1601383	Residual Solvent Class 2 - Chloroform (1.2 mL/ampule; 3 ampules)	F0D186	0.293 mg/mL (ai)			n/f	$168
1601408	Residual Solvent Class 2 - Cyclohexane (1.2 mL/ampule; 3 ampules)	F0D047	18.0 mg/mL (ai)			n/f	$168
1601420	Residual Solvent Class 2 - 1,2-Dichloroethene (1.2 mL/ampule; 3 ampules)	F0D040	9.2 mg/mL (ai)			n/f	$168
1601463	Residual Solvent Class 2 - 1,2-Dimethoxyethane (1.2 mL/ampule; 3 ampules)	F0D185	0.479 mg/mL (ai)			n/f	$168
1601485	Residual Solvent Class 2 - N,N-Dimethylacetamide (1.2 mL/ampule; 3 ampules)	F0D169	5.44 mg/mL (ai)			n/f	$168
1601500	Residual Solvent Class 2 - N,N-Dimethylformamide (1.2 mL/ampule; 3 ampules)	F0D189	4.42 mg/mL (ai)			n/f	$168
1601521	Residual Solvent Class 2 - 1,4-Dioxane (1.2 mL/ampule; 3 ampules)	F0D050	1.89 mg/mL (ai)			n/f	$168
1601543	Residual Solvent Class 2 - 2-Ethoxyethanol (1.2 mL/ampule; 3 ampules)	F0D195	0.80 mg/mL (ai)			n/f	$168
1601565	Residual Solvent Class 2 - Ethylene Glycol (1.2 mL/ampule; 3 ampules)	F0D191	3.07 mg/mL (ai)			n/f	$168
1601587	Residual Solvent Class 2 - Formamide (1.2 mL/ampule; 3 ampules)	F0D188	1.10 mg/mL (ai)			n/f	$168
1601601	Residual Solvent Class 2 - Hexane (1.2 mL/ampule; 3 ampules)	F0D268	0.256 mg/mL (ai)			n/f	$168
1601623	Residual Solvent Class 2 - Methanol (1.2 mL/ampule; 3 ampules)	F0D045	14.8 mg/mL (ai)			n/f	$168
1601645	Residual Solvent Class 2 - 2-Methoxyethanol (1.2 mL/ampule; 3 ampules)	F0D194	0.253 mg/mL (ai)			n/f	$168
1601667	Residual Solvent Class 2 - Methylbutylketone (1.2 mL/ampule; 3 ampules)	F0D202	0.248 mg/mL (ai)			n/f	$168
1601689	Residual Solvent Class 2 - Methylcyclohexane (1.2 mL/ampule; 3 ampules)	F0D044	5.46 mg/mL (ai)			n/f	$168
1601441	Residual Solvent Class 2 - Methylene Chloride (1.2 mL/ampule; 3 ampules)	F0D046	2.90 mg/mL (ai)			n/f	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1601703	Residual Solvent Class 2 - N-Methylpyrrolidone (1.2 mL/ampule; 3 ampules)	F0D183	2.63 mg/mL (ai)			n/f	$168
1601725	Residual Solvent Class 2 - Nitromethane (1.2 mL/ampule; 3 ampules)	F0D210	0.248 mg/mL (ai)			n/f	$168
1601747	Residual Solvent Class 2 - Pyridine (1.2 mL/ampule; 3 ampules)	F0D215	0.99 mg/mL (ai)			n/f	$168
1601769	Residual Solvent Class 2 - Sulfolane (1.2 mL/ampule; 3 ampules)	F0D187	0.80 mg/mL (ai)			n/f	$168
1601770	Residual Solvent Class 2 - Tetrahydrofuran (1.2 mL/ampule; 3 ampules)	F0D043	3.49 mg/mL (ai)			n/f	$168
1601780	Residual Solvent Class 2 - Tetralin (1.2 mL/ampule; 3 ampules)	F0D228	0.493 mg/mL (ai)			n/g	$168
1601805	Residual Solvent Class 2 - Toluene (1.2 mL/ampule; 3 ampules)	F0D042	4.39 mg/mL (ai)			n/f	$168
1601827	Residual Solvent Class 2 - Trichloroethylene (1.2 mL/ampule; 3 ampules)	F0D221	0.391 mg/mL (ai)			n/f	$168
1601849	Residual Solvent Class 2 - Xylenes (1.2 mL/ampule; 3 ampules)	F0D041	10.7 mg/mL (ai)			n/f	$168
1602003	Resorcinol (200 mg)	I0D135	0.998 mg/mg (ai)		H-1 (10/05) H (04/01)	[108-46-3]	$168
1602706	Ribavirin (200 mg)	H1C335			H (03/05) G (08/01)	[36791-04-5]	$313
1603006	Riboflavin (500 mg) (Vitamin B2)	N0C021			M-1 (09/04) M (11/00)	[83-88-5]	$168
1603800	Rifabutin (50 mg)	G0B040			F (11/02)	[72559-06-9]	$168
1604009	Rifampin (300 mg)	J			I (09/00)	[13292-46-1]	$168
1604202	Rifampin Quinone (50 mg)	H			G (12/01)	[13983-13-6]	$526
1604508	Rimantadine Hydrochloride (300 mg)	F0C266				[1501-84-4]	$168
1604600	Rimexolone (100 mg)	F				[49697-38-3]	$168
1604701	Ritodrine Hydrochloride (200 mg)	G-1				[23239-51-2]	$168
1604803	Ritonavir (200 mg)	F0F049	0.992 mg/mg (ai)	1		[155213-67-5]	$168
1605500	Ropivacaine Hydrochloride (200 mg)	F0E334	0.943 mg/mg (ai)			[132112-35-7]	$168
1605512	Ropivacaine Related Compound A (25 mg) (2,6-dimethylaniline hydrochloride)	F0E315	1.00 mg/mg (ai)			[21436-98-6]	$526
1605523	Ropivacaine Related Compound B (50 mg) ((R)-(+)-1-Propylpiperidine-2-carboxylic acid (2,6-dimethylphenyl)-amide hydrochloride monohydrate)	F0E318				[112773-90-7]	$526
1606208	Roxarsone (200 mg)	F				[121-19-7]	$168
1606503	Rutin (100 mg)	G0C355			F (09/05)	[153-18-4]	$168
1607007	Saccharin (200 mg)	G4C375			G-3 (03/06) G-2 (12/01)	[81-07-2]	$168
1608000	Salicylamide (200 mg)	F-4			F-3 (05/03)	[65-45-2]	$168
1609002	Salicylic Acid (125 mg)	J3C400	0.994 mg/mg (ai)		J2B147 (01/06) J-1 (10/03) J (10/02) I (07/99)	[69-72-7]	$134
1609013	Salicylic Acid Related Compound A (100 mg) (4-hydroxybenzoic acid)	F0F108	0.99 mg/mg (ai)	1		[99-96-7]	$526
1609501	Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (30 tablets)	Q0D200			P0C404 (10/06) O (01/06) N (02/02)	[69-72-7]	$168
1609807	Salsalate (125 mg)	G				[552-94-3]	$134

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1609829	Saquinavir Mesylate (200 mg)	F0B008				[149845-06-7]	$168
1609831	Saquinavir Related Compound A (25 mg) (N-*tert*-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide)	F0B009				n/f	$526
1610001	Scopolamine Hydrobromide (250 mg)	J0B051			I-1 (01/03)	[6533-68-2]	$168
1610090	Scopoletin (20 mg)	F0C329				[92-61-5]	$168
1611004	Secobarbital **CII** (200 mg)	H				[76-73-3]	$224
1611900	Selegiline Hydrochloride (200 mg)	G				[14611-52-0]	$168
1611955	Selenomethionine (100 mg)	F0B006				[1464-42-2]	$168
1612007	Sennosides (250 mg)	H1B223			H (04/04)	[81-27-6] (A) [128-57-4] (B)	$168
1612506	L-Serine (200 mg)	G			F-3 (11/00)	[56-45-1]	$168
1612404	Sesame Oil (1 mL/ampule; 2 ampules) (AS)	F0E134				[8008-74-0]	$168
1612415	Sesame Oil Related Compound A (6 mg/vial; 3 vials) (1,2-dilinoleoyl-3-oleoyl-rac-glycerol)	F0E131				[2190-21-8]	$526
1612426	Sesame Oil Related Compound B (6 mg/vial; 3 vials) (1,2-dilinoleoyl-3-palmitoyl-rac-glycerol, PLL)	F0E132				[64550-34-1]	$526
1612540	Sevoflurane (1 mL)	F0C219				[28523-86-6]	$168
1612550	Sevoflurane Related Compound A (0.2 mL) (1,1,3,3,3-Pentafluoroisopropenyl fluoromethyl ether)	F0C261				[58109-34-5]	$526
1612572	Sevoflurane Related Compound B (0.2 mL) (1,1,1,3,3,3-hexafluoro-2-methoxypropane)	F0D140	1.00 mg/mg (ai)			[13171-18-1]	$526
1612594	Sevoflurane Related Compound C (0.2 mL) (1,1,1,3,3,3-hexafluoro-2-propanol)	F0D142	1.00 mg/mg (ai)			[920-66-1]	$526
1612608	Silver Sulfadiazine (200 mg)	I			H (04/01)	[22199-08-2]	$168
1612630	Silybin (50 mg)	G0D392	0.94 mg/mg (ai)		F (01/06)	[22888-70-6]	$168
1612641	Silydianin (20 mg)	F				[29782-68-1]	$168
1612652	Simethicone (50 g)	H0D084	5.3% SiO2 (ai)		G (11/04) F (07/00)	[8050-81-5]	$168
1612700	Simvastatin (200 mg)	I0D382	0.994 mg/mg (ai)		H1B093 (02/06) H (07/03) G (02/02) F-1 (05/99)	[79902-63-9]	$168
1612801	Sisomicin Sulfate (500 mg)	I0C238			H (04/04) G (10/00)	[53179-09-2]	$168
1612947	Beta-Sitosterol (300 mg)	F0D217	0.98 mg/mg (an)			[83-46-5]	$563
1613407	Sodium Acetate (1 g) (AS)	F0D083	99.8% (dr)			[127-09-3]	$168
1613509	Sodium Ascorbate (200 mg)	G2C067			G-1 (03/05)	[134-03-2]	$168
1613564	Sodium Benzoate (1 g)	F0E025				[532-32-1]	$168
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	99.7% (dr)			[144-55-8]	$168
1613600	Sodium Butyrate (25 mg)	F				[156-54-7]	$168
1613757	Sodium Carbonate Anhydrous (1 g) (AS)	F0D100	100.0% (dr)			[497-19-8]	$168
1613804	Sodium Chloride (1 g) (AS)	F0D269	100.0% (ai)			[7647-14-5]	$168
1613859	Sodium Citrate (1 g) (AS)	F0D172	100.0% (an)			[6132-04-3]	$168
1614002	Sodium Fluoride (1 g)	I0E033	1.000 mg/mg (ai)		H-1 (03/06) H (05/01)	[7681-49-4]	$168
1614308	Sodium Lactate (200 mg)	J0E249	1.000 mg/mg (dr)		I0C299 (12/06) H (04/05) G (06/00)	[867-56-1]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1614363	Sodium Lauryl Sulfate (1 g) (AS)	F0D381				[151-21-3]	$168
1614396	Sodium Metabisulfite (1 g) (AS)	F0D111	98.6% (ai)			[7681-57-4]	$168
1614454	Sodium Nitrite (1 g) (AS)	F0D117	99.6% (dr)			[7632-00-0]	$168
1614501	Sodium Nitroprusside (500 mg)	H			G (11/99)	[13755-38-9]	$168
1614603	Sodium Propionate (200 mg)	F-1			F (03/02)	[6700-17-0]	$168
1614669	Sodium Starch Glycolate Type A (400 mg)	G0E221			F0C087 (11/06)	[9063-38-1]	$168
1614670	Sodium Starch Glycolate Type B (400 mg)	F0E222				[9063-38-1]	$168
1614705	Sodium Stearyl Fumarate (200 mg)	G			F-2 (05/01)	[4070-80-8]	$168
1614807	Sodium Sulfate Anhydrous (1 g) (AS)	F0D112	99.8% (dr)			[7757-82-6]	$168
1615107	Sodium Thiosulfate (1 g) (AS)	F0D178	100.2% (an)			[10102-17-7]	$168
1615708	Somatropin (8.63 USP Somatropin Units/vial)	F0E191				[12629-01-5]	$182
1615956	Sorbic Acid (1 g) (AS)	F0D129	99.4% (ai)			[110-44-1]	$168
1616008	1,4-Sorbitan (200 mg)	I0A003			H (04/03) G (02/00)	[27299-12-3]	$168
1617000	Sorbitol (125 mg)	H1B139			H (01/04)	[50-70-4]	$134
1617408	Sotalol Hydrochloride (300 mg)	G0E198	0.997 mg/mg (ai)		F0C234 (09/06)	[959-24-0]	$197
1617419	Sotalol Related Compound A (50 mg) (N-[4-[[(1-Methylethyl)amino]acetyl]phenyl]methanesulfonamide monohydrochloride)	F0C235				n/f	$526
1617420	Sotalol Related Compound B (50 mg) (N-(4-Formylphenyl)methanesulfonamide)	F0C236				n/f	$526
1617430	Sotalol Related Compound C (50 mg) (N-[4-[2-[(1-Methylethyl)amino]ethyl]phenyl]methanesulfonamide hydrochloride)	F0C237				n/f	$526
1618003	Spectinomycin Hydrochloride (200 mg)	G0C310	650 ug/mg (ai)		F-2 (01/05)	[22189-32-8]	$168
1619006	Spironolactone (125 mg)	J-1				[52-01-7]	$134
1619017	Spironolactone Related Compound A (100 mg) (Canrenone (3-Oxo-17-alpha-pregna-4,6-diene-21, 17-carbolactone)) (AS)	F0E184				[976-71-6]	$526
1619505	Squalane (500 mg)	G-1				[111-01-3]	$168
1620005	Stanozolol **CIII** (200 mg)	F-3			F-2 (02/01)	[10418-03-8]	$224
1620209	Stavudine (250 mg)	F0E050	0.997 mg/mg (ai)			[3056-17-5]	$260
1620220	Stavudine System Suitability Mixture (20 mg)	F0E051				n/f	$526
1621008	Stearic Acid (500 mg)	J1D360			J (02/06) I (10/01)	[57-11-4]	$168
1621507	Stearoyl Polyoxyglycerides (100 mg)	F0C286				n/f	$168
1622000	Stearyl Alcohol (125 mg)	H2B217			H-1 (12/04) H (09/99)	[112-92-5]	$134
1623003	Streptomycin Sulfate (200 mg)	J0B195			I (04/03)	[3810-74-0]	$168
1623502	Succinylcholine Chloride (500 mg)	H1E325	0.995 mg/mg (an)		H (12/06)	[71-27-2]	$168
1623604	Succinylmonocholine Chloride (150 mg)	G			F-1 (02/01)	n/f	$526
1623626	Sucralose (400 mg)	G1E317	0.998 mg/mg (ai)	2	G0B028 (02/07) F (04/03)	[56038-13-2]	$168
1623637	Sucrose (100 mg)	H1C223			H0B002 (11/04) G-1 (03/03) G (05/99)	[57-50-1]	$168
1623648	Sufentanil Citrate **CII** (25 mg)	H1E105	1.000 mg/mg (dr)		H0B208 (09/06) G (05/03) F-1 (04/02) F (09/99)	[60561-17-3]	$238

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1623670	Sulbactam (250 mg)	H0C396	0.976 mg/mg (ai)		G (05/05) F-1 (05/00)	[68373-14-8]	$168
1623681	Sulconazole Nitrate (200 mg)	F-1			F (05/02)	[61318-91-0]	$168
1623706	Sulfabenzamide (200 mg)	G				[127-71-9]	$168
1623808	Sulfacetamide (300 mg)	G-2			G-1 (11/06)	[144-80-9]	$168
1624006	Sulfacetamide Sodium (500 mg)	I1B318			I (09/04) H (08/01)	[6209-17-2]	$168
1624505	Sulfachlorpyridazine (200 mg)	F				[80-32-0]	$168
1625009	Sulfadiazine (200 mg)	J			I (03/04)	[68-35-9]	$168
1626001	Sulfadimethoxine (200 mg)	G0D249	0.998 mg/mg (ai)		F4C298 (09/05) F-3 (11/04) F-2 (03/99)	[122-11-2]	$168
1626500	Sulfadoxine (200 mg)	F3C336	0.999 mg/mg (ai)		F-2 (10/05) F-1 (07/02)	[2447-57-6]	$168
1628007	Sulfamerazine (500 mg)	H1C171			H (12/04)	[127-79-7]	$168
1629000	Sulfamethazine (1 g)	G-3				[57-68-1]	$168
1630009	Sulfamethizole (200 mg)	F-3			F-2 (01/03)	[144-82-1]	$168
1631001	Sulfamethoxazole (200 mg)	I-1			I (04/02)	[723-46-6]	$168
1631500	Sulfamethoxazole N4-glucoside (25 mg)	H1D290	0.98 mg/mg (ai)		H (01/06) G (11/01)	n/f	$526
1632004	Sulfanilamide (5 g)	O0B047			N (01/04)	[63-74-1]	$168
1633007	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)	K0B133			J-1 (03/04) J (09/99)	[63-74-1]	$81
1633506	Sulfanilic Acid (200 mg)	G			F-2 (09/00)	[121-57-3]	$526
1634000	Sulfapyridine (200 mg)	I0B298			H (07/04)	[144-83-2]	$168
1635002	Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees)	J1E042			J (11/06) I (07/00)	[144-83-2]	$100
1635206	Sulfaquinoxaline (200 mg)	F0A005				[59-40-5]	$168
1635228	Sulfaquinoxaline Related Compound A (25 mg) (N1,N2-diquinoxalin-2-ylsulfanilamide)	F0E093	0.96 mg/mg (ai)			n/f	$526
1636005	Sulfasalazine (125 mg)	G3F035	1.000 mg/mg (dr)		G-2 (02/07) G-1 (06/99)	[599-79-1]	$134
1636504	Sulfathiazole (350 mg)	H			G (08/00)	[72-14-0]	$168
1637008	Sulfinpyrazone (200 mg)	H0C416	0.992 mg/mg (ai)		G (03/05)	[57-96-5]	$168
1638000	Sulfisoxazole (200 mg)	J			I-1 (06/99)	[127-69-5]	$168
1639003	Sulfisoxazole Acetyl (200 mg)	H-1				[80-74-0]	$168
1640002	Sulfisoxazole Diolamine (500 mg) **DISCONTINUED**				F (02/07)	[4299-60-9]	$168
1642008	Sulindac (200 mg)	H			G-1 (12/01)	[38194-50-2]	$168
1642019	Sulindac Related Compound A (20 mg) (trans-sulindac)	F0E314				[53933-60-1]	$526
1642100	Sulisobenzone (500 mg)	F0F074	1.00 mg/mg (an)	1		[4065-45-6]	$194
1642154	Sumatriptan (50 mg)	F0C220				[103628-46-2]	$225
1642201	Sumatriptan Succinate (200 mg)	F1E256	0.989 mg/mg (ai)		F0C231 (10/06)	[103628-48-4]	$225
1642212	Sumatriptan Succinate Related Compound A (15 mg) ([3-[2-(dimethylamino)ethyl]-2-[[3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl]-1H-indol-5-yl]-N-methylmethansulfonamide, succinate salt)				F0C221 (01/07)	n/f	$675

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1642223	Sumatriptan Succinate Related Compound C (50 mg) ([3-[2-(dimethylamino)ethyl]-1-(hydroxymethyl)-1H-indol-5-yl]-N-methylmethanesulfonamide succinate salt)	F0C230				n/f	$675
1642256	Sumatriptan Succinate Related Impurities (25 mg)	F0E046				n/f	$675
1642507	Suprofen (200 mg)	F				[40828-46-4]	$168
1642700	Tacrine Hydrochloride (500 mg)	F0C119				[1684-40-8]	$168
1642904	Tagatose (200 mg)	F0E017	0.996 mg/mg (dr)			[87-81-0]	$189
1643000	Talbutal **CIII** (250 mg)	F				[115-44-6]	$224
1643306	Tamoxifen Citrate (200 mg)	I0D294	0.994 mg/mg (ai)		H (10/05) G-2 (09/01) G-1 (05/00)	[54965-24-1]	$168
1643328	Tannic Acid (2 g) (AS)	F0D292				[1401-55-4]	$168
1643340	Tartaric Acid (1 g) (AS)	F0D176	100.0% (dr)			[87-69-4]	$168
1643361	Taurine (100 mg)	F0C104				[107-35-7]	$168
1643408	Temazepam **CIV** (200 mg)	H0C205			G (06/04) F (12/99)	[846-50-4]	$224
1643452	Terazosin Hydrochloride (200 mg)	F0C244				[70024-40-7]	$168
1643463	Terazosin Related Compound A (50 mg) (1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride)	F0C245				n/f	$526
1643474	Terazosin Related Compound B (50 mg) (1-(4-hydroxy-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine)	F0C218				n/f	$526
1643485	Terazosin Related Compound C (25 mg) (1,4-bis(4-amino-6,7-dimethoxy-2-quinazolinyl)piperazine dihydrochloride)	F0C257				n/f	$526
1643500	Terbutaline Sulfate (125 mg)	H			G (04/99)	[23031-32-5]	$134
1643510	Terbutaline Related Compound A (50 mg) (tert-butylamino-3,5-dihydroxyacetophenone sulfate)	F0D289				n/f	$526
1643703	Terconazole (200 mg)	H0E229			G3C322 (09/06) G-2 (08/05) G-1(04/01) G (03/99)	[67915-31-5]	$168
1643805	Terfenadine (200 mg)	H			G (12/99)	[50679-08-8]	$168
1643907	Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanone)	G				n/f	$526
1643929	Terfenadine Related Compound B (50 mg) (Terfenadine-N-oxide)	F				n/f	$526
1644003	Terpin Hydrate (750 mg)	H0C395	0.999 mg/mg (an)		G (06/06)	[2451-01-6]	$168
1645006	Testolactone **CIII** (125 mg)	F-1				[968-93-4]	$179
1646009	Testosterone **CIII** (125 mg)	I1B253			I (08/04)	[58-22-0]	$179
1647001	Testosterone Cypionate **CIII** (200 mg)	H0D162	1.000 mg/mg (ai)		G-1 (03/05) G (08/01)	[58-20-8]	$224
1648004	Testosterone Enanthate **CIII** (200 mg)	K0D253	0.998 mg/mg (ai)		J (07/06)	[315-37-7]	$224
1649007	Testosterone Propionate **CIII** (200 mg)	L1C005			L (08/04) K-1 (11/01)	[57-85-2]	$224
1650006	Tetracaine Hydrochloride (200 mg)	J				[136-47-0]	$168
1651009	Tetracycline Hydrochloride (200 mg)	L0C216	976 ug/mg (ai)		K (12/04)	[64-75-5]	$168
1652001	Tetrahydrozoline Hydrochloride (200 mg)	G1A015			G (03/03)	[522-48-5]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1652500	Thalidomide (200 mg)	F0C107				[50-35-1]	$197
1653004	Theophylline (200 mg)	J0B180			I (01/04)	[58-55-9]	$168
1655000	Thiabendazole (100 mg)	G0A027			F-1 (04/03) F (04/01)	[148-79-8]	$168
1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O			N (11/02) M-1 (04/99)	[67-03-8]	$168
1656308	Thiamylal **CIII** (200 mg)	F				[77-27-0]	$224
1657005	Thiethylperazine Malate (200 mg)	G			F-1 (09/00)	[52239-63-1]	$168
1658008	Thiethylperazine Maleate (200 mg)	F-1				[1179-69-7]	$168
1659000	Thimerosal (500 mg)	H1B205			H (09/04) G (12/99)	[54-64-8]	$168
1660000	Thioguanine (200 mg)	F-1				[154-42-7]	$168
1661002	Thiopental **CIII** (250 mg)	I1D198	1.000mg/mg (dr)		I (09/05)	[76-75-5]	$224
1662504	Thioridazine (200 mg)	H				[50-52-2]	$168
1663008	Thioridazine Hydrochloride (200 mg)	H				[130-61-0]	$168
1663700	Thiostrepton (200 mg)	G0E175	1075 USP Thiostrepton Units/mg (dr)		F1B022 (10/06) F (11/02)	[1393-48-2]	$168
1664000	Thiotepa (500 mg)	I			H (01/99)	[52-24-4]	$168
1665003	Thiothixene (250 mg)	G				[3313-26-6]	$168
1666006	(E)-Thiothixene (100 mg)	H			G-1 (05/00)	[3313-27-7]	$526
1667100	Thonzonium Bromide (200 mg)	F				[553-08-2]	$168
1667202	L-Threonine (200 mg)	G			F-3 (12/00)	[72-19-5]	$168
1667213	Thymol (500 mg)	F0D391				[89-83-8]	$168
1667280	Tiagabine Hydrochloride (300 mg)	F0E178	0.998 mg/mg (an)			[145821-59-6]	$260
1667235	Racemic Tiagabine Hydrochloride Mixture (25 mg) ((S)-(+),(R)-(-)-1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]nipecotic acid, hydrochloride)	F0E179				n/f	$526
1667224	Tiagabine Related Compound A (15 mg) ((R)-ethyl 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate, hydrochloride)	F0E177				n/f	$526
1667355	Tiamulin (100 mg)	F0E219				[55297-95-5]	$168
1667290	Tiamulin Fumarate (250 mg)	F0C327				[55297-96-6]	$168
1667337	Tiamulin Related Compound A (50 mg) (Tosyl pleuromutilin)	F0C328				n/f	$535
1667304	Ticarcillin Monosodium Monohydrate (200 mg)	H			G-1 (03/99)	[74682-62-5]	$168
1667359	Tiletamine Hydrochloride (200 mg)	F0C019				[14176-50-2]	$168
1667370	Tilmicosin (400 mg)	F0D393	830 ug/mg cis (an) 126 ug/mg trans (an)			[108050-54-0]	$168
1667406	Timolol Maleate (200 mg)	G-1				[26921-17-5]	$168
1667520	Tinidazole (200 mg)	F0C093				[19387-91-8]	$168
1667530	Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole)	F0C091				[696-23-1]	$526
1667541	Tinidazole Related Compound B (20 mg) (1-(2-ethyl-sulfonylethyl)-2-methyl-4-nitroimidazole)	F0E274	1.00 mg/mg (ai)			[25459-12-5]	$526
1667439	Tioconazole (200 mg)	H			G (04/02)	[65899-73-2]	$168
1667450	Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride)	H0F095	0.95 mg/mg (ai)	2	G (02/07)	n/f	$526
1667461	Tioconazole Related Compound B (25 mg) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]-phenethyl]imidazole Hydrochloride)	G				n/f	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1667472	Tioconazole Related Compound C (25 mg) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride)	G				n/f	$526
1667585	Titanium Dioxide (1 g) (AS)	F0D079	99.6% (dr)			[13463-67-7]	$168
1667508	Tobramycin (350 mg)	L0E077	970 ug/mg (an)		K0B248 (07/06) J (08/03)	[32986-56-4]	$182
1667552	Tocainide Hydrochloride (125 mg)	F-1			F (04/99)	[35891-93-1]	$134
1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M			L-1 (01/00)	[10191-41-0]	$168
1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K			J (06/99)	[7695-91-2]	$168
1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)	G0D077	0.995 mg/mg GC 0.978 mg/mg HPLC (ai)		F-5 (05/05) F-4 (01/02)	[4345-03-3]	$168
1668001	Tolazamide (200 mg)	G-2			G-1 (06/00)	[1156-19-0]	$168
1669004	Tolazoline Hydrochloride (300 mg)	F				[59-97-2]	$168
1670003	Tolbutamide (200 mg)	I			H (06/00)	[64-77-7]	$168
1670207	Tolcapone (200 mg)	F0D280	0.999 mg/mg (ai)			[134308-13-7]	$168
1670218	Tolcapone Related Compound A (25 mg) (4'-methyl-3,4-dihydroxybenzophenone)	F0D282				n/f	$526
1670229	Tolcapone Related Compound B (25 mg) (4-hydroxy-3-methoxy-4'-methyl-5-nitrobenzophenone)	F0D284				n/f	$526
1670502	Tolmetin Sodium (500 mg)	I0B064			H (09/03)	[64490-92-2]	$168
1671006	Tolnaftate (200 mg)	J0C405	1.000 mg/mg (dr)		I (02/05)	[2398-96-1]	$168
1672009	Toluenesulfonamides, ortho and para (200 mg of each supplied in a set) **DISCONTINUED**				F-4 (07/06) F-3 (11/99)	[88-19-7] (o) [70-55-3] (p)	$526
1672010	o-Toluenesulfonamide (200 mg)	F0E163	1.00 mg/mg (ai)			[88-19-7]	$263
1672020	p-Toluenesulfonamide (200 mg)	F0E162	1.00 mg/mg (ai)			[70-55-3]	$263
1672304	Torsemide (200 mg)	F0B090				[56211-40-6]	$168
1672315	Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B071				n/f	$526
1672326	Torsemide Related Compound B (75 mg) (N-[(n-butylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B083				n/f	$526
1672337	Torsemide Related Compound C (75 mg) (N-[(ethylamino)carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B078				n/f	$526
1672803	Transplatin (25 mg)	H0B287			G (03/04)	[14913-33-8]	$526
1673500	Trazodone Hydrochloride (200 mg)	G0F069	0.998 mg/mg (dr)	2	F-2 (04/07)	[25332-39-2]	$168
1673806	Trenbolone **CIII** (50 mg)	F0D389	0.99 mg/mg (ai)			[10161-33-8]	$179
1673828	Trenbolone Acetate **CIII** (200 mg)	F0D390	0.999 mg/mg (ai)			[10161-34-9]	$179
1674004	Tretinoin (30 mg/vial; 5 vials)	J0D145	0.996 mg/mg (ai)		I2B185 (01/06) I-1 (01/04) I (01/02) H (06/01)	[302-79-4]	$168
1675007	Triacetin (1 g)	H0C413			G-1 (02/05) G (06/01)	[102-76-1]	$168
1676000	Triamcinolone (250 mg)	H-1				[124-94-7]	$168
1677002	Triamcinolone Acetonide (500 mg)	K			J (03/99)	[76-25-5]	$168
1678005	Triamcinolone Diacetate (200 mg)	G				[67-78-7]	$168
1679008	Triamcinolone Hexacetonide (125 mg)	G				[5611-51-8]	$134
1680007	Triamterene (200 mg)	I				[396-01-0]	$168

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1680506	Triazolam **CIV** (200 mg)	H0B041			G-1 (03/03)	[28911-01-5]	$224
1680608	Tributyl Citrate (500 mg)	G0C227			F (01/05)	[77-94-1]	$168
1680801	Trichlorfon (200 mg)	F				[52-68-6]	$168
1681000	Trichlormethiazide (200 mg)	H				[133-67-5]	$168
1682206	Triclosan (200 mg)	G0D001	0.997 mg/mg (ai)		F0B135 (05/05)	[3380-34-5]	$168
1682217	Triclosan Related Compounds Mixture A (1.2 mL/ampule; 3 ampules)	F0E292				n/f	$526
1683005	Tridihexethyl Chloride (200 mg)	F-1				[4310-35-4]	$168
1683504	Trientine Hydrochloride (125 mg)	F2B257			F-1 (09/03) F (08/96)	[38260-01-4]	$134
1683606	Triethyl Citrate (500 mg)	G0C393			F-1 (10/05) F (03/02)	[77-93-0]	$168
1685000	Trifluoperazine Hydrochloride (200 mg)	H0A010			G (03/03)	[440-17-5]	$168
1685500	2-[N-(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone (25 mg)	F				n/f	$526
1686003	Triflupromazine Hydrochloride (200 mg)	F-2			F-1 (03/04)	[1098-60-8]	$168
1686309	Trifluridine (200 mg)	F				[70-00-8]	$194
1686310	Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine)	G0E004	1.00 mg/mg (ai)		F (02/06)	[14599-46-3]	$526
1687006	Trihexyphenidyl Hydrochloride (200 mg)	J			I (07/01)	[52-49-3]	$168
1689001	Trimeprazine Tartrate (200 mg)	F-3			F-2 (08/01)	[4330-99-8]	$168
1690000	Trimethadione (200 mg)	G				[127-48-0]	$168
1692006	Trimethobenzamide Hydrochloride (500 mg)	H-2			H-1 (06/02)	[554-92-7]	$168
1692505	Trimethoprim (300 mg)	J0B228			I (01/04)	[738-70-5]	$168
1693009	Trioxsalen (200 mg)	H0C278			G (04/04)	[3902-71-4]	$168
1694001	Tripelennamine Citrate (200 mg) **DISCONTINUED**				G (02/07) F (02/03)	[6138-56-3]	$168
1695004	Tripelennamine Hydrochloride (200 mg)	J				[154-69-8]	$168
1696007	Triprolidine Hydrochloride (500 mg)	I			H-1 (02/02)	[6138-79-0]	$168
1696109	Triprolidine Hydrochloride Z-Isomer (100 mg)	G			F-1 (02/02)	n/f	$526
1696200	Trisalicylic Acid (100 mg)	G			F-1 (10/99)	n/f	$526
1696958	Trolamine (3 mL)	F0D120				[102-71-6]	$168
1697000	Troleandomycin (250 mg)	F-1				[2751-09-9]	$168
1698002	Tromethamine (125 mg)	G			F-3 (07/99)	[77-86-1]	$134
1699005	Tropicamide (200 mg)	H0E307	0.99 mg/mg (ai)		G-1 (01/07) G (02/99)	[1508-75-4]	$134
1700002	Trypsin Crystallized (300 mg)	I0E055	3250 USP Trypsin Units/mg (dr)		H (01/06) G (12/99)	[9002-07-7]	$168
1700501	L-Tryptophan (200 mg)	G2E237			G-1 (12/06) G (09/00)	[73-22-3]	$168
1702008	Tubocurarine Chloride (250 mg)	K-1				[6989-98-6]	$168
1703805	Tylosin (250 mg)	F0C008				[1401-69-0]	$168
1703850	Tylosin Tartrate (100 mg)	F0D333				[1405-54-5]	$168
1704003	Tyloxapol (600 mg)	I0E111			H (07/06) G (02/00)	[25301-02-4]	$168
1704502	Tyropanoate Sodium (500 mg)	F				[7246-21-1]	$168
1705006	L-Tyrosine (500 mg)	K0C141	1.00 mg/mg (ai)		J (05/05)	[60-18-4]	$168
1705301	Ubidecarenone (200 mg)	G0E154	0.999 mg/mg (ai)		F0B191 (04/06)	[303-98-0]	$270
1705323	Ubidecarenone Related Compound A (15 mg) (Coenzyme Q9)	F0E210				[303-97-9]	$526
1705312	Ubidecarenone for System Suitability (25 mg)	F0B194				[303-98-0]	$526

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Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1705505	Undecylenic Acid (200 mg)	G2C018			G-1 (11/04) G (01/02)	[112-38-9]	$168
1705800	Uracil Arabinoside (50 mg)	G			F-1 (06/99)	[3083-77-0]	$168
1706009	Uracil Mustard (500 mg) (FOR U.S. SALE ONLY)	F				[66-75-1]	$168
1706698	Urea (200 mg)	F0D331	1.00 mg/mg (ai)			[57-13-6]	$168
1706701	Urea C 13 (100 mg)	H0E110	0.999 mg/mg (dr)		G0D374 (11/06) F0C078 (12/05)	[58069-82-2]	$197
1707806	Ursodiol (125 mg)	G			F-1 (11/01) F (09/99)	[128-13-2]	$134
1707908	Valerenic Acid (15 mg)	H0D126	1.00 mg/mg (ai)		G0B146 (05/05) F (01/04)	[3569-10-6]	$753
1708503	L-Valine (200 mg)	F-2			F-1 (05/02)	[72-18-4]	$168
1708707	Valproic Acid (500 mg)	L0E030	0.998 mg/mg (ai)	2	K0D224 (04/07) J1B127 (08/05) J (01/04) I-1 (11/00)	[99-66-1]	$168
1708729	Valproic Acid Related Compound A (0.25 mL) (diallylacetic acid)	G0C398			F2C386 (02/06) F1B156 (05/05) F (01/03)	[99-67-2]	$526
1708718	Valproic Acid Related Compound B (50 mg) ((2RS)-2-(1-methylethyl)pentanoic acid) (AS)	F0E201				[62391-99-5]	$526
1708762	Valsartan (350 mg)	G0F065	0.997 mg/mg (an)	2	F0C147 (03/07)	[137862-53-4]	$168
1708773	Valsartan Related Compound A (10 mg) ((R)-N-Valeryl-N-([2'-(1H-tetrazole-5-yl)-biphen-4-yl]-methyl)-valine)	F1E272	0.96 mg/mg (ai)		F0C215 (10/06)	n/f	$675
1708795	Valsartan Related Compound C (10 mg) ((S)-N-Valeryl-N-([2'-(1-H-tetrazole-5-yl)biphenyl-4-yl]-methyl)valine benzyl ester)	F1D025	0.99 mg/mg (ai)		F0C208 (09/05)	n/f	$675
1709007	Vancomycin Hydrochloride (4 vials, each vial contains 100,500 mcg of vancomycin activity)	L1D039			L (07/05) K (08/01)	[1404-93-9]	$168
1710006	Vanillin (200 mg)	J0A021			I (03/05) H (04/99)	[121-33-5]	$168
1711009	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)	J1C303			J (06/05) I-1 (03/03) I (11/00)	[121-33-5]	$100
1711155	Vecuronium Bromide (50 mg)	F0C367				[50700-72-6]	$168
1711166	Vecuronium Bromide Related Compound A (25 mg) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan)	F0B178				n/f	$526
1711202	Verapamil Hydrochloride (200 mg)	G1E095	0.999 mg/mg (dr)		G (08/06) F-4 (06/00)	[152-11-4]	$168
1711304	Verapamil Related Compound A (50 mg) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-alpha-(1-methylethyl)-benzeneacetonitrile mono-Hydrochloride)	H			G (01/01)	n/f	$526
1711406	Verapamil Related Compound B (50 mg) (alpha-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-alpha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride)	G				[1794-55-4]	$526
1711428	Verapamil Related Compound D (50 mg) (5,5'-[[2-(3,4)dimethoxyphenyl)ethyl]imino]bis[2-(3,4-dimethoxyphenyl)-2-(1-methylethyl)pentanenitrile] hydrochloride)	F0E342				[190850-50-1]	$526

USP Reference Standards and Authentic Substances

Cat. No.	Description	Curr. Lot.	Purity Value/Conc.	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1711461	Verteporfin (200 mg)	F0C166				[129497-78-5]	$168
1711472	Verteporfin Related Compound A (50 mg) ((+/-)18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-benzo[b]-prophine-9,13-dipropanoic acid)	F0C167				n/f	$526
1711508	Vidarabine (200 mg)	G-2	939 ug/mg (ai)		G-1 (09/05)	[24356-66-9]	$168
1713004	Vinblastine Sulfate (50 mg)	M0B308			L (12/04) K (05/99)	[143-67-9]	$383
1714007	Vincristine Sulfate (50 mg/ampule)	O0B062			N (01/03) M (04/99)	[2068-78-2]	$518
1714506	Vinorelbine Tartrate (200 mg)	F1E133	0.994 mg/mg (an)		F0C243 (08/05)	[125317-39-7]	$1,631
1714528	Vinorelbine Related Compound A (25 mg) (4-O-Deacetylvinorelbine tartrate)	F0C242				n/f	$815
1715000	Viomycin Sulfate (200 mg)	F				[37883-00-4]	$168
1716002	Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil)				V0C258 (12/05) U (04/04)	[127-47-9]	$168
1717504	Vitamin D Assay System Suitability (1.5 g)	F-1			F (08/06)	[67-97-0]	$168
1717708	Vitexin (30 mg)	F0C142				[3681-93-4]	$563
1719000	Warfarin (200 mg)	I0B305			H-2 (08/04) H-1 (11/01)	[81-81-2]	$168
1719102	Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one)	H0E268			G1B111 (02/07) G (01/04)	[37209-23-7]	$168
1720000	Xanthanoic Acid (100 mg)	G-1			G (12/00)	[82-07-5]	$526
1720203	Xanthone (100 mg)	F-1				[90-47-1]	$526
1720407	Xylazine (200 mg)	F1C001			F (02/05)	[7361-61-7]	$168
1720429	Xylazine Hydrochloride (200 mg)	F				[23076-35-9]	$168
1720600	Xylitol (1 g)	G0B037			F-3 (11/02) F-2 (05/00)	[87-99-0]	$168
1721002	Xylometazoline Hydrochloride (125 mg)	I0B101			H-1 (05/03)	[1218-35-5]	$134
1722005	Xylose (1 g)	F				[58-86-6]	$168
1724000	Yohimbine Hydrochloride (200 mg)	F				[65-19-0]	$168
1724306	Zalcitabine (200 mg)	F				[7481-89-2]	$168
1724317	Zalcitabine Related Compound A (50 mg) (2',3'-Didehydro-2',3'-dideoxycytidine)	F0B234				[7481-88-1]	$526
1724500	Zidovudine (400 mg)	G1D319	0.991 mg/mg (ai)		G (10/05) F (09/01)	[30516-87-1]	$168
1724521	Zidovudine Related Compound B (25 mg) (3'-chloro-3'-deoxythymidine)	G0B116			F-1 (03/03) F (06/01)	[25526-94-7]	$526
1724532	Zidovudine Related Compound C (100 mg) (thymine)	F-1			F (09/01)	[65-71-4]	$526
1724656	Zileuton (150 mg)	F0C062				[111406-87-2]	$168
1724667	Zileuton Related Compound A (50 mg) (N-(1-Benzo[b]thien-2-ylethyl) urea)	F0B316				n/f	$526
1724678	Zileuton Related Compound B (50 mg) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene)	F0B313				n/f	$526
1724689	Zileuton Related Compound C (50 mg) (1-Benzo[b]thien-2-ylethanone)	F0B299				n/f	$526
1724747	Zinc Oxide (2 g) (AS)	F0D170	99.7% (ig)			[1314-13-2]	$168
1724769	Zinc Sulfate (1 g) (AS)	F0D133	56.4% (ai)			[7446-20-2]	$168
1724805	Zolazepam Hydrochloride (500 mg)	G0C023			F-1 (03/04) F (05/02)	[33754-49-3]	$168

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
00200-6	5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid (50 mg) (Limit Test)	1184027	Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid)
1008002	alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane	1008002	Propoxyphene Related Compound B (50 mg) (alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane)
1021703	N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine (25 mg)	1021703	Nitrofurantoin Related Compound A (25 mg) (N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine)
02200-3	3-Amino-4-carboxamidopyrazole Hemisulfate (50 mg) **(Limit Test)**	1013024	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)
02250-2	4-Amino-6-chloro-1,3-benzenedisulfonamide (100 mg) **(Limit Test)**	1057507	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)
1023403	3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg)	1023403	Diazepam Related Compound B (25 mg) (3-Amino-6-chloro-1-methyl-4-phenylcarbostyril)
02380-0	2-Amino-2'-chloro-5-nitrobenzophenone (25 mg) **(Limit Test)**	1140338	Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone)
02420-2	4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide (100 mg) (Limit Test)	1424018	Methyclothiazide Related Compound A (100 mg) (4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide)
02240-6	2-Amino-4-chlorophenol (50 mg) **(Limit Test)**	1130527	Chlorzoxazone Related Compound A (25 mg) (2-Amino-4-chlorophenol)
02460-0	3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril (25 mg) **(Limit Test)**	1140327	Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril)
02490-5	2-Amino-2',5-dichlorobenzophenone (25 mg) **(Limit Test)**	1370338	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)
02610-6	3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) **(Limit Test)**	1078325	Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)
02620-8	alpha-Aminopropiophenone Hydrochloride (50 mg) **(Limit Test)**	1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)
1042000	Aprobarbital **CIII** (200 mg) (AS) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/07)
06300-0	5-Benzyl-3,6-dioxo-2-piperazineacetic Acid (250 mg) **(Limit Test)**	1043728	Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid)
07350-3	2-(4-Biphenylyl)propionic Acid (100 mg) **(Limit Test)**	1285760	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)
07480-1	N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide (50 mg) **(Limit Test)**	1344724	Iopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide)
07500-4	4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone (25 mg) (Limit Test)	1303013	Haloperidol Related Compound A (25 mg) (4,4-Bis[4-p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone
1076002	4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone (25 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: G (05/03)
08650-5	Calcium Formyltetrahydrofolate (50 mg) (AS) (For Qualitiative Use Only)	1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)
11230-0	p-Chlorobenzhydrylpiperazine (25 mg)	1333058	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)
11310-9	6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde (25 mg) **(Limit Test)**	1370349	Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde)
11320-0	6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid (25 mg) **(Limit Test)**	1370350	Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid)
11330-2	6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol (25 mg) **(Limit Test)**	1370360	Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol)
11400-0	7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (50 mg) **(Limit Test)**	1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)
11500-2	7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (25 mg) **(Limit Test)**	1110020	Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide)
11510-4	2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid (50 mg) **(Limit Test)**	1287020	Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
11550-1	2-Chloro-3,5-dimethyl-phenol (50 mg) **(Limit Test)**	1122722	Chloroxylenol Related Compound A (50 mg) (2-Chloro-3,5-dimethyl-phenol)
11650-4	(o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test)	1141024	Clotrimazole Related Compound A (25 mg) ((o-Chlorophenyl)diphenyl-methanol)
11670-8	4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) **(Limit Test)**	1048222	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)
11900-3	4-Chloro-5-sulfamoylanthranilic Acid (100 mg) **(Limit Test)**	1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)
1119309	4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid (100 mg)	1119309	Chlorthalidone Related Compound A (25 mg) (4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid)
1153001	Cyclizine (1 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (04/04)
15870-8	Cyclosporine U (25 mg) **DISCONTINUED**	1158650	Cyclosporine Resolution Mixture (25 mg) (Replaces Cat. No. 15870-8 Cyclosporine U (25 mg))
21000-3	alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (125 mg) **(Limit Test)**	1575206	Propoxyphene Related Compound A (50 mg) (alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride)
1216000	Diphemanil Methylsulfate (500 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H(03/06)
1268820	Etoposide Related Compound A (25 mg) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) **DISCONTINUED**	1268852	Etoposide Resolution Mixture (30 mg)
1269006	Evans Blue (200 mg)	N/A	DISCONTINUED, Last Lot/Valid Use Date: G (04/04)
1277208	Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) (180 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (01/04)
1286209	4-Formylbenzenesulfonamide (50 mg)	1286209	Mafenide Related Compound A (50 mg) (4-Formylbenzenesulfonamide)
1294003	Glucagon (25 mg, 0.95 U/mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H (01/05)
1312003	Hyaluronidase (500 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H (06/05)
32720-4	3-Hydroxy-1-methylquinuclidinium Bromide (250 mg) **(Limit Test)**	1135021	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)
1329505	9-Hydroxypropantheline Bromide (50 mg)	1329505	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)
1330005	Hydroxypropyl Methylcellulose (250 mg)	1330005	Hypromellose (250 mg) (Hydroxypropyl Methylcellulose)
33010-7	Hydroxypropyl Methylcellulose Phthalate (100 mg)	1335304	Hypromellose Phthalate (100 mg)
1359007	Levallorphan Tartrate (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: G-1 (09/04)
1362001	Levo-alpha-acetylmethadol Hydrochloride **CII** (25 mg) (AS) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (08/03)
	Melting Point Standard - Acetanilide (500 mg; approximately 114 degrees)	1004001	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)
	Melting Point Standard - Caffeine (1 g; approximately 236 degrees)	1086006	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)
	Melting Point Standard - Phenacetin (500 mg; approximately 135 degrees)	1514008	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)
	Melting Point Standard - Sulfanilamide (1 g; approximately 165 degrees)	1633007	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)
	Melting Point Standard - Sulfapyridine (2 g; approximately 191 degrees)	1635002	Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees)
	Melting Point Standard - Vanillin (1 g; approximately 82 degrees)	1711009	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)
1384004	Mephentermine Sulfate (250 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (04/05)
1420006	3-Methoxytyrosine (50 mg)	1420006	Levodopa Related Compound B (50 mg) (3-Methoxytyrosine)
42420-0	2-Methylamino-5-chlorobenzophenone (25 mg) **(Limit Test)**	1185020	Diazepam Related Compound A (25 mg) (2-Methylamino-5-chlorobenzophenone)
42430-2	3-O-Methylcarbidopa (50 mg)	1095517	Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
1434000	Methylphenidate Hydrochloride Erythro Isomer **CII** (25 mg) **DISCONTINUED**; Last Lot/Valid Use Date: J0B294 (04/05); please order 1434011	1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)
1445222	Mitoxantrone Related Compound A Hydrochloride (30 mg) (8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride) **DISCONTINUED**; Please order 1445211	1445211	Mitoxantrone System Suitability Mixture (0.3 mg)
46600-7	5-Nitro-2-furfuraldazine (500mg)	1466007	Nitrofurazone Related Compound A (500mg) (5-Nitro-2-furfuraldazine)
46660-8	3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) **(Limit Test)**	1078336	Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid)
1477900	Octyl Methoxycinnamate (500 mg)	1477900	Octinoxate (500 mg) (Octyl Methoxycinnamate)
1477943	Octyl Salicylate (400 mg)	1477943	Octisalate (400 mg) (Octyl Salicylate)
1481500	Oxamniquine (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/05)
1481703	Oxamniquine Related Compound A (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/05)
1481805	Oxamniquine Related Compound B (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/05)
1489002	Oxyphenbutazone (1 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: H(12/05)
1500229	Paroxetine Related Compound A (10 mg) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F1D058 (10/05)
49400-2	Pancreatin (2 g)	1494057 and/or 1494079	Pancreatin Amylase and Protease (2 g) and/or Pancreatin Lipase (2 g)
1527000	Phenprocoumon (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (02/04)
53180-1	Phenylcyclohexylglycolic Acid (100 mg) **(Limit Test)**	1485114	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)
53350-1	alpha-Phenyl-2-piperidineacetic Acid Hydrochloride (50 mg) **(Limit Test)**	1434022	Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride)
54500-1	Plastic, Negative Control	1546707	Polyethylene, High Density (3 strips)
1576720	Propylene Glycol Diacetate (250 mg) **DISCONTINUED**	N/A	**DISCONTINUED**, Last Lot/Valid Use Date: F (09/05)
61500-5	Sodium Taurocholate (20 g)	1071304	Bile Salts (10 g) (Sodium Taurocholate)
1640002	Sulfisoxazole Diolamine (500 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (02/07)
1653106	Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F-1 (11/04)
1667279	Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: F (10/04)
1672009	Toluenesulfonamides, ortho and para (200 mg of each supplied in a set) **DISCONTINUED**, Last Lot/Valid Use Date: F-4 (07/06)	1672010 and 1672020	o-Toluenesulfonamide (200 mg) and p-Toluensulfonamide (200 mg)
68800-9	3-(3,4,6-Trihydroxyphenyl)-alanine (50 mg) **(Limit Test)**	1361010	Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)-alanine)
1694001	Tripelennamine Citrate (200 mg) **DISCONTINUED**	N/A	DISCONTINUED, Last Lot/Valid Use Date: G (02/07)
	Vitamin B1 Hydrochloride	1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)
	Vitamin B2	1603006	Riboflavin (500 mg) (Vitamin B2)
	Vitamin B3	1462006	Niacinamide (500 mg) (Vitamin B3)
	Vitamin B5	1087009	Calcium Pantothenate (200 mg) (Vitamin B5)
	Vitamin B6	1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)
	Vitamin B12	1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)

Cross Reference List

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
	Vitamim Bc	1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)
	Vitamin C	1043003	Ascorbic Acid (1 g) (Vitamin C)
	Vitamin D2	1239005	Ergocalciferol (150 mg; 30 mg/ampule; 5 ampules) (Vitamin D2)
	Vitamin D3	1131009	Cholecalciferol (30 mg/ampul; 5 ampuls) (Vitamin D3)
	Vitamin E Alcohol	1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)
	Vitamin E Acetate	1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)
	Vitamin E Acid Succinate	1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)
	Vitamin K1	1538006	Phytonadione (500 mg) (Vitamin K1)
	Vitamin K3	1381006	Menadione (200 mg) (Vitamin K3)
	Vitamin M	1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
1005706	Glacial Acetic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D002	$168
1012076	Acyclovir Related Compound A (50 mg) (AS) (2-[(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)methoxy]ethyl acetate)	F0F010	$535
1036507	3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile (25 mg) (AS)	G2D383	$526
1017364	Aluminum Sulfate (2 g) (AS)	F0D342	$168
1019712	Amiloride Related Compound A (30 mg) (AS) (Methyl 3,5-diamino-6-chloropyrazine-2-carboxylate)	F0E287	$526
1029942	Ammonium Carbonate (2 g) (AS)	F0D102	$168
1029986	Ammonium Phosphate Dibasic (1 g) (AS)	F0D104	$168
1042000	Aprobarbital **CIII** (200 mg) (AS)	F-1	$224
1043105	Ascorbyl Palmitate (2 g) (AS)	F0D326	$168
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272	$224
1075600	Bismuth Subcarbonate (1 g) (AS)	F0D324	$168
1075622	Bismuth Subgallate (2 g) (AS)	F0D323	$168
1075644	Bismuth Subnitrate (1.5 g) (AS)	F0D388	$168
1076341	Boric Acid (1 g) (AS)	F0D036	$216
1076465	Bromazepam **CIV** (100 mg) (AS)	F0F064	$224
1082708	Butylated Hydroxytoluene (500 mg) (AS)	F0D122	$168
1086334	Calcium Acetate (1 g) (AS)	F0D156	$168
1086403	Calcium Carbonate (1 g) (AS)	F0D099	$168
1086436	Calcium Chloride (1 g) (AS)	F0D153	$168
1086855	Calcium Hydroxide (1 g) (AS)	F0D168	$168
1086935	Calcium Levulinate (1 g) (AS)	F0E142	$168
1087031	Tribasic Calcium Phosphate (1 g) (AS)	F0D394	$168
1087359	Calcium Stearate (2 g) (AS)	F0D255	$168
1087406	Calcium Sulfate (1 g) (AS)	F0D236	$168
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2	$526
1090003	Cannabinol **CI** (25 mg) (AS)		$224
1096531	Carboxymethylcellulose Calcium (1.5 g) (AS)	F0D336	$168
1096699	Carprofen (200 mg) (AS)	F0D335	$168
1098388	Microcrystalline Cellulose (1 g) (AS)	F0D362	$168
1098402	Powdered Cellulose (1 g) (AS)	F0D364	$168
1133503	Cholic Acid (2 g) (AS)	F3B159	$168
1134346	Ciprofloxacin Related Compound A (25 mg) (AS) (7-Chloro-1-cyclopropyl-4-oxo-6-(piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid hydrochloride salt)	F0E333	$526
1148806	Corn Oil (1 g) (AS)	F0D181	$168
1150207	Cottonseed Oil (1 g) (AS)	F0D173	$168
1150513	Cromolyn Sodium Related Compound A (25 mg) (1,3-Bis-(2-acetyl-3-hydroxyphenoxy)-2-propanol) (AS)	F0E045	$526
1171251	2-Deoxy-D-Glucose (100 mg) (AS)	F0E006	$177
1183002	Diacetylmorphine Hydrochloride **CI** (25 mg) (AS) (Heroin Hydrochloride)	J	$224
1187091	Dibutyl Sebacate (1 mL) (AS)	F0D128	$168
1188301	Dichlorvos (150 mg) (2,2-dichlorovinyl dimethyl phosphate) (AS)	F0D141	$173
1210105	N-(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS)	F	$168
1235900	Enrofloxacin (200 mg) (AS)	F0E094	$168
1237509	Epitetracycline Hydrochloride (200 mg) (AS)	G0E261	$526
1251000	Estradiol Benzoate (250 mg) (AS)	H0C332	$168
1268965	Eugenol (500 mg) (AS)	F0D303	$168
1270355	Ferrous Sulfate (1.5 g) (AS)	F0D196	$168
1270446	Fexofenadine Related Compound C (15 mg) ((+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene) (AS)	F0E291	$526

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
1286606	L-Fucose (200 mg) (AS)	F0E007	$177
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224	$224
1338812	Indapamide Related Compound A (50 mg) (4-Chloro-N-(2-methyl-indol-1-yl)-3-sulfamoylbenzamide) (AS)	F0E052	$526
1350308	Isopropyl Alcohol (1.5 mL/ampule; 3 ampules) (AS)	F0D261	$168
1356643	Ketoprofen Related Compound A (25 mg) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid) (AS)	H0E028	$526
1356734	Lactic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D027	$168
1371002	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) (AS) (LSD)	I	$584
1374226	Magnesium Carbonate (2 g) (AS)	F0D256	$168
1374248	Magnesium Chloride (1 g) (AS)	F0D157	$168
1374260	Magnesium Hydroxide (1 g) (AS)	F0D158	$168
1374292	Magnesium Phosphate (2 g) (AS)	F0E107	$168
1374340	Magnesium Stearate (5 g) (AS)	F0D214	$168
1374361	Magnesium Sulfate (1 g) (AS)	F0D160	$168
1375127	Manganese Chloride (1 g) (AS)	F0D150	$168
1375149	Manganese Sulfate (1 g) (AS)	F0D151	$168
1379140	Meglumine (500 mg) (AS)	F0D385	$168
1381005	Melatonin (100 mg) (AS)	F0E027	$179
1396364	Methacholine Chloride (500 mg) (AS)	F0D222	$182
1410002	Methicillin Sodium (500 mg) (AS)	J0C333	$168
1424506	Methylcellulose (1 g) (AS)	G0B222	$168
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) (AS) (STP)	F	$224
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) (AS) (MDA)	F-1	$224
1437450	Methyl Salicylate (2 mL) (AS)	F0D070	$168
1446600	Monosodium Glutamate (1 g) (AS)	F0D387	$168
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G	$224
1478254	Olive Oil (1 g) (AS)	F0D175	$168
1478516	Omeprazole Related Compound A (15 mg) (Omeprazole Sulfone) (AS)	F0D363	$526
1479010	Orphenadrine Related Compound A (50 mg) ((RS)-N,N-dimethyl-2-[(3-methylphenyl)-phenylmethoxy]ethanamine citrate) (AS)	F0F042	$526
1491015	Oxytetracycline Hydrochloride (200 mg) (AS)	F0E258	$168
1492040	Palm Oil (1 g) (AS)	F0D179	$168
1500251	Paroxetine Related Compound D (10 mg) (AS) (cis-Paroxetine hydrochloride)	G0E096	$526
1500557	Peanut Oil (1 g) (AS)	F0D171	$168
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025	$224
1525707	Phenothiazine (500 mg) (AS)	F0D231	$168
1535802	Phosphoric Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D026	$168
1547346	Polyoxyl 2 Stearyl Ether (1 g) (AS)	F0D353	$168
1372606	Polyoxyl 10 Stearyl Ether (1 g)	F0D354	$168
1547925	Polysorbate 20 (2 g) (AS)	F0D130	$168
1547936	Polysorbate 40 (2 g) (AS)	F0D204	$168
1547947	Polysorbate 60 (2 g) (AS)	F0D131	$168
1547969	Polysorbate 80 (2 g) (AS)	F0D132	$168
1549807	Potassium Acetate (500 mg) (AS)	F0E083	$168
1548101	Potassium Benzoate (1 g) (AS)	F0D161	$168
1548134	Potassium Bicarbonate (1 g) (AS)	F0D074	$168
1549840	Potassium Bitartrate (3 g) (AS)	F0D384	$168
1548167	Potassium Carbonate (1 g) (AS)	F0D075	$168
1548190	Potassium Chloride (1 g) (AS)	F0D127	$168
1548225	Potassium Citrate (1 g) (AS)	F0D201	$168
1548280	Potassium Iodide (1 g) (AS)	F0D078	$168

USP Authentic Substances

Cat. No.	Description	Curr. Lot	Price
1548349	Potassium Nitrate (5 g) (AS)	F0D325	$168
1551128	Dibasic Potassium Phosphate (5 g) (AS)	F0D281	$168
1551139	Monobasic Potassium Phosphate (5 g) (AS)	F0D313	$168
1551140	Potassium Sodium Tartrate (2 g) (AS)	F0D380	$168
1548407	Potassium Sorbate (1 g) (AS)	F0D264	$168
1572208	Propionic Acid (1.5 mL/ampule; 3 ampules) (AS)	F0D029	$168
1612404	Sesame Oil (1 mL/ampule; 2 ampules) (AS)	F0E134	$168
1613407	Sodium Acetate (1 g) (AS)	F0D083	$168
1613655	Sodium Bicarbonate (3 g) (AS)	F0D235	$168
1613757	Sodium Carbonate Anhydrous (1 g) (AS)	F0D100	$168
1613804	Sodium Chloride (1 g) (AS)	F0D269	$168
1613859	Sodium Citrate (1 g) (AS)	F0D172	$168
1614363	Sodium Lauryl Sulfate (1 g) (AS)	F0D381	$168
1614396	Sodium Metabisulfite (1 g) (AS)	F0D111	$168
1614454	Sodium Nitrite (1 g) (AS)	F0D117	$168
1614807	Sodium Sulfate Anhydrous (1 g) (AS)	F0D112	$168
1615107	Sodium Thiosulfate (1 g) (AS)	F0D178	$168
1615956	Sorbic Acid (1 g) (AS)	F0D129	$168
1619017	Spironolactone Related Compound A (100 mg) (Canrenone (3-Oxo-17-alpha-pregna-4,6-diene-21, 17-carbolactone)) (AS)	F0E184	$526
1643328	Tannic Acid (2 g) (AS)	F0D292	$168
1643340	Tartaric Acid (1 g) (AS)	F0D176	$168
1667585	Titanium Dioxide (1 g) (AS)	F0D079	$168
1708718	Valproic Acid Related Compound B (50 mg) ((2RS)-2-(1-methylethyl)pentanoic acid) (AS)	F0E201	$526
1724747	Zinc Oxide (2 g) (AS)	F0D170	$168
1724769	Zinc Sulfate (1 g) (AS)	F0D133	$168

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
AMINO ACIDS			
1012509	L-Alanine (200 mg)	G0E002	$168
1021000	Aminocaproic Acid (200 mg)	G0D101	$168
1042500	L-Arginine (200 mg)	G-1	$168
1042601	Arginine Hydrochloride (125 mg)	G0B060	$134
1043502	Asparagine Anhydrous (200 mg)	F0E013	$168
1043513	Asparagine Monohydrate (200 mg)	F0E012	$168
1161509	L-Cysteine Hydrochloride (200 mg)	H	$168
1294976	Glutamic Acid (200 mg)	F0C069	$168
1294808	Glutamine (100 mg)	F0B244	$168
1295800	Glycine (200 mg)	G0E099	$168
1308505	L-Histidine (200 mg)	G0A018	$168
1349502	L-Isoleucine (200 mg)	F-2	$168
1357001	L-Leucine (200 mg)	H0B237	$168
1359903	Levocarnitine (400 mg)	G0B197	$168
1359925	Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride)	F-1	$526
1371501	L-Lysine Acetate (200 mg)	F1C027	$168
1372005	L-Lysine Hydrochloride (200 mg)	I0E230	$168
1411504	L-Methionine (200 mg)	G1D398	$168
1530503	L-Phenylalanine (200 mg)	H	$168
1568506	L-Proline (200 mg)	G0D146	$168
1612506	L-Serine (200 mg)	G	$168
1667202	L-Threonine (200 mg)	G	$168
1700501	L-Tryptophan (200 mg)	G2E237	$168
1705006	L-Tyrosine (500 mg)	K0C141	$168
1708503	L-Valine (200 mg)	F-2	$168
BOTANICALS			
BLACK COHOSH			
1076206	Powdered Black Cohosh Extract (1.5 g)	F0D086	$563
CAPSAICIN/CAPSICUM			
1091108	Capsaicin (100 mg)	G2D136	$168
1200600	Dihydrocapsaicin (25 mg)	G0C071	$281
CHAMOMILE			
1040708	Apigenin-7-Glucoside (30 mg)	F	$526
CHASTE TREE			
1012203	Agnuside (25 mg)	F0D397	$920
1096779	Casticin (25 mg)	F0D358	$957
1105009	Powdered Chaste Tree Extract (1.5 g)	F0C406	$563
RED CLOVER			
1286060	Formononetin (50 mg)	F0C196	$563
1599500	Powdered Red Clover Extract (500 mg)	F0C188	$281
CRANBERRY LIQUID			
1134368	Citric Acid (200 mg)	F2E269	$168
1181302	Dextrose (500 mg)	J2E294	$134
1286504	Fructose (125 mg)	I3E340	$134
1374601	Malic Acid (200 mg)	G0B158	$168
1594506	Quinic Acid (200 mg)	F	$168
1617000	Sorbitol (125 mg)	H1B139	$134
1623637	Sucrose (100 mg)	H1C223	$168

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
ELEUTHERO			
1234704	Powdered Eleuthero Extract (1.5 g)	F0C291	$563
1234668	Eleutheroside B (15 mg) (Syringin)	F0E056	$884
1234680	Eleutheroside E (15 mg) (Syringaresinol diglucoside)	F0E057	$884
ECHINACEA			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1231728	Powdered Echinacea Purpurea Extract (1 g)	F0D018	$563
1231706	Powdered Echinacea Angustifolia Extract (1 g)	F0D019	$563
1305507	2E, 4E-Hexadienoic Acid Isobutylamide (25 mg)	F0C353	$584
FEVERFEW			
1500400	Parthenolide (25 mg)	F	$168
1606503	Rutin (100 mg)	G0C355	$168
GARLIC			
1012145	Agigenin (25 mg)	F	$526
1012950	Alliin (25 mg)	F	$1,649
1115556	beta-Chlorogenin (20 mg)	F	$526
1294848	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F	$730
1411504	L-Methionine (200 mg)	G1D398	$168
GARLIC FLUID EXTRACT			
1013057	S-Allyl-L-Cysteine (25 mg)	F	$526
GINGER			
1091108	Capsaicin (100 mg)	G2D136	$168
1291504	Powdered Ginger (500 mg)	F	$281
GINKGO			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1592409	Quercetin (500 mg)	G0D407	$168
1606503	Rutin (100 mg)	G0C355	$168
AMERICAN GINSENG			
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289	$563
ASIAN GINSENG			
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289	$563
GOLDENSEAL			
1065210	Berberine Chloride (50 mg)	F0E185	$281
1313210	Hydrastine (10 mg)	F0E204	$281
HAWTHORN LEAF WITH FLOWER			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1335202	Hyperoside (50 mg)	F	$925
1592409	Quercetin (500 mg)	G0D407	$168
1606503	Rutin (100 mg)	G0C355	$168
1717708	Vitexin (30 mg)	F0C142	$563
HORSE CHESTNUT			
1249202	Escin (350 mg)	F0F088	$185
KAVA			
1355709	Powdered Kava Extract (1 g)	F0C161	$281
KAWAIN			
1355753	Kawain (200 mg)	F0C160	$225
LICORICE			
1295888	Glycyrrhizic Acid (25 mg)	F0C006	$526
MILK THISTLE			

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
1443850	Powdered Milk Thistle Extract (250 mg)	F0B321	$281
1612630	Silybin (50 mg)	G0D392	$168
1612641	Silydianin (20 mg)	F	$168
PYGEUM			
1612947	Beta-Sitosterol (300 mg)	F0D217	$563
ST. JOHN S WORT			
1115545	Chlorogenic Acid (50 mg)	F0C420	$168
1335202	Hyperoside (50 mg)	F	$925
1485001	Oxybenzone (150 mg)	H0B263	$168
1606503	Rutin (100 mg)	G0C355	$168
SAW PALMETTO			
1424233	Methyl Caprate (300 mg)	G0D087	$168
1424244	Methyl Caproate (300 mg)	F	$168
1424255	Methyl Caprylate (300 mg)	G0D064	$168
1430305	Methyl Laurate (500 mg)	G0C356	$168
1430327	Methyl Linoleate (5 x 50 mg)	G0D107	$168
1430349	Methyl Linolenate (5 x 50 mg)	F	$168
1431501	Methyl Myristate (300 mg)	G0C357	$168
1431556	Methyl Oleate (500 mg)	G0C148	$168
1431603	Methyl Palmitate (300 mg)	G0E329	$168
1431625	Methyl Palmitoleate (300 mg)	F	$168
1437508	Methyl Stearate (300 mg)	G0E290	$168
1612947	Beta-Sitosterol (300 mg)	F0D217	$563
STINGING NETTLE			
1043819	Aspartic Acid (100 mg)	F0B087	$168
1294976	Glutamic Acid (200 mg)	F0C069	$168
1610090	Scopoletin (20 mg)	F0C329	$168
1612947	Beta-Sitosterol (300 mg)	F0D217	$563
VALERIAN			
1707908	Valerenic Acid (15 mg)	H0D126	$753
MISCELLANEOUS DIETARY SUPPLEMENTS			
1133536	Choline Bitartrate (200 mg)	F0C057	$168
1133547	Choline Chloride (200 mg)	F0C058	$168
1133570	Chondroitin Sulfate Sodium (300 mg)	G0E236	$168
1133638	Chromium Picolinate (100 mg)	F	$168
1150353	Creatinine (100 mg)	F	$168
1294207	Glucosamine Hydrochloride (200 mg)	F0C363	$168
1381005	Melatonin (100 mg) (AS)	F0E027	$179
1611955	Selenomethionine (100 mg)	F0B006	$168
1705301	Ubidecarenone (200 mg)	G0E154	$270
1705323	Ubidecarenone Related Compound A (15 mg) (Coenzyme Q9)	F0E210	$526
1705312	Ubidecarenone for System Suitability (25 mg)	F0B194	$526
VITAMINS-MINERALS			
1043003	Ascorbic Acid (1 g) (Vitamin C)	Q0B012	$168
1071508	Biotin (200 mg)	I0D114	$168
1086356	Calcium Ascorbate (200 mg)	F-1	$168
1087009	Calcium Pantothenate (200 mg) (Vitamin B5)	O0C331	$168
1131009	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157	$172
1131803	Delta-4,6-cholestadienol (30 mg)	F	$526

Dietary Supplement Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N	$168
1179504	Dexpanthenol (500 mg)	J0C293	$173
1239005	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275	$182
1241007	Ergosterol (50 mg)	H	$168
1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P	$168
1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176	$168
1370804	Lutein (1 mL)	F0D291	$919
1381006	Menadione (200 mg) (Vitamin K3)	H-3	$168
1461003	Niacin (200 mg)	I0E295	$168
1462006	Niacinamide (500 mg) (Vitamin B3)	N0E024	$168
1494501	Panthenol, Racemic (200 mg)	G	$168
1494807	Pantolactone (500 mg)	F	$526
1538006	Phytonadione (500 mg) (Vitamin K1)	N0B303	$168
1550001	Potassium Gluconate (200 mg)	H0C064	$168
1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P	$168
1603006	Riboflavin (500 mg) (Vitamin B2)	N0C021	$168
1613509	Sodium Ascorbate (200 mg)	G2C067	$168
1614002	Sodium Fluoride (1 g)	I0E033	$168
1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O	$168
1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M	$168
1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K	$168
1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)	G0D077	$168
1716002	Vitamin A (10 ampules containing vitamin A acetate in cottonseed/peanut oil)		$168
1717504	Vitamin D Assay System Suitability (1.5 g)	F-1	$168

Controlled Substances Reference Standards Available from USP

Cat. No.	Description	Curr. Lot	Price
1012906	Alfentanil Hydrochloride **CII** (500 mg)	F0B016	$224
1014005	Alphaprodine Hydrochloride **CII** (250 mg)	F	$224
1015008	Alprazolam **CIV** (200 mg)	H1C133	$224
1030001	Amobarbital **CII** (200 mg)	F-2	$224
1036008	Anileridine Hydrochloride **CII** (250 mg)	F	$224
1059003	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F2C272	$224
1076465	Bromazepam **CIV** (100 mg) (AS)	F0F064	$224
1078700	Buprenorphine Hydrochloride **CIII** (50 mg)	G0E026	$224
1078711	Buprenorphine Related Compound A **CII** (50 mg) (21-[3-(1-propenyl)]-7alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine)	F1C076	$526
1079000	Butabarbital **CIII** (200 mg)	H0C007	$224
1081002	Butalbital **CIII** (200 mg)	H0C054	$224
1082504	Butorphanol Tartrate **CIV** (500 mg)	J	$224
1089004	Cannabidiol **CI** (25 mg) (AS)	F-2	$526
1090003	Cannabinol **CI** (25 mg) (AS)		$224
1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I	$605
1109000	Chlordiazepoxide **CIV** (200 mg)	I0B063	$224
1110009	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4	$224
1140305	Clonazepam **CIV** (200 mg)	H0E003	$224
1140509	Clorazepate Dipotassium **CIV** (125 mg)	G0B027	$224
1143008	Cocaine Hydrochloride **CII** (250 mg)	I0B074	$224
1143802	Codeine N-Oxide **CI** (50 mg)	G0A034	$224
1144000	Codeine Phosphate **CII** (100 mg)	J0C200	$224
1145003	Codeine Sulfate **CII** (250 mg)	H-2	$224
1180004	Dextroamphetamine Sulfate **CII** (500 mg)	I0C311	$234
1183002	Diacetylmorphine Hydrochloride (Heroin Hydrochloride) **CI** (25 mg) (AS)	J	$224
1185008	Diazepam **CIV** (100 mg)	I1C364	$224
1187207	Dichloralphenazone **CIV** (200 mg)	F0B010	$224
1194009	Diethylpropion Hydrochloride **CIV** (200 mg)	H	$224
1200804	Dihydrocodeine Bitartrate **CII** (200 mg)	I0D205	$224
1219008	Diphenoxylate Hydrochloride **CII** (200 mg)	I1D339	$224
1258305	Ethchlorvynol **CIV** (0.7 ml)	F0B011	$224
1270005	Fentanyl Citrate **CII** (100 mg)	K0C264	$260
1280009	Fluoxymesterone **CIII** (200 mg)	G-2	$224
1285002	Flurazepam Hydrochloride **CIV** (200 mg)	J0C365	$224
1295006	Glutethimide **CII** (500 mg)	F	$224
1302305	Halazepam **CIV** (200 mg) (AS)	F1C224	$224
1307003	Hexobarbital **CIII** (500 mg)	F	$224
1315001	Hydrocodone Bitartrate **CII** (250 mg)	L0E176	$224
1315012	Hydrocodone Bitartrate Related Compound A **CII** (70 mg) (Morphinan-6-one, 4-hydroxy-3-methoxy-17-methyl)	F0C214	$555
1323000	Hydromorphone Hydrochloride **CII** (50 mg)	J0C372	$224
1356009	Ketamine Hydrochloride **CIII** (250 mg)	H0E091	$224
1359506	Levmetamfetamine **CII** (75 mg)	F1C113	$224
1364007	Levorphanol Tartrate **CII** (500 mg)	I0D138	$224
1370305	Lorazepam **CIV** (200 mg)	I1D404	$224
1371002	Lysergic Acid Diethylamide Tartrate (LSD) **CI** (10 mg) (AS)	I	$584
1375309	Mazindol **CIV** (350 mg)	H	$224
1383001	Meperidine Hydrochloride **CII** (200 mg)	I	$224
1386000	Mephobarbital **CIV** (250 mg)	G	$224
1389008	Meprobamate **CIV** (200 mg)	G-1	$224

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Cat. No.	Description	Curr. Lot	Price
1398009	Methadone Hydrochloride **CII** (200 mg)	I0B163	$224
1399001	Methamphetamine Hydrochloride **CII** (125 mg)	I	$224
1404000	Methaqualone **CI** (500 mg)	F-1	$224
1405002	Metharbital **CIII** (200 mg)	F-2	$224
1413000	Methohexital **CIV** (500 mg)	G0D252	$224
1425000	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride (STP) **CI** (25 mg) (AS)	F	$224
1429000	Methylenedioxy-3,4-amphetamine Hydrochloride (MDA) **CI** (25 mg) (AS)	F-1	$224
1433008	Methylphenidate Hydrochloride **CII** (125 mg)	I1C241	$179
1434011	Methylphenidate Hydrochloride Erythro Isomer Solution **CII** (0.5 mL)	F0C368	$605
1438001	Methyltestosterone **CIII** (200 mg)	J1E324	$224
1445404	Modafinil **CIV** (200 mg)	F0D351	$270
1447002	Morphine Monohydrate **CII** (50 mg) (AS)	G	$224
1448005	Morphine Sulfate **CII** (500 mg)	N0E161	$359
1452002	Nalorphine Hydrochloride **CIII** (250 mg)	I	$224
1453526	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone hydrochloride)	F	$526
1454008	Nandrolone **CIII** (50 mg)	F4D144	$605
1455000	Nandrolone Decanoate **CIII** (250 mg)	J0D218	$224
1456003	Nandrolone Phenpropionate **CIII** (250 mg)	H	$224
1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)	H1B035	$605
1473002	Noroxymorphone Hydrochloride **CII** (50 mg)	H1C177	$605
1482003	Oxandrolone **CIII** (50 mg)	H0E223	$224
1483006	Oxazepam **CIV** (200 mg)	H0D259	$224
1485191	Oxycodone **CII** (200 mg)	J0F026	$224
1487007	Oxymetholone **CIII** (200 mg)	G1B247	$224
1488000	Oxymorphone **CII** (500 mg)	H0B214	$224
1505007	Pentazocine **CIV** (500 mg)	I0C418	$224
1507002	Pentobarbital **CII** (200 mg)	I0D359	$224
1516003	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025	$224
1516502	Phendimetrazine Tartrate **CIII** (350 mg)	G	$224
1523009	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2	$224
1524001	Phenobarbital **CIV** (200 mg)	J	$224
1528501	Phentermine Hydrochloride **CIV** (200 mg)	H0B309	$224
1554501	Prazepam **CIV** (500 mg)	G0C066	$224
1574000	Propoxyphene Hydrochloride **CII** (1 g)	L0C285	$224
1575002	Propoxyphene Napsylate **CII** (1 g)	H1C323	$224
1592205	Quazepam **CIV** (200 mg)	F	$224
1611004	Secobarbital **CII** (200 mg)	H	$224
1620005	Stanozolol **CIII** (200 mg)	F-3	$224
1623648	Sufentanil Citrate **CII** (25 mg)	H1E105	$238
1643000	Talbutal **CIII** (250 mg)	F	$224
1643408	Temazepam **CIV** (200 mg)	H0C205	$224
1645006	Testolactone **CIII** (125 mg)	F-1	$179
1646009	Testosterone **CIII** (125 mg)	I1B253	$179
1647001	Testosterone Cypionate **CIII** (200 mg)	H0D162	$224
1648004	Testosterone Enanthate **CIII** (200 mg)	K0D253	$224
1649007	Testosterone Propionate **CIII** (200 mg)	L1C005	$224
1656308	Thiamylal **CIII** (200 mg)	F	$224
1661002	Thiopental **CIII** (250 mg)	I1D198	$224
1673806	Trenbolone **CIII** (50 mg)	F0D389	$179

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Cat. No.	Description	Curr. Lot	Price
1673828	Trenbolone Acetate **CIII** (200 mg)	F0D390	$179
1680506	Triazolam **CIV** (200 mg)	H0B041	$224

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This is an update based on the proposals published in this issue of *PF*.

CHROMATOGRAPHIC REAGENTS USED IN *USP–NF* AND *PHARMACOPEIAL FORUM*

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Chromatographic Reagents Used in *USP-NF* and *Pharmacopeial Forum*

July–Aug. 2006

ALMOND OIL (DSD Mgh #1510)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	G27	SPB-5	Sterol composition	0.32 mm × 30 m, 0.25 µm, manufacturer Supelco.

BISOPROLOL FUMARATE TABLETS (DSD Mgh #9794)

PF	LGS#	Reagent Brand	Type of Test	Comments
0(0)	L7	Pecosphere 3CR C8	Dissolution	4.6 mm × 33 mm, manufacturer PerkinElmer, catalog number 0250191.

CARPROFEN (DSD Mgh #13600)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(5)	L1	Zorbax ODS	Assay and Related compounds	4.6 mm × 25 cm, 5 µm, manufacturer Agilent.

CHOLINE CHLORIDE (DSD Mgh #17320)

PF	LGS#	Reagent Brand	Type of Test	Comments
0(0)	L7	Zorbax SB C8	Chromatographic purity	4.6 mm × 25 cm, manufacturer Agilent.

CISAPRIDE (DSD Mgh #17895)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(5)	L1	Hypersil BDS C-18	Related compounds	4.0 mm × 10 cm, 3 µm, manufacturer Thermo Electron.

DOXAZOSIN MESYLATE (DSD Mgh #28090)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L7	LiChrospher 60 RP-Select B	Related compounds and Chromatographic purity	4 mm × 25 cm, 5 µm, manufcturer Merck KGaA.

ETHYL ACETATE (DSD Mgh #31860)

PF	LGS#	Reagent Brand	Type of Test	Comments
0(0)	G16	DB Wax	Organic volatile impurities	0.53 mm × 10 m, 1 µm, manufacturer J&W Scientific.

FLUDARABINE PHOSPHATE INJECTION (DSD Mgh #1516)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Discovery C18	Assay and Related compounds	4.6 mm × 25 cm, 5 µm, manufacturer Supelco.

FLUOXETINE ORAL SOLUTION (DSD Mgh #33785)

PF	LGS#	Reagent Brand	Type of Test	Comments
25(2)	L1	Supelcosil LC-18-DB	Chromatographic purity	4.6 mm × 25 cm, 5 µm, manufacturer Supelco.

GLUCOSAMINE AND METHYLSULFONYLMETHANE TABLETS (DSD Mgh #2188)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	G2	Zebron ZB-1	Content of	Content of methylsulfonylmethane. 0.53 mm × 30 m, 5 µm, manufacturer Phenomenex.
32(4)	L1	Genesis C18	Content of	Content of glucosamine. 3.0 mm × 5 cm, 5 µm, manufacturer Grace-Jones.

HYDROMORPHONE HYDROCHLORIDE (DSD Mgh #38640)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Symmetry C-18	Related compounds	3.9 mm × 15 cm, 5 µm, manufacturer Waters.

MELOXICAM ORAL SUSPENSION (DSD Mgh #2140)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L1	Kromasil C18	Assay and Chromatographic purity	4 mm × 12.5 cm, manufacturer EKA Nobel.

MELOXICAM TABLETS (DSD Mgh #48124)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(5)	L1	Kromasil C18	Assay and Related compounds	4.0 mm × 10 cm, 10 µm, manufacturer EKA Nobel.

PANTOPRAZOLE SODIUM (DSD Mgh #60470)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(5)	L1	Nova-Pak C18	Assay and Related compounds	3.9 mm × 15 cm, 4 µm, manufacturer Waters.

POLYDEXTROSE (DSD Mgh #66235)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L25	Ultrahydrogel 250	Mol. wt. distrib., Ave. mol. wt.	7.8 mm × 30 cm, 6 µm, manufacturer Waters.
32(4)	L25	Ultrahydrogel 250	Molecular size distribution	7.8 mm × 30 cm, 6 µm, manufacturer Waters.

TRANEXAMIC ACID (DSD Mgh #84413)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(5)	L1	Nucleosil C18	Assay and Related compounds	250 × 4.6 mm 5 µm, manufacturer Agilent.

TRIMIPRAMINE MALEATE (DSD Mgh #85990)

PF	LGS#	Reagent Brand	Type of Test	Comments
32(4)	L7	Luna C8	Assay and Related compounds	4.6 mm × 25 cm, 5 µm, manufacturer Phenomenex.

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PHARMACOPEIAL FORUM VOL. 32 NO. 5 SEPT.–OCT. 2006

* The *USP–NF* (*USP 30–NF 25*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

Please address comments on *PF* content to Executive Secretariat
USP–NF, 12601 Twinbrook Pkwy.,
Rockville, MD 20852

Telephone: 1-301-816-8345
Fax: 1-301-816-8373
http://www.usp.org

Pharmacopeial Forum is covered in *Current Contents/Life Sciences* and in the *Science Citation Index (SCI),* in *International Pharmaceutical Abstracts*, and in *Current Awareness in Biological Sciences.*

The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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Our subscribers' records and publication labels are computer-generated. Please send your new address, and your latest label, or an exact copy of it, to: USPC, *PF* Customer Service Dept., 12601 Twinbrook Parkway, Rockville, MD 20852.
Fax: (301) 816-8148.

STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through *Pharmacopeial Forum* (*PF*), for the development of official pharmaceutical standards.

USP publishes *Pharmacopeial Forum* (*PF*) bimonthly as the working vehicle of the USP Council of Experts. *PF* provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the *United States Pharmacopeia* and the *National Formulary* (*USP–NF*).

PF includes the following:

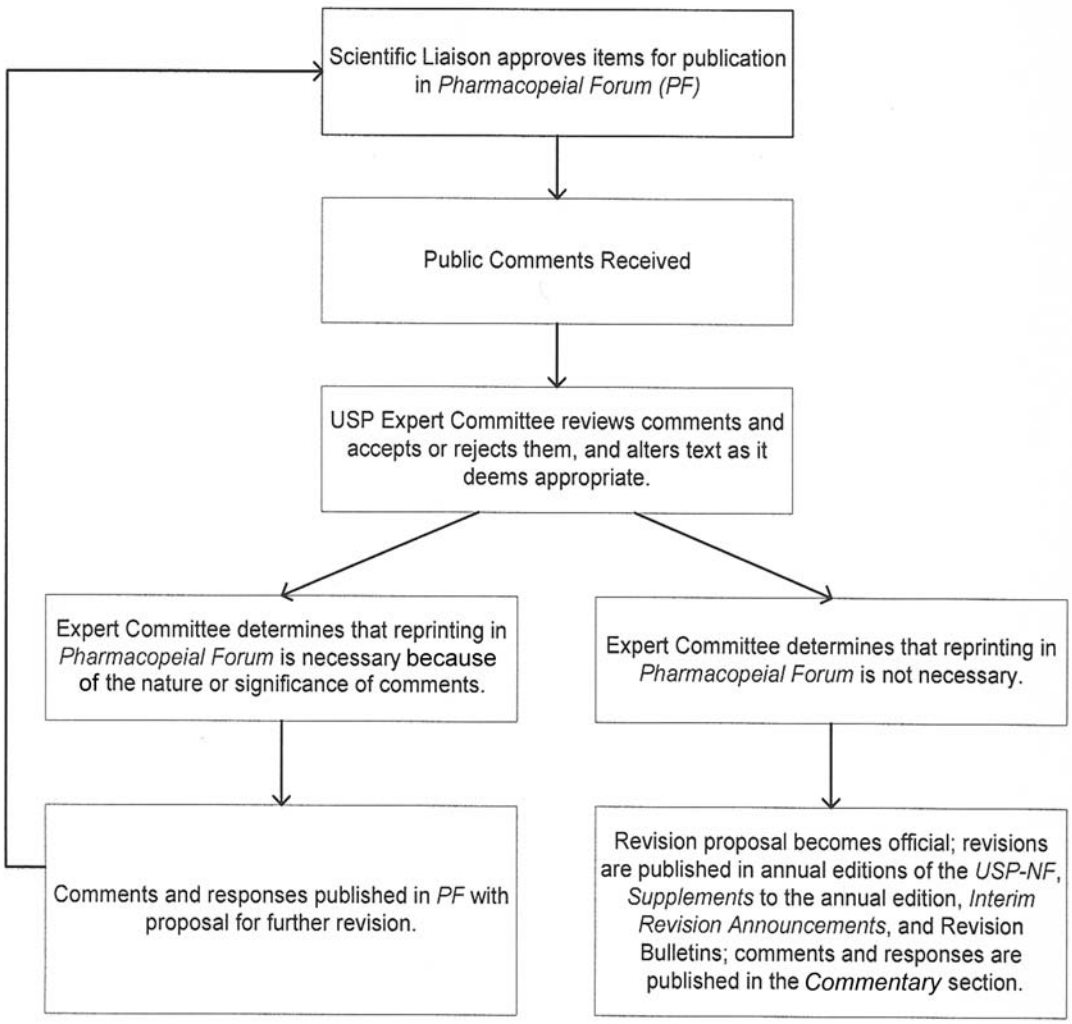
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official and binding before the publication of the next *USP–NF* or *Supplement* (*Interim Revision Announcement*)

USP welcomes comments and data on potential, proposed, or official standards.* Comments, along with USP's responses, will be published either in *PF Briefings*, the *Commentary* section of *PF*, the *Commentary* section of *Supplements* to *USP–NF*, or the *Commentary* section of *USP–NF*.

* If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before the section *Chromatographic Reagents Used in USP–NF and PF*.

The chart below shows the public review and comment process and its relationship to standards development.

Public Review and Comment Process for *USP-NF* Standards Development



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@usp.org).

HOW TO USE *PF*

This section provides descriptions of the various parts of *PF*. It also includes *Committee Designations* and the *Staff Directory*.

The content of the different sections of *PF* is briefly described below. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a *Request for Revision* is available in the *Guideline for Submitting Requests for Revision to the USP–NF* on the USP website (www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP–NF*

Section	Content	How Readers Can Respond
Pharmacopeial Previews Early ideas for revisions	•BRIEFING: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. •Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: — the controversial nature of an item; — the application of new technologies that require further study; and — articles produced by multiple sources.	Review drafts and provide comments to the appropriate staff liaison cited in the *Briefing* preceding each *Preview.*
In-Process Revision Revisions targeted for adoption	•BRIEFING: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. •New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see *Standards Development*). New or revised text is marked with symbols (■ or ● or ▲) to specify the tentative earliest date on which the revision would be officially adopted.	Review material and send comments promptly to USP staff liaison (see the *Staff Directory*). Guidelines on how to comment are found at the end of the *Policies and Announcements* section.
Harmonization Items the Pharmacopeial Discussion Group (PDG) is working to harmonize internationally	•BRIEFING: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under *Pharmacopeial Previews* or under *In-Process Revision,* both separate sections of *Harmonization.* •For *In-Process Revision,* new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted.	Review material and provide comments to the appropriate staff liaison cited in the *Briefing* preceding each *Preview* or *In-Process Revision.*
Interim Revision Announcement Adopted standards	Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols ●.	Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance.
Pending Proposals	In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *PF* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in either the *USP–NF*, its supplements, or an *IRA*. Those items that have not yet been adopted are still pending.	Review items to track pending proposals.
Canceled Proposals	Canceled proposals are items that were published in *PF* and were pending, but have since been canceled. Note that canceled proposals may be republished to be considered in the future for adoption into the *USP–NF.*	Review items to track canceled proposals.

Other Sections

Committee Designations
Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

Staff Directory
Names of all USP scientific staff liaisons with contact information.

Policies and Announcements
- General scientific and policy issues affecting *USP–NF* standards and processes
- Update on standards-related issues being considered by USP
- Where to find summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules

Stimuli to the Revision Process
- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development

Nomenclature
- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the *USP Dictionary of USAN and International Drug Names*
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues

Index
Cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

Reference Standards Catalog
List of official USP Reference Standards specified in *USP–NF*, along with availability and ordering information.

Chromatographic Reagents Used in USP–NF and Pharmacopeial Forum
Update of chromatographic reagents based on the proposals published in this issue of *PF*.

EXPERT COMMITTEE DESIGNATIONS*

2005–2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell, Gene, and Tissue Therapies
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding
RMI	Radiopharmaceuticals and Medical Imaging Agents
RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics

VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005–2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

STAFF	E-MAIL	PHONE	ASSIGNMENT
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POLICIES AND ANNOUNCEMENTS

This section includes information about general scientific and policy issues that may have an impact on *USP–NF* standards and processes and announcements about issues being considered by USP. This section also includes publication and comment schedules.

***USP 30–NF 25* TO BE PRINTED AS A THREE-VOLUME SET.** USP is pleased to announce that the *USP–NF* will now be printed as a three-volume set because of the increase in content which no longer fits into one volume. *USP 30–NF 25* will be the first edition to be printed as three volumes.

- Volume 1 includes Front Matter (Mission and Preface, People, Collaborators, Members, Preambles [formerly called Appendices], Admissions/Annotations, and Commentary). It also includes USP General Notices, General Chapters, Dietary Supplement Chapters, Reagents, Reference Tables, Dietary Supplement Monographs, *NF* General Notices, Excipients, and *NF* Monographs.
- Volume 2 includes *USP* monographs A–L.
- Volume 3 includes *USP* monographs M–Z.

Each volume includes the General Notices, the full Table of Contents, the General Chapters Table of Contents, and full Index. The new format will be easier to use and will allow for printing on a heavier weight of paper.

IMPLEMENTATION PERIOD EXTENDED FOR UPCOMING OFFICIAL REVISIONS TO THE *USP–NF*. To provide additional time to adopt revisions made to the compendia, USP is pleased to announce that effective beginning with the publication of *USP 30–NF 25,* implementation periods for revisions to official text in *United States Pharmacopeia–National Formulary (USP–NF)* and its *Supplements* are being extended. This change is a response to stakeholder requests (see the *Pharmacopeial Forum* [*PF* 31(2)] *Stimuli* article, ''The USP Revision Process: Recommendations for Enhancements''). As a result of this change, users will have six months from the publication date to implement new official texts as opposed to the previous 60-day period. The complete revised Publication Schedule for *USP 30–NF 25* reflecting this new 6-month implementation period is outlined below.

Publication Schedule for *USP 30–NF 25*

***USP–NF* Publication**	**Publication Date**	**Official Date**
USP–NF (Book)	November 2006	May 1, 2007
Supplement One	February 2007	August 1, 2007
Supplement Two	June 2007	December 1, 2007

Users may implement the newly official texts prior to the official date and the use becomes mandatory on the official date.

Please direct any comments or questions on this topic to Beryl Voigt, Director, Executive Secretariat (301-816-8155 or execsec@usp.org).

COORDINATION OF *PF* SUBMISSIONS AND NEW USP REFERENCE STANDARDS. USP recently announced a new process in which revisions and new monographs will not be published as official standards until the required USP Reference Standards are available for purchase [see *Policies and Announcements, PF* 32(3)]. We are pleased to announce another process change to better synchronize the availability of USP Reference Standards and the adoption of new documentary standards in the *USP–NF.* Effective March 28, 2006, any revision proposal involving the use of a first-time USP Reference Standard or new use of an existing USP Reference Standard will be scheduled for publication in the *PF* only after a suitable reference standard bulk candidate has been received by USP. The timing of this new process affects regular revisions (not new monographs/general chapters) submitted to *PF* 32(4) and all revisions and new monographs/general chapters beginning with *PF* 32(5). While we acknowledge that this may cause a brief delay in publication of some proposed revisions and new monographs, we believe this process change is a benefit to USP customers and will ultimately lead to better public standards. It is anticipated that there may be some exceptions to this new process on a case-by-case basis.

Please direct any comments or questions on this topic to Beryl Voigt, Director, Executive Secretariat (301-816-8155 or execsec@usp.org).

REVISION BULLETINS. In accordance with Section 9.01 of the Rules and Procedures of the Council of Experts, a *Revision Bulletin* is an official publication of the United States Pharmacopeia and the National Formulary. *Revision Bulletins* are posted on USP's website and sent to affected manufacturers via mail and e-mail, and are used to make revisions effective immediately when the need arises.

ALENDRONIC ACID TABLETS: NOTICE OF POSTPONEMENT. In accordance with Section 9.06(c) of the Rules and Procedures of the Council of Experts, the USP Nomenclature Expert Committee has postponed the official date of the title for this new monograph, which was published on page 64 of *USP 28–NF 23,* from July 1, 2006, to May 1, 2008. The postponement is intended to provide additional time for product label changes to be completed and for healthcare practitioners and consumers to become familiar with the terminology. Use of this title has been permitted since January 1, 2005, when the monograph first became official, but will not become mandatory until May 1, 2008, the official date of *USP 31–NF 26*.

The Salt Nomenclature Policy, on which this monograph title is based, was published for public review and comment in the July–August 2006 issue of *Pharmacopeial Forum* as part of the revised general information chapter *Nomenclature* ⟨1121⟩. The postponement is effective immediately and also appears in this *PF* in the *Fifth Interim Revision Announcement* to *USP 29–NF 24*. This postponement has been approved by

the Nomenclature Expert Committee and Chair of the Council of Experts in accordance with Section 9.06(c) of the Rules and Procedures of the Council of Experts.

Should you have any questions, please contact Dr. W. Larry Paul, Scientific Fellow and Scientific Liaison to the Nomenclature Expert Committee (301-816-8331 or wlp@usp.org).

AMIFOSTINE FOR INJECTION: NOTICE OF REVISION. In accordance with Section 9.06(c) of the Rules and Procedures of the Council of Experts, the USP Cardiovascular Expert Committee has made official the following revision to this monograph.

Delete the word ''lyophilized'' from the product Definition in the monograph.

This revision is effective immediately and also appears in the *Fifth Interim Revision Announcement* in this *PF*. This revision is intended to accommodate and provide flexibility for marketed products to be manufactured without the process of lyophilization while still meeting the product specifications.

Should you have any questions, please contact Dr. S. Ramakrishna, Scientist and Scientific Liaison to the Monograph Development—Cardiovascular Expert Committee (301-816-8349 or syk@usp.org).

IMMEDIATE IRA COMMENTARY

INDOCYANINE GREEN—As the current Definition does not adequately describe the article of commerce, the rubric is being revised from ''not less than 94.0 percent and not more than 105.0 percent of $C_{43}H_{47}N_2NaO_6S_2$, calculated on the dried basis'' to ''not less than 89.0 percent and not more than 100.0 percent of $C_{43}H_{47}N_2NaO_6S_2$, calculated on the dried basis.''

Please direct any comments or questions to Radhakrishna S. Tirumalai, Ph.D., Scientist and Scientific Liaison to the General Toxicity and Medical Device Biocompatibility Expert Committee (301-816-8339 or rst@usp.org).

NITROFURANTOIN CAPSULES—The *Nitrofurantoin Capsules* test for *Dissolution* is being revised to include an additional dissolution procedure (*Test 3*) to provide appropriate standards for an FDA-approved product.

Please direct any comments or questions to Margareth Marques, Ph.D., Senior Scientist (301-816-8106 or mrm@usp.org) or Behnam Davani, Ph.D., M.B.A., Senior Scientist (301-816-8394 or bd@usp.org).

CATALOG TO BE REMOVED FROM *PHARMACOPEIAL FORUM* PRINT PUBLICATION. Starting with *Pharmacopeial Forum* 33(1), the *USP Catalog* will no longer be included in the back of the publication. This change was made to reduce the bulk of the publication and, therefore, increase ease of handling and use.

The *USP Catalog* is still available in online and stand-alone print versions. Online bi-monthly and daily catalogs can be accessed at www.usp.org/referenceStandards/catalog.html. To receive the *USP Catalog* in print (via postal mail) along with monthly e-mail alerts that will keep you informed about new Reference Standards, availability, and current lots, send an e-mail to marketing@usp.org or call 301-816-8237.

USP ANNUAL SCIENTIFIC MEETING 2006. USP will host its third Annual Scientific Meeting, September 26–29, 2006, at the Marriott Denver City Center, Denver, Colorado. This year's topics include the following:

- Track I: Biologics and Biotechnology
- Track II: Reference Standards
- Track III: Dietary Supplements
- Track IV: Excipients
- Track V: USP—Working for You
- Track VI: Impurities in Drug Substances and Products
- One Day Track: Chromatography
- Special Topic: International Quality and Performance Topics

Many members of USP's Council of Experts' Expert Committees are presenting at the various track sessions and attending the meeting. USP anticipates that the collegial exchange of comments during session discussions and networking events will provide Expert Committees with a better understanding of the varied perspectives of USP's many audiences.

This year's Annual Scientific Meeting also will feature an expanded exhibit program and a spouse/guest program.

For more information and to register, go to www.usp.org/conferences, call 301-816-8134, or e-mail conferences@usp.org.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, other scientists, and professionals in the pharmaceutical and allied industries. USP scientists who play a key role in establishing official USP standards teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2006 are listed below. For more information and to register, visit www.usp.org. To discuss how USP can bring courses to a location of your choice or design a custom course package for you, call 301-816-8237, or e-mail PharmacopeialEducation@usp.org.

Calendar of Forthcoming Pharmacopeial Education Courses as of September 1, 2006

Date	Name of Course	Location	Price
26-Sep-06	Effectively Using the *USP–NF*—Sessions I and II	Denver, CO (USP Annual Scientific Meeting)	$595
26-Sep-06	Fundamentals of Microbiological Testing	Denver, CO (USP Annual Scientific Meeting)	$595
3-4 Oct-06	Fundamentals of Dissolution—Lecture and Laboratory	North Brunswick, NJ (with Distek)	$1,695
10-11 Oct-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for German)	Basel, Switzerland (with Sotax)	[1]
12-13 Oct-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for French)	Basel, Switzerland (with Sotax)	[1]
18-Oct-06	Effectively Using the *USP–NF*—Sessions I and II	Brussels, Belgium	$595
19-Oct-06	Analytical Method Validation	Brussels, Belgium	$595
7-Nov-06	Analytical Method Validation	Milan, Italy	[2]
8-9 Nov-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for Italian)	Milan, Italy (with Sotax)	[1]
14-15 Nov-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for Italian)	Rome, Italy (with Sotax)	[1]

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Munchensteinerstrasse 41
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Phone: +41 61 316 30 10
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VISIT THE USP WEB SITE AT ⟨http://www.usp.org⟩. Various resources related to Pharmacopeial standards are presented, including highlights from *PF*.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia, with a copy to USP, for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the European
Pharmacopoeia Commission
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HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that has appeared in an issue of *PF* should be submitted to the appropriate USP scientific staff liaison identified at the end of the *Briefing* accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the *Staff Directory* included in every *PF*.

Please note that *USP–NF* is being published in an annual edition with one main book and two *Supplements* a year. In addition, the schedule provided below will repeat every year so that users will know what to expect and become familiar with the deadlines.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

***PHARMACOPEIAL FORUM* PUBLIC REVIEW AND COMMENT PERIOD DEADLINES.** The full year's listing of comment period deadlines, including the targeted official publications, appears in the table below. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts*, USP has implemented a 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing.

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Publication Date	Official Date
PF 32(4)	October 16, 2006	*USP 30–NF 25 2nd Supplement*	June 2007	December 2007
PF 32(5)	December 15, 2006			
PF 32(6)	February 15, 2007	*USP 31–NF 26*	November 2007	May 2008
PF 33(1)	April 16, 2007			
PF 33(2)	June 15, 2007	*USP 31–NF 26 1st Supplement*	February 2008	April 2008
PF 33(3)	August 15, 2007			
PF 33(4)	October 15, 2007	*USP 31–NF 26 2nd Supplement*	June 2008	December 2008
PF 33(5)	December 15, 2007			

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, official revisions are published in *PF* in the *Interim Revision Announcement;* these revisions are also incorporated in the upcoming *Supplement.* The official publication in which an *IRA* is incorporated will depend upon publication deadlines. The 5th *IRA* and the 6th *IRA* will not appear until *Supplement 1*. See table below. The electronic version of *USP–NF* is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement.* The new table below outlines the publications and their release and official dates, and the book or supplement which supersedes them.

* ***Section 9.04(b) of the Rules and Procedures of the 2005–2010 Council of Experts***
A period of at least ninety (90) days from the date of publication will be allowed for public review and comment. The time allowed for public comments shall be noted in the publication in the PF. For good cause shown, the Chairperson may alter the time specified.

Publication Schedules

Publication	Release Date	Official Date	Superseded by
4th *IRA* [*PF* 32(4)]	July 1, 2006	Aug. 1, 2006	*USP 30–NF 25*
5th *IRA* [*PF* 32(5)]	Sept. 1, 2006*	Oct. 1, 2006*	*1st Supplement*
6th *IRA* [*PF* 32(6)]	Nov. 1, 2006*	Dec. 1, 2006*	*1st Supplement*
USP 30–NF 25	Nov. 1, 2006*	May 1, 2007*	*1st Supplement*
1st *IRA* [*PF* 33(1)]	Jan. 1, 2007*	Feb. 1, 2007*	*2nd Supplement*
1st Supplement	Feb. 1, 2007*	Aug. 1, 2007*	*2nd Supplement*
2nd *IRA* [*PF* 33(2)]	Mar. 1, 2007*	Apr. 1, 2007*	*2nd Supplement*
3rd *IRA* [*PF* 33(3)]	May 1, 2007*	June 1, 2007*	*USP 31–NF 26*
2nd Supplement	June 1, 2007*	Dec. 1, 2007*	*USP 31–NF 26*
4th *IRA* [*PF* 33(4)]	July 1, 2007*	Aug. 1, 2007*	*USP 31–NF 26*
5th *IRA* [*PF* 33(5)]	Sept. 1, 2007*	Oct. 1, 2007*	*1st Supplement to USP 31–NF 26*
6th *IRA* [*PF* 33(6)]	Nov. 1, 2007*	Dec. 1, 2007*	*1st Supplement to USP 31–NF 26*
USP 31–NF 26	Nov. 1, 2007*	May 1, 2008*	*1st Supplement to USP 31–NF 26*

*Tentative

PRIORITY NEW MONOGRAPH ITEMS. USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monographs are marked received upon receipt of monograph proposal. Received monographs are removed from this list upon publication in *Pharmacopeial Forum*. (This list has been updated as of July 5, 2006.) For additional information, contact Karen A. Russo, Ph.D., kar@usp.org. Monograph sponsors should consult USP's *Guideline for Submitting Requests for Revision to the USP–NF.*

Noncomplex Actives (Drug Substances)

Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Anagrelide Hydrochloride	Arsenic Trioxide	Azelaic Acid
Balsalazide Disodium	Bentoquatam	Bepridil Hydrochloride
Bivalirudin	Cabergoline	Calcipotriene
Calcium Trisodium Pentetate	Calfactant	Candesartan Cilexetil
Carmustine ***(Received)***	Cefdinir ***(Received)***	Cefditoren Pivoxil
Ceftibuten	Cetrorelix	Cevimeline
Chloroxine	Colfosceril	Cytarabine Liposome
Dalfopristin	Dapirazole Hydrochloride	Desirudin
Desonide ***(Received)***	Dexrazoxane	Difloxacin Hydrochloride
Docosanol	Entacapone	Epoprostenol Sodium ***(Received)***
Erythromycin Phosphate	Erythromycin Thiocyanate	Esmolol
Esomeprazole Magnesium ***(Received)***	Estazolam	Estradiol Benzoate
Estramustine Phosphate Sodium	Ethanolamine Oleate	Etomidate
Etoposide Phosphate	Exemestane	Felbamate
Flavoxate Hydrochloride	Fluoromethane F 18	Foscarnet Sodium
Fosfomycin Tromethamine	Gadobenate Dimeglumine	Gadopentetic Acid
Galantamine Hydrobromide ***(Received)***	Gallium Nitrate	Ganirelix
Glyceryl Aminobenzoate	Granisetron	Halobetasol Propionate
Haloperidol Decanoate ***(Received)***	Hydrocodone Polistirex	Ibandronate Sodium
Imipramine Pamoate	Imiquimod	Irinotecan
Isosulfan Blue	Itraconazole	Lamotrigine ***(Received)***

Noncomplex Actives (Drug Substances) *(Continued)*

Latanoprost	Lawsone	Levetriacepam
Levobetaxolol	Levomethadyl Acetate	Lomustine
Lopinavir	Metipranolol Hydrochloride	Midazolam Hydrochloride
Mifepristone	Miglitol	Misoprostol ***(Received)***
Mivacurium	Moexipril	Nalbuphine Hydrochloride
Nalmefene Hydrochloride	Nateglinide ***(Received)***	Nedocromil Sodium
Nicardipine Hydrochloride	Nilutamide	Nisoldipine
Olopatadine	Olsalazine Sodium ***(Received)***	Orbifloxacin ***(Received)***
Orlistat ***(Received)***	Oxcarbazepine ***(Received)***	Pantoprazole Sodium ***(Received)***
Pemoline	Pentamidine Isethionate	Piperonyl Butoxide
Pirbuterol Acetate	Poractant Alpha	Proguanil
Quetiapine Fumarate ***(Received)***	Rose Bengal	Salmeterol Xinafoate
Sertraline Hydrochloride ***(Received)***	Sodium Phenylbutyrate	Sterile Methotrexate Sodium
Streptozocin	Sulfacytine	Tacrolimus
Terbinafine Hydrochloride	Terconazole	Tiludronate Disodium
Tiopronin	Tranexamic Acid ***(Received)***	Trimipramine Maleate ***(Received)***
Trovafloxacin Mesylate	Voriconazole	Zinc Tridosium Pentetate

Noncomplex Actives (Drug Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate, and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol for Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Suppository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Aminopterin Sodium Tablets	Amlodipine and Benazepril Hydrochloride Capsules
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Bivalirudin Injection
Brompheniramine Maleate, Dextromethorphan Hydrobromide, and Pseudoephedrine Hydrochloride Oral Solution	Budesonide Inhalation Aerosol	Bupivacaine and Lidocaine Hydrochlorides Injection
Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules	Butalbital and Acetaminophen Tablets
Calcipotriene Cream	Calcipotriene Ointment	Calcipotriene Topical Solution
		Cabergoline Tablets
Calcitriol Capsules	Calcitriol Oral Solution	Calcium Acetate Capsules
Calcium Trisodium Pentetate Injection	Calfactant Intratracheal Suspension	Carbidopa and Levodopa Extended-Release Tablets
Carbidopa and Levodopa Tablets for Oral Suspension ***(Received)***	Carbidopa, Levodopa, and Entacapone Tablets	Carmustine for Injection ***(Received)***
Carmustine Implant	Carvedilol Tablets ***(Received)***	Cefdinir Tablets
Cefditoren Pivoxil Tablets	Ceftibuten Capsules	Ceftibuten for Oral Suspension

Noncomplex Actives (Drug Products) *(Continued)*		
Ceftiofur Hydrochloride Oral Suspension	Cetirizine Hydrochloride Oral Solution	Cetirizine Hydrochloride Tablets ***(Received)***
Cetrorelix Injection	Cevimeline Hydrochloride Capsules	Chloroxine Cream
Chlorpromazine Hydrochloride Extended-Release Capsules	Choline and Magnesium Salicylates Oral Solution	Choline and Magnesium Salicylates Tablets
Choline Salicylate Oral Solution	Ciclopirox Shampoo	Ciclopirox Topical Gel
Ciclopirox Topical Solution	Cilostazol Tablets ***(Received)***	Cimetidine Oral Solution
Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	Ciprofloxacin Otic Solution	Citalopram Hydrobromide Oral Solution
Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation	Cladribine Injection	Clemastine Fumarate Syrup
Clobetasol Propionate Gel	Clonazepam Orally-Disintegrating Tablets	Clorazepate Dipotassium Capsules
Clorazepate Dipotassium Extended-Release Tablets	Clotrimazole and Betamethasone Dipropionate Lotion	Colestipol Hydrochloride Tablets
Colfosceril and Tyloxapol Suspension	Compound Undecylenic Acid Cream	Compound Undecylenic Acid Topical Powder
Conjugated Estrogens and Medroxyprogesterone Acetate Tablets	Cromolyn Sodium Nasal Solution	Cyclosporine Modified Capsules
Cyclosporine Modified Oral Solution	Cyclosporine Ointment	Cyclosporine Topical Solution
Cysteamine Bitartrate Capsules	Cytarabine Liposome Injection	Dalfopristin and Quinupristin Injection
		Dantrolene Sodium Oral Suspension
Dapiprazole for Ophthalmic Solution	Desirudin for Injection	Desonide Cream
Dexrazoxane for Injection	Dextroamphetamine Sulfate Extended-Release Capsules	Dextromethorphan Polistirex Extended-Release Oral Suspension
Diazepam Injectable Emulsion	Diclofenac Sodium Ophthalmic Solution	Diethylpropion Hydrochloride Extended-Release Tablets
Difenoxin and Atropine Tablets	Difloxacin Hydrochloride Tablets	Dihydroergotamine Mesylate Metered Spray
Diltiazem Malate Extended-Release Tablets	Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets
Divalproex Sodium Delayed-Release Capsules	Dorzolamide and Timolol Ophthalmic Solution	Dorzolamide Ophthalmic Solution
Doxacurium Chloride Injection	Doxepin Hydrochloride Cream	Doxycycline Oral Gel
Econazole Nitrate Cream	Edrophonium Chloride and Atropine Sulfate Injection	Enalapril Maleate and Diltiazem Malate Extended-Release Tablets
Enalapril Maleate and Felodipine Extended-Release Tablets	Enalaprilat Injection	Entacapone Tablets
Ephedrine Sulfate and Guaifenesin Tablets	Epoprostenol for Injection	Epoprostenol Injection
Esmolol Hydrochloride Injection	Esomeprazole Magnesium Capsules	Estazolam Tablets
Estramustine Phosphate Sodium Capsules	Ethanolamine Oleate Injection	Etidronate Disodium Injection Concentrate
Etomidate Injection	Exemestane Tablets	Famotidine Orally Disintegrating Tablets
Felbamate Oral Suspension	Felbamate Tablets	Fentanyl Lozenges
Fentanyl Transdermal System ***(Received)***	Ferrous Fumarate and Docusate Sodium Extended-Release Capsules	Flavoxate Hydrochloride Tablets
Fluconazole Injection ***(Received)***	Fluconazole Tablets	Flunisolide Inhalation Aerosol
Flunisolide Nasal Spray	Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution
Fluorometholone Ointment	Fluticasone Propionate Cream ***(Received)***	Fluticasone Propionate Inhalation Powder
Fluticasone Propionate Ointment ***(Received)***	Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection
Fosfomycin for Oral Solution	Gabapentin Oral Solution	Gabapentin Tablets ***(Received)***
Gadobenate Dimeglumine Injection	Galantamine Tablets ***(Received)***	Gallium Nitrate Injection
Ganciclovir Capsules	Ganirelix Acetate Injection	Gatifloxacin Injection
Gatifloxacin Tablets	Gentamicin Sulfate Oral Solution	Gentamicin Sulfate Soluble Powder
Glimepiride Tablets ***(Received)***	Glipizide Extended-Release Tablets	Granisetron Injection
Granisetron Tablets	Guaifenesin and Salts of Dextromethorphan and Pseudoephedrine Oral Solution	Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets
Guanidine Hydrochloride	Guanidine Hydrochloride Tablets	Halobetasol Propionate Cream
Halobetasol Propionate Ointment	Haloperidol Decanoate Injection	Haloperidol Lactate Injection
Haloperidol Lactate Oral Concentrate	Hydralazine Hydrochloride and Hydrochlorothiazide Capsules	Hydrochlorothiazide Capsules
Hydrochlorothiazide Oral Solution Concentrate	Hydrocodone Bitartrate and Acetaminophen Oral Solution	Hydrocodone Bitartrate and Aspirin Tablets

Noncomplex Actives (Drug Products) *(Continued)*

Hydrocodone Bitartrate and Guaifenesin Oral Solution	Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrocodone Bitartrate and Homatropine Methylbromide Tablets
Hydrocortisone Acetate Dental Paste	Hydrocortisone Acetate Rectal Foam Aerosol	Hydrocortisone Butyrate Lotion
Hydroflumethiazide and Reserpine Tablets	Hydromorphone Hydrochloride Oral Solution	Hydroquinone Lotion
Ibandronate Sodium Tablets	Ibuprofen Capsules	Idarubicin Hydrochloride Injection
Imipramine Pamoate Capsules	Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol
Ipratropium Bromide Inhalation Solution	Irinotecan Hydrochloride Injection	Isosulfan Blue Injection
Isradipine Extended-Release Tablets	Itraconazole Injection	Itraconazole Oral Solution
Ketoconazole Cream	Ketoconazole Shampoo	Ketoprofen Capsules ***(Received)***
Ketoprofen Extended-Release Capsules	Ketoprofen Tablets	Ketotifen Fumarate
Ketotifen Fumarate Ophthalmic Solution	Lactic Acid Lotion	Lamivudine Tablets
Latanoprost Ophthalmic Solution	Leucovorin Calcium for Injection	Levetriacepam Tablets
Levobetaxolol Ophthalmic Suspension	Levocabastine Ophthalmic Suspension	Levofloxacin Solution
Levomethadyl Acetate Hydrochloride Oral Concentrate	Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder	Liothyronine Injection
Lisinopril and Hydrochlorothiazide Tablets	Lomustine Capsules	Lopinavir and Ritonavir Solution
Lopinavir Capsules	Lopinavir Solution	Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***
Loratadine Orally-Disintegrating Tablets	Losartan Potassium Tablets	Mefloquine Hydrochloride Tablets
Melphalan for Injection	Mesalamine Suppositories	Mesoridazine Besylate Concentrate
Metaraminol Bitartrate Injection	Methacholine Chloride for Inhalation Solution	Methadone Hydrochloride Oral Concentrate
Methocarbamol and Aspirin Tablets	Methoxsalen Softgels	Methyclothiazide and Deserpidine Tablets
Methylphenidate Hydochloride Chewable Tablets	Metipranolol Ophthalmic Solution	Metronidazole Capsules
Metronidazole Cream	Metronidazole Extended-Release Tablets	Metronidazole Hydrochloride for Injection
Metronidazole Lotion	Miconazole Nitrate Topical Aerosol	Midazolam Hydrochloride Injection ***(Received)***
Mifepristone Tablets	Miglitol Tablets	Milrinone Injection
Misoprostol Tablets ***(Received)***	Mivacurium In Dextrose Injection	Mivacurium Injection
Moexipril Hydrochloride and Hydrochlorothiazide Tablets	Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution
Morphine Sulfate for Injection Concentrate	Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate
Morphine Sulfate Tablets	Mycophenolate Mofetil Capsules	Mycophenolate Mofetil Oral Solution
Mycophenolate Mofetil Tablets	Nalbuphine Hydrochloride Injection	Nalmefene Hydrochloride Injection
Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution	Naproxen Extended-Release Tablets	Nateglinide Tablets
Nedocromil Sodium Inhalation Aerosol	Neomycin Sulfate Oral Powder	Nicardipine Hydrochloride Capsules
Nilutamide Tablets	Nimodipine Capsules	Nisoldipine Extended-Release Tablets
Nitroglycerin Solution in Acrylic Adhesive	Nizatidine Tablets	Ofloxacin in Dextrose Injection
Ofloxacin Injection	Ofloxacin Tablets ***(Received)***	Olopatadine Ophthalmic Solution
Olsalazine Sodium Capsules	Ondansetron Tablets	Orbifloxacin Tablets ***(Received)***
Orlistat Capsules ***(Received)***	Orphenadrine Citrate Extended-Release Tablets	Orphenadrine Citrate, Aspirin, and Caffeine Tablets
Oxcarbazepine Suspension	Oxcarbazepine Tablets	Oxiconazole Cream
Pantoprazole Sodium for Injection	Paroxetine Hydrochloride Extended-Release Tablets	Pemirolast Potassium Ophthalmic Solution
Pantoprazole Sodium Tablets	Paroxetine Oral Suspension	
Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution	Pentaerythritol Tetranitrate Extended-Release Capsules
Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation	Pentamidine Isethionate for Injection
Pentazocine Hydrochloride and Acetaminophen Tablets	Phendimetrazine Tartrate Extended-Release Capsules	Phenobarbital Capsules
Phentermine Resin Complex	Phentermine Resin Complex Capsules	Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules

Noncomplex Actives (Drug Products) *(Continued)*		
Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pilocarpine Hydrochloride Ophthalmic Gel	Pilocarpine Hydrochloride Ophthalmic Ointment
Pilocarpine Hydrochloride Tablets	Piperonyl Butoxide and Pyrethrins Aerosol Foam	Pirbuterol Acetate Inhalation Aerosol
Poractant Alpha Supension	Porfimer Sodium for Injection	Povacrylate Solution
Povacrylate-Iodine Topical Solution	Povidone-Iodine Gauze	Povidone-Iodine Swabsticks
Povidone-Iodine Topical Aerosol Foam	Povidone-Iodine Vaginal Suppositories	Pramipexole Dihydrochloride Tablets
Prazosin Hydrochloride and Polythiazide Capsules	Prednisolone Sodium Phosphate Oral Solution	Prochlorperazine Maleate Extended-Release Capsules
Progesterone Capsules	Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup	Promethazine and Phenylephrine Hydrochlorides Syrup
Promethazine Hydrochloride and Codeine Phosphate Oral Solution	Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup	Propafenone Hydrochloride Tablets
Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets	Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution
Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution
Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	Quinidine Sulfate Injection	Ramipril Capsules
Ranitidine Capsules	Rauwolfia Serpentina and Endroflumethiazide Tablets	Reserpine and Polythiazide Tablets
Rimantadine Hydrochloride Oral Solution	Risperidone Oral Solution	Risperidone Orally Disintegrating Tablets
Rivastigmine Tartrate Capsules	Rocuronium Bromide Injection	Rose Bengal Ophthalmic Solution
Rivastigmine Tartrate Oral Solution	Ropinirole Hydrochloride Tablets	
Rosiglitazone Maleate Tablets	Salicylic Acid and Sulfur Cleansing Lotion	Salicylic Acid and Sulfur Lotion
Salicylic Acid and Sulfur Shampoo	Salicylic Acid Cream	Salicylic Acid Ointment
Salmeterol Inhalation Aerosol	Salmeterol Xinafoate Inhalation Powder	Scopolamine Transdermal System
Selegiline Hydrochloride Capsules	Serpacwa Topical Cream	Sertraline Hydrochloride Oral Solution
Sibutramine Hydrochloride Capsules	Sodium Bicarbonate and Sodium Citrate for Oral Solution	Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension
Sodium Chlorophyllin Copper Complex Tablets	Sodium Iodide Injection	Sodium Phenylbutyrate Oral Powder
Sodium Phenylbutyrate Tablets	Sodium Phosphates for Oral Suspension	Sodium Phosphates Tablets
Sodium Salicylate and Sulfur Shampoo	Sterile Talc Aerosol	Streptozocin for Injection
Sucralfate Oral Suspension	Sulconazole Nitrate Cream	Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension
Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sulfacytine Tablets	Sulfanilamide Vaginal Cream
Sulfasalazine Oral Suspension	Sulisobenzone Lotion	Sumatriptan Injection
Sumatriptan Tablets	Tacrolimus Capsules	Tacrolimus Injection
Tacrolimus Ointment	Tamsulosin Hydrochloride Capsules	Technetium Tc 99m Teboroxime Injection
Tenofovir Disoproxil Fumarate Tablets	Terbinafine Hydrochloride Cream	Terbinafine Tablets
Terbinafine Topical Solution	Terconazole Vaginal Cream	Terconazole Vaginal Suppositories
Testosterone Transdermal System	Tetracycline Hydrochloride Periodontal Fiber	Theophylline Extended-Release Tablets
Tioconazole Vaginal Ointment	Tiopronin Tablets	Tolnaftate Topical Aerosol Solution
Topiramate Capsules	Topiramate Tablets	Torsemide Injection
Torsemide Tablets ***(Received)***	Trandolapril and Verapamil Hydrochloride Extended-Release Tablets	Trandolapril Tablets
Tranexamic Acid Injection	Tranylcypromine Sulfate	Tranylcypromine Sulfate Tablets
Tretinoin Capsules	Tretinoin Microsphere Gel	Triamcinolone Acetonide Nasal Suspension
Trifluridine Ophthalmic Solution	Trimetrexate for Injection	Trimipramine Maleate Capsules
Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup	Trolamine Salicylate Cream	Trolamine Salicylate Gel
Trolamine Salicylate Topical Emulsion	Trovafloxacin Injection	Trovafloxacin Mesylate for Injection
Undecylenic Acid Topical Foam Aerosol	Unoprostone Isopropyl Ophthalmic Solution	Urea Cream

Noncomplex Actives (Drug Products) *(Continued)*

Vecuronium Bromide for Injection	Venlafaxine Extended-Release Capsules ***(Received)***	Venlafaxine Tablets
Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules	Voriconazole Injection
Voriconazole Oral Suspension	Voriconazole Tablets	Yttrium Y-90 Chloride Solution
Yttrium Y-90 Glass Microspheres	Yttrium Y-90 Microspheres Injection	Zidovudine and Lamivudine Tablets ***(Received)***
Zinc Acetate Capsules	Zinc Tridosium Pentetate Injection	Ziprasidone Hydrochloride Capsules
Zoledronic Acid for Injection		

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	Aconitic Acid (Achilleic Acid)
Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal	Aliphatic Polyesters
Allantoin-Sodium Pyrrolidone Carboxylate	Aluminum Ammonium Sulfate	Aluminum Lactate
Aluminum Oxide	Aluminum Potassium Sulfate	Aluminum Silicate
Aluminum Sodium Sulfate	Aluminum Stearate	Ammonium Bicarbonate
Ammonium Calcium Alginate	Ammonium Phosphate	Batylalcohol Monostearate
Beeswax, Synthetic	Benzododecinium Bromide	Benzyl Chloride
Benzyl Nicotinate	Beta Naphthol	Brominated Vegetable Oil
Butadiene-Styrene Rubber	Butylated Hydromethylphenol	Butylene Glycol
Butylphthalyl Butylglycolate	Calcium Acid Pyrophosphate	Calcium Alginate
Calcium Alginate and Ammonium Alginate	Calcium Bromide	Calcium Chloride Solution
Calcium Glycerophosphate ***(Received)***	Calcium Phosphate Monobasic	Calcium Propionate
Calcium Pyrophosphate	Calcium Sorbate	Calcium Stearoyl Lactylate
Caldiamide Sodium	Calteridol Calcium	Canola Oil
Capric Acid	Caprylic/Capric Diglyceryl Succinate	Carbon
Carboxymethyl Starch	Carboxymethylamylopectin Sodium	Carboxymethylcellulose Potassium
Cetostearyl Isononanoate	Chlorodifluoroethane	Cholic Acid
Cinnamaldehyde	Cocamide Diethanolamine	Cocamide Oxide
Cocoyl Caprylocaprate	Crystal Gum	Cutina
Cystine	Dammar Gum	Decanoic Acid
Decyl Oleate	Dehydroacetic Acid	Desoxycholic Acid
Dextrin Palmitate	Dextrins Modified	Diacetyl Tartaric Acid Esters of Mono- and Diglycerides
Dicetyl Phosphate	Dichlorofluoromethane	Diethyl Sebacate
Difluoroethane	Diglycol Stearate	Diisobutyl Adipate
Diisopropyl Adipate	Diisopropylbenzothiazyl-2-Sulfenamide	Dilauryl Thiodipropionate
Dimethyl Dicarbonate	Dimyristoyl Lecithin	Dimyristoyl Phosphatidylglycerol
Dipropylene Glycol	Disodium Edisylate	Disodium Guanylate
Disodium Inosinate	Disodium Monooleamide Sulfasuccinate	D-Mannose
Docusate Sodium/Sodium Benzoate	Erythorbic Acid	Erythrosine
Ethoxylated Mono- and Diglycerides	Ethoxyquin	Ethyl Hexanediol
Ethyl Linoleate	Ethyl Maltol	Ethylene Dichloride
Ethylurea	Ferric Ammonium Citrate	Ferric Citrate
Ferric Oxide, Brown	Ferric Phosphate	Ferric Pyrophosphate
Ferrous Citrate	Ferrous Glycinate	Ferrous Lactate
Fluorochlorohydrocarbons	Formic Acid	Furcelleran
Gamma-Cyclodextrin	Gentistic Acid	Geraniol
Glutamic Acid Hydrochloride	Gluten	Glycerol Ester Of Gum Rosin (Ester Gum)
Glyceryl Laurate	Glyceryl Palmitate	Glyceryl Ricinoleate
Glyceryl Tristearate	Glycine Hydrochloride	Glycofurol
Glycol Stearate	Heptafluoropropane	Heptylparaben
Hexadecyl Isostearate	Hexane	Hexanetriol(-1,2,6-)
Hydrocarbon Gel	Hydroxyethylmethylcellulose	Hydroxypropyl Beta Cyclodextrin
Hydrogenated Starch Hydrolysate	Hydroxylated Lecithin	
Indigotine	Inositol	Iron Carbonyl

Excipients *(Continued)*		
Iron Subcarbonate	Isobutylated-Isoprene Copolymer	Isooctylacrylate
Isopropyl Isostearate	Isopropyl Stearate	Isostearic Acid
Isostearyl Alcohol	Lactobionic Acid	Lactose Ferrin, Bovine
Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol	Lactylic Esters of Fatty Acids	Lanolin (Wool Fat), Hydrogenated
Lanolin Alcohols, Acetylated	Lanolin Hydrous	L-Ascorbyl Stearate
Lauramine Oxide	Lauric Myristic Diethanolamide	Lauric Acid
Lauric Diethanolamide	Lavender Oil	L-Cysteine Monohydrochloride
Lecithin, Hydroxylated	L-Glutamic Acid	L-Leucine
	Linoleic Acid	
Macrogol Sorbitan Tristearate	Macrogolglycerol Cocoates	Macrogolglycerol Triisostearate
Magnesium Aluminum Silicate Hydrate	Magnesium Aspartame Dihydrate	Magnesium Aspartate
Magnesium Phosphate Tribasic	Magnesium Phosphate, Dibasic, Trihydrate	Magnesium Tartrate
Malt Syrup	Maltitol Syrup	Maltol Isobutyrate
Manganese Chloride	Manganese Citrate	Manganese Glycerophosphate
Manganese Hypophosphite	Medical Antifoam Emulsion C	Medronate Disodium
Medronic Acid	Methyl Chloride	Methylchloroisothiazolinone
Methylisothiazolinone	Microcrystalline Cellulose, Silicified ***(Received)***	Mineral Spirits
Monoisostearyl Glyceryl Ester	Monopotassium Glutamate Monohydrate	Monosodium Citrate
Mullein Leaf	Myristyl Gamma-Picolinium Chloride	Myristyl Lactate
N,N-Bis(2-Hydroxyethyl)Stearamide	*N*-Acetyl-L-Methionine	*N*-Methylpyrrolidone ***(Received)***
	Naphtha	
Non-Pareil Seeds	Nutmeg Oil	Octanoic Acid
Oxystearin	Palm Kernel Oil ***(Received)***	Palm Oil
Pentasodium Triphosphate	Pentetate Calcium Trisodium	Pentetate Pentasodium
Phenprobamate	Phenylmercuric Acetate	Phenylmercuric Nitrate
Pine Oil	Polacrilin	Polydextrose ***(Received)***
Polydextrose Solution	Polyglycerol Esters Of Fatty Acids	Polyglycerol Polyricinoleic Acid
Polyoxyethylene Castor Oil (USP has 35)	Polyoxyl Stearate (USP has 40)	Polypropylene Oleate
Polypropylene Stearyl Ether	Polysorbate 65	Polyvinyl Acetal
		Polyvinylacetal Diethylanoacetate
Polyvinylpolypyrrolidone	Polyvinylpyrrolidone Ethylcellulose	Potassium Acid Tartrate
Potassium Bromate	Potassium Carbonate Solution	Potassium Dichloroisocyanurate
Potassium Gibberellate	Potassium Glycerophospate	Potassium Iodate
Potassium Nitrite	Potassium Phosphate	Potassium Phosphate Tribasic
Potassium Polymetaphosphate	Potassium Pyrophosphate	Potassium Stearate
Potassium Sulfate	Potassium Sulfite	Potassium Tripolyphosphate
Propyl Propionate	Propylene Glycol Diacetate	Propylene Glycol Mono- and Diesters
Purified Polyoxyl 35 Castor Oil ***(Received)***	Rapeseed Oil, Hydrogenated ***(Received)***	Rapeseed Oil, Superglycerinated ***(Received)***
Rice Bran Wax	Rosin	Silicone
Sodium Acid Pyrophosphate	Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic
Sodium Aluminum Phosphate Basic	Sodium Aspartate	Sodium Bisulfate
Sodium Bisulfite	Sodium Carbonate Hydrate	Sodium Carboxymethyl Betaglucan
Sodium Caseinate	Sodium Chlorate	Sodium Citrate, Dibasic
Sodium Citrate, Monobasic	Sodium Dehydroacetate	Sodium Diacetate
Sodium Erythorbate	Sodium Ferric Pyrophosphate	Sodium Ferrocyanide
Sodium Hypophosphite	Sodium Laureth Sulfate	Sodium Lauroyl Sarcosinate
Sodium Lauryl Sulfoacetate	Sodium Magnesium Aluminosilicate	Sodium Magnesium Silicate
Sodium Malate	Sodium Metaphosphate, Insoluble	Sodium Metasilicate
Sodium Methylate	Sodium Polyphosphates Glassy	Sodium Potassium Tripolyphosphate
Sodium Pyrophosphate	Sodium Pyrrolidone Carboxylate	Sodium Sesquicarbonate
Sodium Sesquinoleate	Sodium Stearoyl Lactylate	Sodium Thiomalate
Sodium Trimetaphosphate	Sodium Trioleate	Sodium Tripolyphosphate
Soy Polysaccharides	Stannous Chloride	Stannous Tartrate

Excipients *(Continued)*

Starch, Pregelatinized Corn	Starch, Pregelatinized Tapioca	Stearalkonium Chloride
Stearyl Citrate	Stearyl Monoglyceridyl Citrate	Succinylated Monoglycerides
Sucrose Acetate Isobutyrate	Sucrose Fatty Acid Esters	Sucrose Stearate
Sugar Fruit Fine	Sulfobutyl Ether Beta Cyclodextran	Tallow
		Tallow Glycerides
Tallow Oil	Tetrafluoroethane	Thioglycerol
Thyme Oil	Tribehenin	Triceteareth-4 Phosphate
Trichloroethylene	Trimyristin	Trisodium Citrate
Trolamine Lauryl Sulfate	Vegetable Oil	Wheat Flour
Wheat Germ Oil	Wheat Gluten ***(Received)***	Whey

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the *USP–NF* that become effective before the effective date of the next *Supplement* or that were not ready for adoption by the closing date for the upcoming *Supplement*. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ▪new text▪, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ▪▪, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement,* and ▪2S (*USP29*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 29*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in future *Supplements,* and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

FIFTH INTERIM REVISION ANNOUNCEMENT to *USP 29* and to *NF 24*

By authority of the United States Pharmacopeial Convention, Inc.
Prepared by the Council of Experts and published by the Board of Trustees

John W. Mauger, *Chair*
USP Board of Trustees

Roger L. Williams, *Executive Vice President*
and *Chairman, USP Council of Experts*

Roger L. Williams, M.D., *Chief Standards Officer, Acting*

Official October 1, 2006 **Released September 1, 2006**

All inquiries and comments regarding *USP 29* text and *NF 24* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were not available when the associated monograph was made official, have since become available. The respective official date of each *USP 29* or *NF 24* standard, test, or assay requiring the use of the following USP Reference Standards is indicated in parentheses after the name of the Reference Standard.

USP Budesonide RS (September 1, 2006)
USP Escin RS (January 1, 2007)
USP Fluticasone Propionate RS (November 1, 2006)
USP Fluticasone Propionate Resolution Mixture RS (September 1, 2006)
USP Fluticasone Propionate System Suitability Mixture RS (September 1, 2006)
USP Fluvastatin Related Compound B RS (November 1, 2006)
USP Fluvastatin Sodium RS (March 1, 2007)
USP Hexacosanol RS (March 1, 2007)
USP Mecamylamine Related Compound A RS (March 1, 2007)
USP Polyisobutylene RS (November 1, 2006)
USP Ropivocaine Hydrochloride RS (November 1, 2006)
USP Ropivacaine Related Compound A RS (September 1, 2006)
USP Ropivacaine Related Compound B RS (September 1, 2006)
USP Saccharin Sodium RS (March 1, 2007)
USP Sulisobenzone RS (January 1, 2007)
USP Tinidazole Related Compound B RS (September 1, 2006)

Unavailable First-Time Official USP Reference Standards

The official dates of any *USP 29* or *NF 24* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards. This listing was updated as of July 5, 2006.

USP Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Aprotinin RS
USP Aprotinin System Suitability RS
USP Cetrimonium Bromide RS
USP Citalopram Hydrobromide RS
USP Cladribine RS
USP Cladribine Related Compound A RS
USP Copolymer Polypropylene RS
USP Decoquinate RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Eucatropine Hydrochloride RS
USP Fluvastatin Related Compound A RS
USP Gabapentin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Alpha Lipoic Acid RS
USP Maritime Pine Extract RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Naratriptan Resolution Mixture RS
USP Near Infrared Calibrator RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS
USP Polyoxyl 10 Oleyl Ether RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Ramipril Related Compound B RS
USP Powdered St. John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tizanidine Hydrochloride RS
USP Tizanidine Related Compound A RS
USP Tizanidine Related Compound B RS
USP Tizanidine Related Compound C RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS

NOTICE OF POSTPONEMENT

Alendronic Acid Tablets

In accordance with Section 9.06(c) of the Rules and Procedures of the Council of Experts, the USP Nomenclature Expert Committee has postponed the official date of the title for this new monograph, which was published on page 72 of *USP 29–NF 24,* from July 1, 2006, until May 1, 2008. The postponement is intended to provide additional time for product label changes to be completed and for healthcare practitioners and consumers to become familiar with the terminology. Use of this title has been permitted since January 1, 2005, when the monograph first became official, but will not become mandatory until May 1, 2008, the official date of *USP 31–NF 26.* The Salt Nomenclature Policy, on which this monograph title is based, was published for public review and comment on page 1228 of *PF* 32(4) [July–Aug. 2006] as part of the revised general information chapter *Nomenclature* ⟨1121⟩. Should you have any questions, please contact Dr. W. Larry Paul, Scientific Fellow and Scientific Liaison to the Nomenclature Expert Committee at 301-816-8331 or wlp@usp.org.

Alendronic Acid Tablets

•(Title for this new monograph—to become official May 1, 2008)•S

Amifostine

Change to read:

Related compounds—

Mobile phase—Dissolve 1.0 mL of nonafluorobutane sulfonic acid in 1200 mL of HPLC grade water, add 400 µL of trifluoroacetic acid, and adjust with triethylamine to a pH of 2.5. Prepare a degassed mixture of this solution and acetonitrile (68 : 32).

Blank solution—Use water.

Standard thiol solution—Transfer about 12.4 mg of USP Amifostine Thiol RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

System suitability solution—Dissolve about 5.0 mg of USP Amifostine RS, accurately weighed, in 1 mL of *Standard thiol solution,* and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 12 hours if maintained at about 5°.]

Test solution—Transfer about 50 mg of Amifostine, accurately weighed, to a 1-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°, and the temperature of the solutions to be injected is maintained at 2° to 8°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution* and the *Standard thiol solution,* and record the peak responses as directed for *Procedure:* the resolution between the amifostine and amifostine thiol peaks is not less than 2.0; the column efficiency calculated for the amifostine thiol peak is not less than 2300 theoretical plates; the tailing factor is not more than 4.0; the capacity factor, k', is more than 0.5; and the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard thiol solution,* the *Test solution,* and the *Blank solution* into the chromatograph, record the chromatograms, and measure the responses of all the peaks, excluding the peaks corresponding to those obtained from the *Blank solution*. Calculate the percentage of amifostine thiol in the portion of Amifostine taken by the formula:

$$\bullet(134.24/207.17)100(C/W)(r_U/r_S)_{\bullet 5}$$

in which 134.24 and 207.17 are the molecular weights of amifostine thiol and amifostine thiol dihydrochloride, respectively; C is the concentration, in mg per mL, of amifostine thiol dihydrochloride in the *Standard thiol solution; W* is the weight, in mg, of Amifostine taken to prepare the *Test solution;* and r_U and r_S are the amifostine thiol peak responses obtained from the *Test solution* and the *Standard thiol solution,* respectively. Calculate the percentage of each of the other impurities in the portion of Amifostine taken by the formula:

$$100(r_i/r_A)$$

in which r_i and r_A are the peak responses for each impurity and amifostine, respectively, obtained from the *Test solution:* not more than 0.1% of any individual impurity, excluding amifostine thiol, is found; and not more than 0.3% of total impurities, including amifostine thiol, is found.

Amifostine for Injection

Change to read:

» Amifostine for Injection is a sterile, •$_{\bullet 5}$ crystalline substance suitable for parenteral use. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of amifostine ($C_5H_{15}N_2O_3PS$).

Change to read:

Related compounds—

Mobile phase, Blank solution, and *System suitability solution* •$_{\bullet 5}$—Prepare as directed in the test for *Related compounds* under *Amifostine.*

Standard thiol solution—Transfer about 40.1 mg of USP Amifostine Thiol RS, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

Standard disulfide solution—Transfer about 18.6 mg of USP Amifostine Disulfide RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]

•*Test solution*—Transfer about 50 mg of Amifostine for Injection, accurately weighed, to a 1-mL volumetric flask, dissolve in and dilute with water to volume, and mix. [NOTE—Inject immediately after preparation, or refrigerate until use. The solution is stable for 48 hours if maintained at about 5°.]•$_{\bullet 5}$

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a detector capable of recording at both 220 nm and 247 nm, and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°, and the temperature of solutions to be injected is maintained at between 2° and 8°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* the *Standard disulfide solution,* and the *Standard thiol solution,* and record the peak responses as directed for *Procedure:* the column efficiency calculated for the amifostine thiol peak is not less than 2300 theoretical plates; the tailing factor is not more than 4.0; the capacity factor, k', is more than 0.5; and the relative standard deviation for replicate injections is not more than 4.0%. The column efficiency calculated for the amifostine disulfide peak is not less than 2000 theoretical plates; the tailing factor is not more than 4.5; the capacity factor, k', is more than 2.2; and the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard thiol solution,* the *Standard disulfide solution,* the *Test solution,* and the *Blank solution* into the chromatograph, record the chromatograms, and measure the responses of all the peaks except the peaks corresponding to those obtained from the *Blank solution.* Calculate the percentage of amifostine thiol in the portion of Amifostine for Injection taken by the formula:

$$\bullet(134.24/207.17)100(C/W)(r_U/r_S)_{\bullet 5}$$

in which 134.24 and 207.17 are the molecular weights of amifostine thiol and amifostine thiol dihydrochloride, respectively; C is the concentration, in mg per mL, of amifostine thiol dihydrochloride in the *Standard thiol solution; W* is the weight, in mg, of amifostine taken to prepare the *Test solution;* and r_U and r_S are the amifostine thiol peak responses recorded at 220 nm, obtained from the *Test solution* and the *Standard thiol solution,* respectively. Calculate the percentage of amifostine disulfide in the portion of Amifostine for Injection taken by the formula:

$$\bullet(266.47/412.31)(100C/W)(r_U/r_S)_{\bullet 5}$$

in which 266.47 and 412.31 are the molecular weights of amifostine disulfide and amifostine disulfide tetrahydrochloride, respectively; C

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is the concentration, in mg per mL, of USP Amifostine Disulfide RS in the *Standard disulfide solution;* and r_U and r_S are the peak responses recorded at 247 nm, obtained from the *Test solution* and the *Standard disulfide solution,* respectively: not more than 2.0% of total impurities, including amifostine thiol and amifostine disulfide, is found. Calculate the percentage of each of the other impurities in the portion of Amifostine for Injection taken by the formula:

$$100(r_i / r_A)$$

in which r_i and r_A are the peak responses for each impurity and amifostine, respectively, obtained from the *Test solution:* not more than 0.1% of any individual impurity except amifostine thiol is found.

Cladribine

Change to read:

Water, *Method I* ⟨921⟩**:** not more than •4.0%.•5

Clarithromycin Extended-Release Tablets

Change to read:

▲**Dissolution** ⟨711⟩—

TEST 1—▲*USP29*

Medium: 0.3 M phosphate buffer, pH 6.0 (prepared by dissolving 816.5 g of monobasic potassium phosphate and 48 g of sodium hydroxide in about 4 L of water, mixing, and diluting with water to 20 L. Adjust with either concentrated phosphoric acid or 1 N sodium hydroxide to a pH of 6.0 ± 0.05); 900 mL.

Apparatus 2: 75 rpm.

Times: 30, 45, 60, and 120 minutes.

Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved using the following method.

Standard solutions—Prepare five solutions of USP Clarithromycin RS dissolved in acetonitrile and diluted in *Medium,* with known concentrations over the range of about 60 to 600 µg per mL.

Test solution—Use portions of the solution under test passed through a 35-µm polyethylene filter.

Chromatographic system—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 50 µL) of the five *Standard solutions* and the *Test solution* into the chromatograph, and measure the responses for the major peaks. Perform a linear regression analysis to generate a standard curve using the peak area of each *Standard solution* versus its concentration. Determine the amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at each specified time interval, using the peak area of each *Test solution* and the linear regression statistics for the *Standard solutions.*

Tolerances—The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to the following *Acceptance Table.*

▲TEST 2—•If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.•5

Medium: 0.05 M phosphate buffer, pH 6.8 containing 0.5% of sodium lauryl sulfate; 900 mL, degassed by sonication and vacuum.

Apparatus 1: 100 rpm.

Times: 2, 12, and 24 hours.

Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved using the following method.

0.067 M Phosphate buffer, pH 2.5—Dissolve 9.2 g of monobasic sodium phosphate monohydrate in about 800 mL of water. Adjust with phosphoric acid to a pH of 2.5. Dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *0.067 M Phosphate buffer, pH 2.5* (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 56 mg of USP Clarithromycin RS, accurately weighed, to a 100-mL volumetric flask. Add 10 mL of methanol, and sonicate to dissolve. Dilute with *Medium* to volume.

Test solution—Centrifuge the solution under test at 2500 rpm for 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. •The column temperature is maintained at 50°.•5 Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the column efficiency is not less than 2000; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of clarithromycin dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

in which C_U is the concentration, in mg per mL, of clarithromycin in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; and C_S is the concentration, in mg per mL, of clarithromycin in the *Standard solution.*

Calculate the amount, in percentage, of clarithromycin dissolved with volume correction:

$$\bullet \frac{[\{C_n \times [900 - V_U(n-1)]\} + [\sum_{i=1}^{n-1} C_i \times V_U]] \times 100}{LC} \bullet 5$$

in which C_n is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; 900 is the volume, in mL, of *Medium;* V_U is the volume, in mL, of sample withdrawn at each time point; *n* is the number of time points [NOTE—The summation of the amount of clarithromycin removed at previous sampling time points is applicable only where n > 1.]; 100 is the conversion factor to percentage; and *LC* is the Tablet label claim.

Tolerances—The percentages of the labeled amounts of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	not more than 20%
12	between 45% and 70%
24	not less than 80%

▲*USP29*

•TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: Acetate buffer, pH 4.75 (prepared by dissolving 3.59 g of sodium acetate trihydrate and 11.0 mL of 2 N acetic acid in 1000 mL of water, and adjusting with 2 N acetic acid to a pH of 4.75); 1000 mL.

Apparatus 1: 10 mesh; 50 rpm.

Times: 1, 2, 4, 8, and 12 hours.

Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved by employing the following method.

0.067 M Phosphate buffer—Dissolve 9.12 g of monobasic potassium phosphate in 1000 mL of water, and mix.

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Acceptance Table

Level	Time (minutes)	Amount dissolved (individual limits)	Amount dissolved (average limits)
L_1	30	not more than 65%	—
	45	between 55% and 85%	—
	60	not less than 75%	—
	120	not less than 85%	—
L_2	30	not more than 75%	not more than 65%
	45	between 45% and 95%	between 55% and 85%
	60	not less than 65%	not less than 75%
	120	not less than 75%	not less than 85%
L_3	30	not more than 2 tablets release more than 75%, and no individual tablet releases more than 85%	not more than 65%
	45	not more than 2 tablets are outside the range of 45% to 95%, and no individual tablet is outside the range of 35% to 105%	between 55% and 85%
	60	not more than 2 tablets release less than 65%, and no individual tablet releases less than 55%	not less than 75%
	120	not more than 2 tablets release less than 75%, and no individual tablet releases less than 65%	not less than 85%

Mobile phase—Prepare a filtered and degassed mixture of methanol and *0.067 M Phosphate buffer* (65 : 35), mix, and adjust with phosphoric acid to a pH of 4.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve quantitatively an accurately weighed quantity of USP Clarithromycin RS in methanol, shaking and sonicating if necessary to ensure dissolution, to obtain a stock solution having a known concentration of about 625 µg of clarithromycin per mL, taking into account the stated potency, in µg per mg, of USP Clarithromycin RS.

Standard solution—Transfer 10.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. This solution contains about 125 µg of clarithromycin per mL.

System suitability solution—Dissolve quantitatively an accurately weighed quantity of USP Clarithromycin Related Compound A RS in methanol to obtain a solution containing about 625 µg of clarithromycin related compound A per mL. Transfer 10 mL of this solution and 10 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Withdraw 10-mL of the solution under test. Transfer 3 mL to a 25-mL volumetric flask, and dilute with *Mobile phase* to volume. Pass portions of this dilution through a 0.45-µm filter. Replace 10 mL of *Medium* in each vessel.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.75 for clarithromycin and 1.0 for clarithromycin related compound A; and the resolution, *R,* between clarithromycin and clarithromycin related compound A is not less than 2.0. Chromatograph the *Standard solution,* and record the responses as directed for *Procedure:* the column efficiency, determined from the clarithromycin peak, is not less than 750 theoretical plates; the tailing factor is not less than 0.9 and not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved by the formula:

$$C_U = \frac{r_U \times C_S \times 100}{r_S \times LC}$$

in which C_U is the concentration, in mg per mL, of clarithromycin in the sample at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; and C_S is the concentration, in mg per mL, of clarithromycin in the *Standard solution;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Calculate the amount, in percentage, of clarithromycin dissolved with volume correction at time points $n \geq 2$:

$$\frac{[\{C_n \times [1000]\} + [\sum_{i=1}^{n-1} C_i \times V_u]] \times 100}{LC}$$

$$C_n = \frac{r_U \times C_S}{r_S}$$

in which C_n is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; 900 is the volume, in mL, of *Medium;* V_U is the volume, in mL, of sample withdrawn at each time point; n is the time point (at 2 hours, n = 2), summation of the concentration of the *Test solution* from the first to the (n –1)th time point (only applicable for $n \geq 2$); 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Tolerances—The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	not more than 15%
2	between 10% and 30%
4	between 35% and 55%
8	not less than 80%
12	not less than 90%

TEST 4 —If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: phosphate buffer, pH 6.0 (prepared by dissolving 68.0 g of potassium dihydrogen phosphate and 1.8 g of sodium hydroxide in 10 L of water, and adjusting with dilute sodium hydroxide or phosphoric acid to a pH of 6.0 ± 0.1); 900 mL.

Apparatus 2: 50 rpm.

Times: 2, 4, 8, and 12 hours.

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Determine the percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved by employing the following method.

Buffer solution—Dissolve 6.8 g of potassium dihydrogen phosphate in 1 L of water. Adjust with dilute sodium hydroxide or phosphoric acid to a pH of 4.5 ± 0.1.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (64 : 36). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 20 mg of USP Clarithromycin RS, accurately weighed, to a 50-mL volumetric flask. Add about 30 mL of *Medium,* and sonicate until dissolved, about 10 minutes. Add 2 mL of methanol, and dilute with *Medium* to volume.

Test solution—Use the solution under test passed through a 0.45-µm suitable filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 203-nm detector and a 4.0-mm × 12.5-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. The column is maintained at 30°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount, in percentage, of clarithromycin dissolved by the formula:

$$C_U = \frac{r_U \times C_S}{r_S}$$

in which C_U is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; and C_S is the concentration, in mg per mL, of clarithromycin in the *Standard solution*.

Calculate the amount, in percentage, of clarithromycin dissolved at each time point by the formula:

$$\frac{C_n \times [900 - (n-1) \times V_S] + (C_1 + C_2 + ... + C_{n-1}) \times V_S \times 100}{LC}$$

in which C_n is the concentration, in mg per mL, of clarithromycin in the *Test solution* at each time point; 900 is the volume, in mL, of *Medium;* V_S is the volume, in mL, of the sample taken at each time point; and *LC* is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$) dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
2	not more than 25%
4	between 20% and 40%
8	between 45% and 75%
12	not less than 80%

•5

Indocyanine Green

Change to read:

» Indocyanine Green contains not less than •89.0•5 percent and not more than •100.0•5 percent of $C_{43}H_{47}N_2NaO_6S_2$, calculated on the dried basis. It contains not more than 5.0 percent of sodium iodide, calculated on the dried basis.

Nefazodone Hydrochloride

Add the following:

•Related compounds—

Diluent—Prepare a solution of water and acetonitrile (50 : 50).

Solution A—Dissolve 0.77 g of ammonium acetate in about 950 mL of water. Adjust with triethylamine to a pH of 7.10 ± 0.05. Dilute with water to 1 L. Filter and degas.

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed amount of USP Nefazodone Hydrochloride RS in *Diluent* to obtain a solution containing 0.1 mg per mL of nefazodone hydrochloride.

Nefazodone related compound A stock solution and *Nefazodone related compound B stock solution*—Transfer about 20 mg each of USP Nefazodone Related Compound A RS and USP Nefazodone Related Compound B RS, accurately weighed, into separate 200-mL volumetric flasks. Dissolve in and dilute with *Diluent* to volume.

Resolution solution—Pipet 5.0 mL of *Nefazodone related compound A stock solution* and 5.0 mL of *Nefazodone related compound B stock solution* into a 100-mL volumetric flask. Dilute with *Standard stock solution* to volume, and mix. This solution contains about 90 µg per mL of nefazodone hydrochloride, and about 5 µg per mL each of nefazodone related compounds A and B.

Standard solution—Pipet 2.0 mL each of the *Standard stock solution, Nefazodone related compound A stock solution,* and *Nefazodone related compound B stock solution* into a 200-mL volumetric flask. Dilute with *Diluent* to volume, and mix well to obtain a final concentration of 1 µg per mL each of nefazodone hydrochloride, nefazodone related compound A, and nefazodone related compound B.

Test solution—Transfer about 100 mg of Nefazodone Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 250-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.7 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	50	50	equilibration
0–10	50→45	50→55	linear gradient
10–16	45→35	55→65	linear gradient
16–25	35	65	isocratic
25–26	35→50	65→50	linear gradient
26–35	50	50	re-equilibration

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Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between nefazodone related compound A and nefazodone hydrochloride is not less than 4.0, and it is not less than 1.5 between nefazodone hydrochloride and nefazodone related compound B. Chromatograph the *Standard solution,* and measure the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0% for nefazodone related compound A and nefazodone related compound B. [NOTE—For identification purposes, the relative retention times are about 1.2 for nefazodone related compound A, 1.0 for nefazodone hydrochloride, and 0.94 for nefazodone related compound B.]

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each nefazodone related compound in the portion of Nefazodone Hydrochloride taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of the relevant USP Reference Standard in the *Standard solution;* C_T is the concentration of Nefazodone Hydrochloride, in mg per mL, in the *Test solution;* and r_U and r_S are the peak areas of the corresponding nefazodone related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.2% of nefazodone related compound A is found; not more than 0.2% of nefazodone related compound B is found; not more than 0.1% of any unknown impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Use the peak area for nefazodone hydrochloride in the *Standard solution* as r_S to calculate any unknown impurity.]•5

Nitrofurantoin Capsules

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Change to read:

Dissolution ⟨711⟩—

TEST 1 (where it is labeled as containing nitrofurantoin macrocrystals)—

Medium: pH 7.2 (±0.05) phosphate buffer; 900 mL.

Apparatus 1: 100 rpm.

Times: 1, 3, and 8 hours.

Procedure—Determine the amount of $C_8H_6N_4O_5$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 375 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Nitrofurantoin RS in the same *Medium.*

Tolerances—The percentage of the labeled amount of $C_8H_6N_4O_5$ dissolved at the 1-hour point conforms to *Acceptance Table 2,* and the percentages dissolved at the 3- and 8-hour points conform to the criteria for the final test time in *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 60%
3	not less than 45%
8	not less than 60%

TEST 2 (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Acid medium: 0.01 N hydrochloric acid for 1 hour; 900 mL.

pH 7.5 Buffer medium—Prepare a pH 7.5 buffer concentrate by dissolving 62.2 g of potassium hydroxide and 129.3 g of monobasic potassium phosphate in water, dilute with water to 1 L, and mix. After 1 hour change the *Acid medium* to *pH 7.5 Buffer medium* by adding 50 mL of pH 7.5 buffer concentrate, for an additional 6 hours.

Apparatus 2: 100 rpm, with sinkers made of teflon-coated steel wire prepared by forming a coil approximately 22 mm long from a 13-cm length of 20-gauge wire (see *Figure 1*).

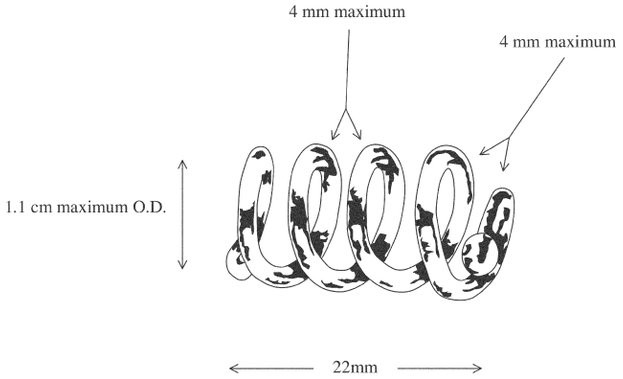

Figure 1. Sinker.

Times: 1, 3, and 7 hours.

Acid-stage standard solution—Prepare a solution of USP Nitrofurantoin RS in *Acid medium* to obtain a solution having a known concentration of about 0.025 mg per mL.

Buffer-stage standard solution—Prepare a solution of USP Nitrofurantoin RS in *pH 7.5 Buffer medium* to obtain a solution having a known concentration of about 0.075 mg per mL.

Procedure—Determine the amount of $C_8H_6N_4O_5$ dissolved from UV absorbances at the isosbestic wavelength at about 375 nm on filtered portions of each solution under test, suitably diluted, if necessary, with *Acid medium* or *pH 7.5 Buffer medium* when appropriate in comparison with the appropriate *Standard solution.*

Tolerances—The percentages of the labeled amount of $C_8H_6N_4O_5$ dissolved at the specified times conform to the accompanying *Acceptance Table.*

Time (hours)	Amount dissolved (individual)	Amount dissolved (mean)
1	between 2% and 16%	between 5% and 13%
3	between 27% and 69%	between 39% and 56%
7	not less than 68%	not less than 81%

Acceptance Table

Level	Number Tested	Criteria
L_1	12	The mean percentage of dissolved label claim lies within the range for the means at each interval and is not less than the stated amount at the final test time. All individual values lie within the ranges for the individuals at each interval and are not less than the stated amount at the final test time.
L_2	12	The mean percentage of dissolved label claim lies within the range for the means at each interval and is not less than the stated amount at the final test time. Not more than 2 of the 24 individual values lie outside the stated range for individuals at each interval, and not more than 2 of 24 are less than the stated amount at the final test time.

(Official April 1, 2006)

•TEST 3 (where it is labeled as containing both nitrofurantoin macrocrystalline and monohydrate forms)—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3.*

Acid medium, pH 7.5 Buffer medium, Apparatus 2, Times, Acid-stage standard solution, Buffer stage standard solution, and *Procedure*—Proceed as directed for *Test 2*.

Tolerances—The percentages of the labeled amount of $C_8H_6N_4O_5$ dissolved at the specified times conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved (individual)	Amount dissolved (mean)
1	between 2% and 16%	between 5% and 13%
3	between 50% and 80%	between 55% and 75%
7	not less than 85%	not less than 90%

•5

Vinorelbine Injection

Change to read:

» Vinorelbine Injection is a sterile solution of Vinorelbine Tartrate in Water for Injection. It contains not less than •90.0•5 percent and not more than •110.0•5 percent of the labeled amount of vinorelbine ($C_{45}H_{54}N_4O_8$).

Caution—Handle Vinorelbine Injection with great care because it is a potent cytotoxic agent.

Change to read:

■**Assay—**

Phosphate buffer, Mobile phase, and *System suitability solution*—Proceed as directed in the test for *Related compounds* under *Vinorelbine Tartrate*.

Standard preparation—Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in water to obtain a solution having a known concentration of about •0.14 mg•5 per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 10 mg of vinorelbine, to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a diode-array detector and a 3.9-mm × 15-cm column that contains packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for the photodegradation product, 1.0 for vinorelbine, and about 1.2 for vinorelbine related compound A; and the relative retention, α, between vinorelbine tartrate and vinorelbine related compound A is not less than 1.1.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the vinorelbine peaks, using a diode-array detector. Calculate the quantity, in mg, of vinorelbine ($C_{45}H_{54}N_4O_8$) in each mL of the Injection taken by the formula:

$$•(778.93/1079.11)C(L/D)(r_U/r_S)$$

in which 778.93 and 1079.11 are the molecular weights of vinorelbine and vinorelbine tartrate, respectively;•5 C is the concentration, in mg per mL, of USP Vinorelbine Tartrate RS in the *Standard preparation; L* is the labeled quantity, in mg, of vinorelbine in each mL of Injection taken; D is the concentration, in mg per mL, of vinorelbine in the *Assay preparation;* and r_U and r_S are the peak responses at 267 nm obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

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ERRATA

Following is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP 29–NF 24*. If necessary, this list will be updated with every issue of *PF*. This information will also be available as a cumulative table in future *Supplements* and will appear in its corrected form in a future annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff is available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
769	*Dronabinol Capsules*	*Assay*	Line 1: Change "*Resolution solution,*" to: *System suitability solution,*
1009	*Glutamine*	*Chromatographic purity*	Line 1 under *Procedure:* Change "as directed for *System Suitability*" to: as directed for *Thin-Layer Chromatography*
1365	*Metformin Hydrochloride Tablets*	*Assay*	Lines 10–11 under *Procedure:* Change "the *Standard preparation* and the *Assay preparation,* respectively." to: the *Assay preparation* and the *Standard preparation,* respectively.
1788	*Prednisolone Tablets*	*Assay*	Line 1: Change ", *Internal standard solution,* and" to: , *Internal standard solution, Standard preparation,* and
2230	*Compound Undecylenic Acid Ointment*	*Assay for zinc undecylenate*	Line 13 under *Procedure:* Change $(431.94/65.38)(0.2/W)C_L + \frac{(C_H - C_L)(A_U - A_L)}{(A_H - A_L)}$ to: $(431.94/65.39)(0.2/W)C_L + \frac{(C_H - C_L)(A_U - A_L)}{(A_H - A_L)}$
3142	*Oxygen-Helium Certified Standard*		Restore reagent text as last published in *USP28:* **Oxygen-Helium Certified Standard**—A mixture of 1.0% oxygen in industrial grade helium. It is available from most suppliers of specialty gases.
Supplement 2			
3736	*Ondansetron Orally Disintegrating Tablets*	*Assay*	Line 2 under *System suitability solution:* Change "8.0 mL of the *Concentrated assay preparation*" to: 8.0 mL of the *Standard preparation*

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IN-PROCESS REVISION

This section contains proposals for adoption as official *USP* or *NF* standards (either proposed *new* standards or proposed *revisions* of current *USP* or *NF* standards). These may be any of the following: (1) items that previously appeared under *Pharmacopeial Previews* and are now formally proposed as revisions, (2) proposed revisions placed directly under *In-Process Revision,* or (3) modifications of revisions previously proposed under *In-Process Revision*. Readers should review material in this section and provide comments to the staff liaison (use the *Staff Directory* to find the contact information). Information on how to comment is found in the *Policies and Announcements* section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

BRIEFING

> **Name of Item**, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How to Use PF*), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
>
> (DSN: L. Evans) RTS—C-55678-1

Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type (print edition only), as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 29–NF 24* (*IRA*);

▲new text▲*USP30*

if slated for *USP 30–NF 25*; and

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, ■2S (*USP 29*) indicates that the proposed revision is slated for the *Second Supplement to USP 29*, and ▲*USP30* and ▲*NF25* indicate that the revisions are proposed for *USP 30* and *NF 25*, respectively.

Official Title Changes Where the specification ***"Monograph title change"*** is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.

MONOGRAPHS (USP)

BRIEFING

Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets. There are two *USP* monographs that have similar titles except for the decongestant active ingredient: (1) *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine* and (2) *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine.* If a product does not contain a decongestant there would not be an official *USP* monograph for that product. To correct this, a separate *USP* monograph is being proposed for Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hyhdrobromide Tablets based on the two aforementioned monographs, which will have a change in title to clarify that tablets must contain either pseudoephedrine or phenylpropanolamine to apply. The liquid chromatographic procedure in the *Assay for acetaminophen* is based on analysis performed with the Zorbax SB-C8 brand of L7 column. The typical retention time for acetaminophen is about 4.4 minutes. The liquid chromatographic procedure in the *Assay for chlorpheniramine maleate* is based on analysis performed with the Zorbax SB Phenyl brand of L11 column. The typical retention time for chlorpheniramine maleate is about 5.5 minutes. The liquid chromatographic procedure in the *Assay for dextromethorphan hydrobromide* is based on analysis performed with the Zorbax SB Phenyl brand of L11 column. The typical retention time for dextromethorphan is about 9.3 minutes.

(MD-CCA: C. Anthony) RTS—C46298

Add the following:

■Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets

» Acetaminophen, Chlorpheniramine Maleate, and Detromethorphan Hydrobromide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of acetaminophen ($C_8H_9NO_2$), chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), and dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

Labeling—The label states the name and quantity of each active ingredient and indicates its function (or purpose) in the article. When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

USP Reference standards ⟨11⟩—*USP Acetaminophen RS. USP Chlorpheniramine Maleate RS. USP Dextromethorphan Hydrobromide RS.*

Identification—

A: The chromatogram of the *Assay preparation,* obtained as directed in the *Assay for acetaminophen,* exhibits a major peak for acetaminophen, the retention time of which corresponds to that exhibited by the *Standard preparation.*

B: The chromatogram of the *Assay preparation,* obtained as directed in the *Assay for chlorpheniramine maleate,* exhibits a major peak for chlorpheniramine, the retention time of which corresponds to that exhibited by the *Standard preparation.*

C: The chromatogram of the *Assay preparation,* obtained as directed in the *Assay for dextromethorphan hydrobromide,* exhibits a major peak for dextromethorphan, the retention time of which corresponds to that exhibited by the *Standard preparation.*

Dissolution, *Procedure for a Pooled Sample* ⟨711⟩—

TEST 1—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Test solution—Mix 9.0 mL of a filtered portion of the solution under test with 1.0 mL of 1% phosphoric acid solution.

Procedure—Determine the amounts of acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide dissolved, employing the procedures set forth in the

In-Process Revision

Assay for acetaminophen, Assay for chlorpheniramine maleate, and *Assay for dextromethorphan hydrobromide,* respectively, making any necessary volumetric adjustments.

Tolerances—Not less than 75% *(Q)* of the labeled amounts of acetaminophen ($C_8H_9NO_2$), chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$), and dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$) are dissolved in 45 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 0.1 M hydrochloric acid; 900 mL.

Apparatus, Time, Test solution, Procedure, and *Tolerances*—Proceed as directed for *Test 1.*

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3.*

Medium: pH 5.8 phosphate buffer (see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions*); 900 mL.

Apparatus, Time, Test solution, Procedure, and *Tolerances*—Proceed as directed for *Test 1.*

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Assay for acetaminophen—

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and glacial acetic acid (79 : 20 : 1). Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 50 mg of USP Acetaminophen RS, accurately weighed, to a 100-mL volumetric flask. Add 4 mL of methanol, and mix until solution is complete. Dilute with 0.1% phosphoric acid to volume, and mix.

Assay preparation—Weigh and powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of acetaminophen, to a 50-mL volumetric flask. Add about 7.5 mL of methanol, and sonicate to disperse the powder. Add 0.5 mL of phosphoric acid, dilute with water to volume, mix, and filter. Transfer 25.0 mL of the filtered solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the acetaminophen peak is not greater than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the acetaminophen peaks. Calculate the quantity, in mg, of acetaminophen ($C_8H_9NO_2$) in the portion of Tablets taken by the formula:

$$200C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Acetaminophen RS in the *Standard preparation;* and r_U and r_S are the acetaminophen peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for chlorpheniramine maleate—

Mobile phase, System suitability solutions, and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride* under *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine.*

Standard preparation—Dissolve an accurately weighed quantity of USP Chlorpheniramine Maleate RS in water to obtain a solution having a known concentration of about 0.8 mg per mL. Quantitatively dilute a portion of this solution with 0.1% phosphoric acid to obtain a solution having a known concentration of about 8 µg per mL.

Assay preparation—Weigh and powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 2 mg of chlorpheniramine

maleate, to a 250-mL volumetric flask. Add about 25 mL of methanol, and sonicate to disperse the powder. Add 1 mL of phosphoric acid, dilute with water to volume, mix, and filter.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the chlorpheniramine peaks. Calculate the quantity, in mg, of chlorpheniramine maleate ($C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$) in the portion of Tablets taken by the formula:

$$250C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Chlorpheniramine Maleate RS in the *Standard preparation;* and r_U and r_S are the peak responses for chlorpheniramine obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for dextromethorphan hydrobromide—

Mobile phase, System suitability solutions, and *Chromatographic system*—Proceed as directed in the *Assay for pseudoephedrine hydrochloride* under *Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine.*

Standard preparation—Dissolve an accurately weighed quantity of USP Dextromethorphan Hydrobromide RS in water to obtain a solution having a known concentration of about 0.6 mg per mL. Quantitatively dilute a portion of this solution with 0.1% phosphoric acid to obtain a solution having a known concentration of about 0.06 mg per mL.

Assay preparation—Weigh and powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6 mg of dextromethorphan hydrobromide, to a 100-mL volumetric flask. Add 10 mL of methanol, and sonicate to disperse the powder. Add 0.4 mL of phosphoric acid, dilute with water to volume, mix, and filter.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the dextromethorphan peaks. Calculate the quantity, in mg, of dextromethorphan hydrobromide ($C_{18}H_{25}NO \cdot HBr \cdot H_2O$) in the portion of Tablets taken by the formula:

$$(370.33 / 352.32)(100C)(r_U / r_S)$$

in which 370.33 and 352.32 are the molecular weights of dextromethorphan hydrobromide monohydrate and anhydrous dextromethorphan hydrobromide, respectively; C is the concentration, in mg per mL, of USP Dextromethorphan Hydrobromide RS in the *Standard preparation;* and r_U and r_S are the dextromethorphan peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

BRIEFING

Albuterol Sulfate, *USP 29* page 63. In the *Assay,* it is proposed to delete the current test and substitute a new, stability-indicating HPLC test. The new method also eliminates the need for the indicator oracet blue B, which is no longer commercially available. The new procedure is based on analyses performed with the Spherisorb CN brand of L10 column.

(AER: K. Zaidi) RTS—C44145

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 80 µg per mL.
Medium: 0.1 N hydrochloric acid.
C: Shake a quantity of it, equivalent to 4 mg of albuterol, with 10 mL of water, and filter: the filtrate so obtained meets the requirements of the tests for *Sulfate* ⟨191⟩.

■**D:** The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*■2S (*USP30*)

In-Process Revision

Change to read:

~~**Assay**— Dissolve about 900 mg of Albuterol Sulfate, accurately weighed, in 50 mL of glacial acetic acid, add 2 drops of oracet blue B TS, and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each 1 mL of 0.1 N perchloric acid is equivalent to 57.67 mg of $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$.~~

■*0.05 ± 0.01 M Ammonium acetate solution*—Dissolve 3.85 g of ammonium acetate in 1000 mL of water, and mix.

Mobile phase—Prepare a degassed mixture of water, *0.05 ± 0.01 M Ammonium acetate solution,* and isopropanol [65: 30: (5 ± 1)], and adjust dropwise with acetic acid to a pH of 4.5 ± 0.3.

Standard preparation—Dissolve an accurately weighed quantity of USP Albuterol Sulfate RS in water, and dilute quantitatively with water to obtain a solution having a known concentration of about 0.6 mg per mL.

Assay preparation—Transfer about 60 mg of Albuterol Sulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 276-nm detector and a 5.0-mm × 20-cm column that contains packing L10. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between albuterol and 4-[2-[(1,1-dimethylethyl)amino]-1-hydroxyethyl]-2-methylphenol sulfate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ in the portion of Albuterol Sulfate taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Albuterol Sulfate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

BRIEFING

Aminosalicylate Sodium Tablets, *USP 29* page 144. Because the internal standard used in the test for *Limit of m-aminophenol* is sulfanilamide and not acetaminophen, it is proposed to correct the cross reference to indicate that the *Internal standard solution* is prepared as directed in the test for *Limit of m-aminophenol* under *Aminosalicylic Acid*.

(MD-AA: B. Davani) RTS—C46431

Change to read:

Limit of *m*-aminophenol—

Mobile phase ~~and *Internal standard solution*~~

■■2S (*USP30*)
—Prepare as directed in the *Assay* under *Aminosalicylic Acid*.

Standard solution,

■*Internal standard solution,*■2S (*USP30*) and *Chromatographic system*—Prepare as directed in the test for *Limit of m-aminophenol* under *Aminosalicylic Acid*.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Procedure—Proceed as directed for *Procedure* in the test for *Limit of m-aminophenol* under *Aminosalicylic Acid*. Calculate the percentage of *m*-aminophenol, in relation to the quantity of aminosalicylate sodium, in the portion of Tablets taken by the formula:

$$100(C / W)(R_U / R_S)$$

in which C is the concentration, in µg per mL, of USP *m*-Aminophenol RS in the *Standard solution; W* is the quantity of aminosalicylate sodium, in mg, in the portion of Tablets taken, as determined in the *Assay;* and R_U and R_S are the ratios of the response of the *m*-aminophenol peak to the response of the sulfanilamide peak obtained from the *Test solution* and the *Standard solution*, respectively: not more than 1.0% of *m*-aminophenol is found.

In-Process Revision

BRIEFING

Aminosalicylic Acid, *USP 29* page 145. It is proposed to revise the *Assay* to correct the dilution factor in the formula used in the *Procedure* to correspond to the volume of the *Assay preparation*.

(MD-AA: B. Davani) RTS—C46432

Change to read:

Assay—

Mobile phase—Prepare a mixture of 425 mL of 0.05 M dibasic sodium phosphate, 425 mL of 0.05 M monobasic sodium phosphate, and 150 mL of methanol containing 1.9 g of tetrabutylammonium hydroxide. Filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of acetaminophen in *Mobile phase* having a concentration of about 5 mg per mL.

Standard preparation—Transfer about 12.5 mg of USP Aminosalicylic Acid RS, accurately weighed, to a 25-mL low-actinic volumetric flask, add 15 mL of *Mobile phase,* and swirl to dissolve. Add 2.5 mL of *Internal standard solution,* dilute with *Mobile phase* to volume, and mix.

Assay preparation—Prepare as directed for *Standard preparation,* except to use Aminosalicylic Acid instead of USP Aminosalicylic Acid RS.

Chromatographic system (see *Chromatography* ⟨621⟩)—The chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.83 for acetaminophen and 1.0 for aminosalicylic acid; the resolution, *R,* between aminosalicylic acid and acetaminophen is not less than 1.7; and the relative standard deviation of the ratios of the response of the aminosalicylic acid peak to the response of the acetaminophen peak is not more than 1.0%.

Procedure—[NOTE—After use, wash the column for 30 minutes with a filtered and degassed mixture of methanol, water, and phosphoric acid (77 : 23 : 0.6), and then wash for 30 minutes with a filtered and degassed mixture of methanol and water (50 : 50).] Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_7H_7NO_3$ in the Aminosalicylic Acid taken by the formula:

~~$100C(R_U / R_S)$~~

■$25C(R_U / R_S)$■2S (*USP30*)

in which C is the concentration, in mg per mL, of USP Aminosalicylic Acid RS in the *Standard preparation;* and R_U and R_S are the ratios of the response of the aminosalicylic acid peak to the response of the acetaminophen peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Apomorphine Hydrochloride, *USP 29* page 189. It is proposed to update the *Packaging and storage* section.

(MD-GRE: E. Gonikberg) RTS—C46745

Change to read:

Packaging and storage—Preserve in ~~small,~~

■■2S (*USP30*)
tight, light-resistant containers. ~~Containers from which Apomorphine Hydrochloride is to be taken for immediate use in compounding prescriptions contain not more than 350 mg.~~

■■2S (*USP30*)

BRIEFING

Benazepril Hydrochloride, page 3713 of the *Second Supplement.* On the basis of the comments received, the following revisions are proposed:

1. The current *Test preparation* in the test for *Absorptivity* prescribes to dissolve 25 mg in 1000 mL of methanol. It is proposed to revise the *Test preparation* such that the final sample concentration is 0.025 mg per mL to avoid unnecessary consumption of the solvent.
2. In the *Chromatographic system* in the *Assay,* it is proposed to correct the guard column dimensions specified from 4.6-mm × 0.3-cm to 4.6-mm × 3-cm.
3. It is proposed to utilize the *Test solution* (from the test for *Related compounds*) in the *Assay preparation,* which will minimize the usage of the benazepril hydrochloride sample.
4. In footnote 5 under *Table 1* in the test for *Related compounds,* the nomenclature of related compound D is revised to match the procured Reference Standard bulk material.

(MD-CV: S. Ramakrishna) RTS—C47274

Change to read:

Absorptivity—

Test preparation— ~~25 mg in 1000 mL of methanol.~~

■Dissolve an accurately weighed quantity of Benazepril Hydrochloride in methanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.025 mg per mL.■2S (*USP30*)

Procedure—Proceed as directed under *Spectrophotometry and Light-Scattering* ⟨851⟩, and measure the absorbance at 238 nm: the absorptivity is between 21.0 and 23.2.

In-Process Revision

Change to read:

Related compounds—

TEST 1 (FOR BENAZEPRIL RELATED COMPOUND A)—

pH 6.0 Phosphate buffer—Dissolve 9.66 g of monobasic potassium phosphate and 2.68 g of dibasic sodium phosphate, heptahydrate in about 900 mL of water, and dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of *pH 6.0 Phosphate buffer* and methanol (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve accurately weighed quantities of USP Benazepril Hydrochloride RS and USP Benazepril Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 1.0 mg per mL and 0.005 mg per mL, respectively.

Standard stock solution—Dissolve an accurately weighed quantity of USP Benazepril Related Compound A RS in *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Standard solution—Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 5 µg per mL.

Dilute standard solution—Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 1 µg per mL.

Test solution—Transfer about 50 mg of Benazepril Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.0-mm × 10-cm column that contains packing L41. The flow rate is about 0.9 mL per minute. The column temperature is maintained at 30°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 2.3 for benazepril related compound A and 1.0 for benazepril hydrochloride; and the resolution, *R,* between benazepril hydrochloride and benazepril related compound A is not less than 2.0. Chromatograph the *Dilute standard solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 10 : 1. Chromatograph the *Standard solution:* the relative standard deviation for replicate injections determined from the benazepril related compound A peak is not more than 10%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area for the benazepril related compound A peak. Calculate the percentage of benazepril related compound A in the portion of Benazepril Hydrochloride taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Benazepril Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Benazepril Hydrochloride in the *Test solution;* r_U is the peak response for benazepril related compound A obtained from the *Test solution;* and r_S is the peak response for benazepril related compound A obtained from the *Standard solution:* not more than 0.1% of benazepril related compound A is found.

TEST 2 (FOR BENAZEPRIL RELATED COMPOUNDS B, C, D, E, F, AND G)—

Tetrabutylammonium bromide solution, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Benazepril Related Compound B RS, USP Benazepril Related Compound C RS, USP Benazepril Related Compound D RS, USP Benazepril Related Compound E RS, USP Benazepril Related Compound F RS, and USP Benazepril Related Compound G RS in *Mobile phase* to obtain a solution having known concentrations of about 10 µg of each related compound per mL.

Test solution—Transfer about 50 mg of Benazepril Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the percentage of benazepril related compounds in the portion of Benazepril Hydrochloride taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of the relevant USP Reference Standard in the *Standard solution;* C_T is the concentration, in mg per mL, of benazepril hydrochloride in the *Test solution;* r_U is the peak response for the relevant benazepril related compound obtained from the *Test solution;* and r_S is the peak response for the relevant benazepril related compound obtained from the *Standard solution* (see *Table 1* for values).

Table 1

Benazepril Related Compound	Relative Retention Time	Limit (%)
E[1]	0.4	0.2
F[2]	0.5	0.2
C[3]	0.6	0.3
B[4]	1.5	0.5
D[5]	1.7	0.2
G[6]	2.0	0.2

[1] 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid

[2] *t*-Butyl-3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid

[3] 3-(1-Carboxy-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid

[4] Mixture of diastereoisomers (3-(1-ethoxycarbonyl-3-phenyl-(1*R*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid and (3-(1-ethoxycarbonyl-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*R*)-benzazepine)-1-acetic acid

[5] 3-(1-Ethoxycarbonyl-3-cyclohexyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid ■monohydrochloride■2S *(USP30)*

[6] 3-(1-Ethoxycarbonyl-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid ethyl ester

In addition to not exceeding the limits for benazepril related compounds in *Table 1,* not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities (excluding benazepril related compound A from *Test 1*) is found.

Change to read:

Assay—

Tetrabutylammonium bromide solution—Dissolve 0.81 g of tetrabutylammonium bromide in 360 mL of water containing 0.2 mL of glacial acetic acid.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Tetrabutylammonium bromide solution* (64 : 36). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Benazepril Hydrochloride RS and USP Benazepril Related Compound B RS in *Mobile phase* to obtain a solution having known concentrations of about 0.4 mg of each per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Benazepril Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.2 mg per mL.

Assay preparation—~~Transfer about 10 mg of Benazepril Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.~~

■Transfer about 10.0 mL of the *Test solution* (from either *Test 1* or *Test 2*), prepared as directed in the test for *Related compounds,* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.■2S *(USP30)*

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × ~~0.3-cm~~

■3-cm■2S *(USP30)*
guard column that contains packing L1 connected to a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between benazepril hydrochloride and benazepril related compound B is not less than 1.7; and the relative standard deviation for replicate injections determined from benazepril hydrochloride and benazepril related compound B is not more than 2.0% for each.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg, of $C_{24}H_{28}N_2O_5 \cdot HCl$ in the portion of Benazepril Hydrochloride taken by the formula:

$$250C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Benazepril Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Bismuth Subsalicylate Tablets, page 741 of *PF* 31(3) [May–June 2005]. It is proposed to revise the *Packaging and storage* statement to be consistent with the labeling for the currently marketed product. The equation in the *Assay* is also revised to include a dilution factor.

(MD-CCA: C. Anthony) RTS—C43293

Add the following:

■Bismuth Subsalicylate Tablets

» Bismuth Subsalicylate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of bismuth subsalicylate ($C_7H_5BiO_4$).

Packaging and storage—Preserve in tight containers. ~~Store between 15° and 30°.~~ Avoid excessive heat (over 40°).

Labeling—Label chewable Tablets to indicate that they are to be chewed before swallowing.

Identification—

A: It meets the requirements of the tests for *Bismuth* ⟨191⟩.

B: After acidifying with nitric acid, it meets the requirements of the test for *Salicylate* ⟨191⟩ with ferric chloride TS.

Disintegration ⟨701⟩**:** 10 minutes. [NOTE—This test does not apply for Tablets labeled as chewable.]

Assay—

Standard preparation—Transfer about 500 mg of bismuth, accurately weighed, to a 200-mL volumetric flask, dissolve in 12 mL of nitric acid, and dilute with 0.01 N nitric acid to volume. Transfer 10.0 mL of the solution so obtained into a 500-mL volumetric flask, and dilute with 1 N nitric acid to volume to obtain a concentration of 50 µg of bismuth per mL.

Assay preparation—Transfer an accurately weighed portion of finely powdered Tablets, equivalent to about 90 mg of bismuth subsalicylate, to a 200-mL volumetric flask, add about 150 mL of 1 N nitric acid, and sonicate for 2 minutes. Dilute with 1 N nitric acid to volume. Transfer 20.0 mL of the solution so obtained to a 100-mL volumetric flask, and dilute with 1 N nitric acid to volume. Centrifuge a portion at 4500 rpm for at least 10 minutes.

Procedure—Transfer 10.0 mL, accurately measured, of the *Assay preparation* and the *Standard preparation* to separate 50.0-mL volumetric flasks. Add 10.0 mL of 10% ascorbic acid solution and 25.0 mL of 20% potassium iodide solution into each volumetric flask, and dilute with 1 N nitric acid to volume. Concomitantly determine the absorbance of the solutions at the wavelength of maximum absorbance at about 463 nm with a suitable spectrophotometer using the combined reagent solutions as the blank. Calculate the quantity, in mg, of $C_7H_5BiO_4$ in the portion of Tablets taken by the formula:

~~$(362.11/208.98)(C)(A_u / A_s)$~~

In-Process Revision

$$(362.11/208.98)(CD)(A_U/A_S)$$

in which, 362.11 and 208.98 are the molecular weights of bismuth subsalicylate and bismuth, respectively; *C* is the concentration, in ~~µg~~ mg per mL, of bismuth in the *Standard preparation; D* is the dilution factor of the *Assay preparation;* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

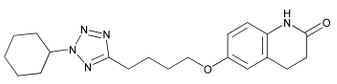
BRIEFING

Cilostazol, page 69 of *PF* 32(1) [Jan.–Feb. 2006]. On the basis of comments received, the nomenclature for the structure of cilostazol related compound C (see *Table 1*) is being revised to represent the structure as given by the innovator. The final concentration of the preparation of the *Control solution* in the test for *Chloride* is also revised.

(MD-CV: S. Ramakrishna) RTS—C47035; C47489

Add the following:

■Cilostazol



$C_{20}H_{27}N_5O_2$ 369.46

2(1*H*)-Quinolinone, 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydro-.

6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyril [*73963-72-1*].

» Cilostazol contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{27}N_5O_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩—*USP Cilostazol RS. USP Cilostazol Related Compound A RS. USP Cilostazol Related Compound B RS. USP Cilostazol Related Compound C RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

Loss on drying ⟨731⟩**—**Dry it at 110° for 3 hours: it loses not more than 0.25% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Chloride ⟨221⟩**—**

Test solution—Dissolve 0.5 g of Cilostazol in 40 mL of dimethylformamide, add 6 mL of diluted nitric acid and dimethylformamide to make 50 mL.

Control solution—To ~~25 mL~~ 0.25 mL of 0.01 M hydrochloric acid add 6 mL of diluted nitric acid and dimethylformamide to make 50 mL.

Procedure—Add 1 mL of silver nitrate TS to the *Test solution* and to the *Control solution,* mix well, and allow to stand for 5 minutes, protecting from direct sunlight. Compare the opalescence developed in both solutions against a black background by viewing downward or transversely. The opalescence developed in the *Test solution* is not more than that of the *Control solution* (0.018%).

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Related compounds—

Diluent, Solution A, Solution B, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

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Standard solution—Dissolve accurately weighed quantities of USP Cilostazol RS and USP Cilostazol Related Compound C RS in acetonitrile, with sonication if necessary, to obtain a solution having known concentrations of about 0.5 mg per mL of each component. Transfer 4 mL of this solution to a 10-mL volumetric flask, and dilute with water to volume. Further dilute this solution, stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 0.4 µg per mL of each component.

Test solution—Transfer about 20 mg of Cilostazol, accurately weighed, to a 50-mL volumetric flask, dissolve in 20 mL of acetonitrile, with sonication if necessary. Dilute with water to volume, and mix.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of cilostazol related compound C by the formula:

$$0.1(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of Cilostazol related compound C in the *Standard solution;* C_T is the concentration, in mg per mL, of Cilostazol in the *Test solution;* r_U is the peak response for Cilostazol related compound C obtained from the *Test solution;* and r_S is the peak response for Cilostazol related compound C obtained from the *Standard solution*. Calculate the percentage of other impurities by the formula:

$$0.1(1/F)(C_S / C_T)(r_U / r_S)$$

in which F is the relative response factor from *Table 1;* C_S is the concentration, in µg per mL, of Cilostazol in the *Standard solution;* C_T is the concentration, in mg per mL, of Cilostazol in the *Test solution;* r_U is the peak response for any other impurity obtained from the *Test solution;* and r_S is the peak response for Cilostazol obtained from the *Standard solution*.

Table 1

Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Cilostazol related compound A[1]	0.2	1.7	0.1
Cilostazol related compound B[2]	0.9	0.58	0.1
Cilostazol	1.0	1.0	—
Cilostazol related compound C[3]	1.9	n/a	0.1
Any other individual impurity	—	1.0	0.1

[1] 6-Hydroxy-3,4-dihydro-1*H*-quinolin-2-one
[2] 6-[4-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one
[3] ~~1,6-Bis-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one~~ 1-(4-(5-Cyclohexyl-1*H*-tetrazol-1-yl)butyl)-6-(4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one

In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.4% of total impurities is found.

Assay—

Diluent—Use a mixture of water and acetonitrile (60 : 40).

Solution A—Use a mixture of water and acetonitrile (70 : 30).

Solution B—Use a mixture of water and acetonitrile (50 : 50).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution in *Diluent* having known concentrations of about 0.05 mg per mL each of USP Cilostazol RS, USP Cilostazol Related Compound A RS, and USP Cilostazol Related Compound B RS.

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Standard preparation—Dissolve an accurately weighed quantity of USP Cilostazol RS in acetonitrile, with sonication if necessary, to obtain a solution having a known concentration of about 1.0 mg per mL. Transfer 4 mL of this solution to a 10-mL volumetric flask, and dilute with water to volume. Further dilute this solution with *Diluent* to obtain a solution having a known concentration of about 0.04 mg per mL.

Assay preparation—Transfer about 20 mg of Cilostazol, accurately weighed, to a 50-mL volumetric flask, dissolve in 20 mL acetonitrile, sonicate if necessary, dilute with water to volume, and mix. Transfer 1 mL of this solution to a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 10-cm column that contains 3.5-µm packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–6.5	100→50	0→50	linear gradient
6.5–10	50→0	50→100	linear gradient
10–20	0	100	isocratic
20–20.1	0→100	100→0	linear gradient
20.1–28	100	0	re-equilibration

Chromatograph the *System suitability solution,* identify the components using *Table 1,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between Cilostazol related compound B and Cilostazol is not less than 3.0; the tailing factor for the cilostazol peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{20}H_{27}N_5O_2$ in the portion of Cilostazol taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of Cilostazol in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP30*)

BRIEFING

Cod Liver Oil, *USP 29* page 581. In *Identification* test *B,* it is proposed to make revisions as follows: to state the concentration of the boron trichloride–methanol solution in the *Standard solution;* to correct the catalog number for the *System suitability mixture;* to correct the names of several fatty acids appearing in the table; in the *Chromatographic system,* to describe the use of the reference chromatogram provided with USP Cod Liver Oil RS; and in the *Procedure,* to add instructions for retention times and limits for fatty acids.

(DSN: L. Evans) RTS—C43958

Change to read:

Identification—

A: *Presence of vitamin A*—To 1 mL of a 1 in 40 solution of it in chloroform, add 10 mL of antimony trichloride TS: a blue color results immediately.

B: *Fatty acid profile*—

Antioxidant solution—Dissolve an accurately weighed quantity of butylated hydroxytoluene in hexanes to obtain a solution having a concentration of 0.05 mg per mL.

Standard solution—Transfer 0.450 g of USP Cod Liver Oil RS, accurately weighed, into a 10-mL volumetric flask, and dissolve in and dilute with *Antioxidant solution* to volume. Transfer 2.0 mL of this solution into a quartz tube, and evaporate with a gentle stream of nitrogen. Add 1.5 mL of a 2% solution of sodium hydroxide in methanol, cap tightly with a polytetrafluoroethylene-lined cap, mix, and heat in a water bath for 7 minutes. Cool, add 2 mL of ~~boron trichloride–methanol solution~~ ■a solution of 120 g of boron trichloride in 1000 mL of methanol, ■2S (*USP30*) cover with nitrogen, cap tightly, mix, and heat in a water bath for 30 minutes. Cool to 40° to 50°, add 1 mL of isooctane, cap, and mix in a vortex mixer or shake vigorously for at least 30 seconds. Immediately add 5 mL of saturated sodium chloride solution, cover with nitrogen, cap, and mix in a vortex mixer or shake thoroughly for at least 15 seconds. Allow the upper layer to become clear, and transfer to a separate tube. Shake the methanol layer once

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more with 1 mL of isooctane, and combine the isooctane extracts. Wash the combined extracts twice with 1 mL of water, and dry over anhydrous sodium sulfate.

System suitability mixture—Prepare a mixture containing accurately weighed and equal amounts of methyl palmitate, methyl stearate, methyl arachidate, and methyl behenate. [NOTE—A suitable mixture is available from Supelco, Bellefonte, PA, as GLC-40 cat. number ~~1985-1AMP~~

■1895-1AMP.]■2S (*USP30*)

Fatty acid	Shorthand notation	Lower limit (area %)	Upper limit (area %)
Saturated fatty acids:			
Myristic acid	14 : 0	2.0	6.0
Palmitic acid	16 : 0	7.0	14.0
Stearic acid	18 : 0	1.0	4.0
Monounsaturated fatty acids:			
~~Palmetoleic~~	16 : 1 n-7	4.5	11.5
■Palmitoleic■2S (*USP30*) acid			
cis-Vaccenic acid	18 : 1 n-7	2.0	7.0
Oleic acid	18 : 1 n-9	12.0	21.0
Gadoleic acid	20 : 1 n-11	1.0	5.5
Gondoic acid	20 : 1 n-9	5.0	17.0
~~Eurieic~~	22 : 1 n-9	0	1.5
■Erucic■2S (*USP30*) acid			
Cetoleic acid	22 : 1 n-11	5.0	12.0
Polyunsaturated fatty acids:			
Linoleic acid	18 : 2 n-6	0.5	3.0
~~γ-Linolenic acid~~	18 : 3 n-3	0	2.0
■α-Linolenic acid■2S (*USP30*)			
Moroctic acid	18 : 4 n-3	0.5	4.5
~~Eicosapentanoic~~	20 : 5 n-3	7.0	16.0
■Eicosapentaenoic■2S (*USP30*) acid			
~~Docosahexanoic~~	22 : 6 n-3	6.0	18.0
■Docosahexaenoic■2S (*USP30*) acid			

Test solution—Proceed as directed for the *Standard solution,* except to use an accurately weighed quantity of Cod Liver Oil.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.25-mm × 30-m fused silica capillary column coated with a 0.25-μm film of G16. The temperature of the detector is maintained at 280° and that of the injection port at 250°. Initially the temperature of the column is equilibrated at 170°, then the temperature is increased at a rate of 1° per minute to 225°, and maintained at 225° for 20 minutes. The carrier gas is helium, with a split flow ratio of 1 : 200. Chromatograph the *Standard solution,* the *System suitability mixture,* and the *Test solution,* and record the peak responses as directed for *Procedure:*

■the chromatogram obtained from the *Standard solution* is similar to the reference chromatogram supplied with USP Cod Liver Oil RS. Identify the retention times of the relevant fatty acid methyl esters by comparing the chromatogram of the *Standard solution* with the reference chromatogram supplied with USP Cod Liver Oil RS.■2S (*USP30*)

The resolution, *R,* between the peaks in the *Standard solution* due to methyl oleate and to methyl *cis*-vaccinate is not less than 1.3, and that between methyl gadoleate and methyl gondoate is sufficient for purposes of identification and area measurement; the theoretical area percentages for methyl palmitate, methyl stearate, methyl arachidate, and methyl behenate

■in the *System suitability mixture*■2S (*USP30*) are 24.4, 24.8, 25.2, and 25.6, respectively. In a suitable instrument, the area percentages from the *System suitability mixture* are within 1% of the theoretical values. The number of fatty acid methyl ester peaks exceeding 0.05% of the total area is at least 24, and the 24 largest peaks of the methyl esters account for more than 90% of the total area. (These correspond to the following, in common elution order: 14 : 0, 15 : 0, 16 : 0, 16 : 1 n-7, 16 : 4 n-1, 18 : 0, 18 : 1 n-9, 18 : 1 n-7, 18 : 2 n-6, 18 : 3 n-3, 18 : 4 n-3, 20 : 1 n-11, 20 : 1 n-9, 20 : 1 n-7, 20 : 2 n-6, 20 : 4 n-6, 20 : 3 n-3, 20 : 4 n-3, 20 : 5 n-3, 22 : 1 n-11, 22 : 1 n-9, 21 : 5 n-3, 22 : 5 n-3, and 22 : 6 n-3.)

Procedure—Separately inject equal volumes (about 1 μL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses.

■Identify the retention times of the relevant fatty acid methyl esters in the *Test solution* by comparing the chromatogram of the *Test solution* with that of the *Standard solution.*■2S (*USP30*)

Calculate the area percentage for each fatty acid methyl ester taken by the formula:

$$100(r_A / r_B)$$

in which r_A is the average peak area of each individual fatty acid; and r_B is the total peak area from all peaks in the chromatogram, except the solvent front and butylated hydroxytoluene.

■The fatty acids observed in the *Test solution* should meet the limits described in the table.■2S (*USP30*)

BRIEFING

Didanosine Tablets, page 784 of *PF* 32(3) [May–June 2006]. It is proposed to add a *Dissolution* test to this new monograph. The liquid chromatographic procedure in this test was validated using the LiChrospher 60 RP-Select brand of column that contains packing L1.

(BPC: M. Marques) RTS—C46520

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Add the following:

■Didanosine Tablets

» Didanosine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of didanosine ($C_{10}H_{12}N_4O_3$).

Packaging and storage—Preserve in tight containers, and store between 15° and 30°.

Labeling—Label ~~chewable~~ the Tablets to indicate that they are to be chewed before swallowing or dispersed in liquid before administration.

USP Reference standards ⟨11⟩—*USP Didanosine RS. USP Didanosine Related Compound A RS.*

Identification—

~~**A:** *Thin-Layer Chromatographic Identification Test* ⟨201⟩—~~

~~*Adsorbent*—Merck silica gel 60 with fluorescent indicator, or equivalent.~~

~~*Test solution*—Place 1 Tablet in sufficient methanol to make a 1 mg per mL solution. Stir to dissolve, and pass through a 0.45-µm filter.~~

~~*Standard solution*—Transfer 10 mg of USP Didanosine RS into a 10 mL volumetric flask. Dissolve in and dilute with methanol to volume.~~

~~*Developing solvent solution:*—A mixture of 1-butanol, methanol, ethyl acetate, and ammonium hydroxide (11 : 3 : 3 : 3).~~

~~*Procedure*—Spot 10 µL each of the *Test solution* and the *Standard solution* onto the chromatographic plate, approximately 2 cm from the bottom and 2 cm apart. Allow the plate to air-dry. Place in a chromatographic chamber, and develop, allowing the developing solution to travel at least 10 cm from the spotting line. Allow the plate to air-dry. View under shortwave light (254 nm). Didanosine appears as a blue spot.~~

~~**B:**~~ The retention time of the major peak in the chromatogram of the *Diluted assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Determine the amount of $C_{10}H_{12}N_4O_3$ dissolved by employing the following method.

0.01 M Ammonium acetate buffer solution, Mobile phase—Proceed as directed in the *Assay.*

Standard stock solution—Transfer about 160 mg of USP Didanosine RS, accurately weighed, to a 200-mL volumetric flask. Add about 100 mL of water, shake, and sonicate for 30 seconds to dissolve. Dilute with water to volume. This solution is stable for 48 hours at 5°.

Working standard solution—Dilute the *Standard stock solution* in water to obtain a concentration of approximately *LC*/900, where *LC* is the label claim of the Tablet for didanosine.

Test solution—Pass a portion of the solution under test through a suitable filter having a porosity of 0.45 µm.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength detector set at 275 nm, and a 4-mm × 12.5-cm column that contains 5-µm packing L7. The flow rate is about 2 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* didanosine elutes at about 4.8 minutes; the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes, equivalent to approximately 2 µg of didanosine, of the *Working standard solution* and the *Test solution* into the chromatograph, record

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the chromatograms for at least 7 minutes, and measure the responses for the didanosine peaks. Calculate the percentage of $C_{10}H_{12}N_4O_3$ released by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution;* 900 is the volume, in mL, of the *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{10}H_{12}N_4O_3$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Loss on drying ⟨731⟩—Dry 4 Tablets at 130° for 16 hours: they lose not more than 6% of their weight.

Related compounds—

0.01 M Ammonium acetate buffer solution—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate buffer solution* and methanol (99 : 1).

Standard stock solution—Transfer 25 mg of USP Didanosine Related Compound A RS to a 200-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. [NOTE—Use this solution within 48 hours of preparation.]

Standard solution—Transfer 3 mL of the *Standard stock solution* to a 250-mL volumetric flask. Dilute with water to volume, and mix. [NOTE—Use this solution within 48 hours of preparation of the *Standard stock solution*.]

Test solution—Proceed as directed for the *Assay preparation.*

Diluted test solution—Dilute the *Test solution* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength detector set at 275 nm, a 4-mm × 12.5-cm column that contains 5-µm packing L7, and a matching guard column. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution* as directed for *Procedure:* ~~the retention time of didanosine related compound A is between 1.5 and 2.5 minutes;~~ the column efficiency is not less than 1000 theoretical plates; and the relative standard deviation for replicate injections is not more than 5.0%. [NOTE—For information purposes only, didanosine related compound A, with a retention time between 1.5 and 2.5 minutes, is hypoxanthine.]

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Diluted test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks, carrying out the chromatography for approximately 30 minutes. Calculate the percentage of didanosine related compound A in the portion of Tablets taken by the formula:

~~$100(CVDL/N)(r_U/r_S)$~~

$$100(CVD/NL)(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Didanosine Related Compound A RS in the *Standard solution; V* is the volume, in mL, of the *Test solution; D* is the dilution factor of the *Diluted test solution; N* is the number of Tablets used to prepare the *Test solution; L* is the label claim of didanosine, in mg per Tablet; and r_U and r_S are the peak responses obtained from the *Diluted test solution* and the *Standard solution,* respectively. Not more than 0.7% of didanosine related compound A is found. Calculate the percentage of any other ~~impurities~~ impurity by the formula:

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$$100(r_i / r_s)$$

in which r_i is the peak response of any other individual impurity in the chromatogram of the *Diluted test solution;* and r_s is the sum of the responses of all the peaks in the chromatogram of the *Diluted test solution,* including those of didanosine and hypoxanthine: not more than 0.2% of any other individual impurity is found; and not more than 1.2% of total impurities, excluding hypoxanthine, is found.

Assay—

0.01 M Ammonium acetate buffer solution—Dissolve 1.54 g of ammonium acetate in a 2000-mL volumetric flask, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Ammonium acetate buffer solution* and methanol (95 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Didanosine RS in water to obtain a solution having a known concentration of 0.1 mg per mL. [NOTE—Use this solution within 24 hours of preparation.]

Assay preparation—Transfer not fewer than 5 crushed Tablets to a 500-mL volumetric flask. Dissolve in 250 mL of water, dilute with water to volume, and shake for about 10 minutes.

Diluted assay preparation—Dilute the *Assay preparation* quantitatively, and stepwise if necessary, with water to obtain a solution containing about 0.1 mg of didanosine per mL. [NOTE—Use this solution within 72 hours of preparation; because of the buffering agents in the Tablets, the *Assay preparation* is stable longer than the *Standard preparation.*]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a variable wavelength detector set at 275 nm, a 4-mm × 12.5-cm column that contains 5-µm packing L7, and a matching guard column. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the retention time of didanosine is greater than 3.0 minutes;~~ the column efficiency is not less than 2000 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%. [NOTE—For information purposes only, the retention time of didanosine is greater than 3.0 minutes.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Diluted assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of didanosine ($C_{10}H_{12}N_4O_3$) taken by the formula:

$$[CVD(r_U / r_S)] / N$$

in which C is the concentration, in mg per mL, of USP Didanosine RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation; D* is the dilution factor of the *Diluted assay preparation;* r_U and r_S are the peak responses of the *Diluted assay preparation* and the *Standard preparation,* respectively; and N is the number of Tablets used to prepare the *Assay preparation.* ■2S (*USP30*)

BRIEFING

Fexofenadine Hydrochloride, *USP 29* page 905; **Fexofenadine Hydrochloride Capsules,** *USP 29* page 906. These monographs were originally slated to become official on April 1, 2005, but the official date was postponed to provide additional time to further evaluate some of the tests, procedures, and acceptance criteria provided in the proposed monographs. On the basis of comments and supporting data received from companies, it is proposed to revise the Fexofenadine Hydrochloride monograph as follows.

1. Delete the *Differential scanning calorimetry* test from *Identification* because the current acceptance criteria are specific to the anhydrous form of the drug substance. USP received comments that there are different melting ranges for the same hydrate forms. It is proposed to delete the test so that no manufacturer is excluded.
2. Revise the test for *Water* to provide separate requirements for the anhydrous and hydrate forms of the drug, and add a labeling requirement if the hydrate form is used. [NOTE—For this monograph, "hydrate" refers to a mixture of dihydrate and trihydrate forms of fexofenadine hydrochloride.]

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3. Add an identification test for chloride in the *Identification* section.
4. Delete the test for *Specific surface area* because this is a manufacturer-specific property and could be an obstacle to other manufacturers entering the market.
5. Revise the acceptance criteria for the test for *Limit of fexofenadine related compound B* and the test for *Related compounds* to align with requirements for approved products.
6. Delete the retention time requirement in the test for *Limit of fexofenadine related compound B* as this is subject to wide variation.

(MD-PS: D. Bempong) RTS— C42017

Add the following:

■**Labeling—**Where it is the hydrate form, the label so indicates.■2S (*USP30*)

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the fexofenadine peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

~~**C:** *Differential scanning calorimetry* ⟨891⟩—Accurately weigh 2 to 6 mg of Fexofenadine Hydrochloride into an aluminum pan, and crimp the pan, using a suitable sample press. Analyze the sample from 25° to 225° at 10° per minute. The sample exhibits a single endotherm between 193° and 199°. [NOTE—The pan can be sealed hermetically, provided a pinhole is punched into the lid so that the sample can degas during heating.]~~

■**C:** Examine the precipitate formed in the *Content of chloride* test: a white precipitate is observed.■2S (*USP30*)

Change to read:

Water, *Method Ic* ⟨921⟩**:** not more than 0.5%

■for the anhydrous form; between 6.0% and 10.0% for the hydrate form. [NOTE—"Hydrate" refers to a mixture of dihydrate and trihydrate forms of fexofenadine hydrochloride.]■2S (*USP30*)

Delete the following:

~~■**Specific surface area,** *Method II* ⟨846⟩—Outgas a portion of Fexofenadine Hydrochloride, 0.2 to 0.5 g, using helium flow for 1 hour at 100° or vacuum for 1 hour at 100°. Test the sample, using gas sorption: between 2.5 and 5.0 m^2 per g is found.■2S (*USP30*)~~

Change to read:

Limit of fexofenadine related compound B—

Ammonium acetate buffer solution—Add 2.3 mL of glacial acetic acid to 2000 mL of water. Adjust with 6 N ammonium hydroxide to a pH of 4.0 ± 0.1.

Mobile phase—Prepare a filtered and degassed mixture of *Ammonium acetate buffer solution* and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Add about 1.2 mg of USP Fexofenadine Related Compound B RS, accurately weighed, to a 5-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix. Transfer 2.0 mL of the solution so obtained into a 100-mL volumetric flask; add about 25 mg of USP Fexofenadine Hydrochloride RS, accurately weighed; dilute with *Mobile phase* to volume; and mix.

Standard solution—Dilute the *System suitability solution* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 2.5 µg of USP Fexofenadine Hydrochloride RS per mL.

Test solution—Dissolve an accurately weighed quantity of Fexofenadine Hydrochloride in *Mobile phase* to obtain a solution having a concentration of about 0.25 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L45. The column is maintained at room temperature. The flow rate is about 0.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the retention time for fexofenadine is between 15 and 23 minutes;~~

■■2S (*USP30*)
the relative retention times are about 0.7 for fexofenadine related compound B and 1.0 for fexofenadine; and the resolution, *R,* between fexofenadine and fexofenadine related compound B is not less than 3.0.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of fexofenadine related compound B in the portion of Fexofenadine Hydrochloride taken by the formula:

$$100/0.8(C_S/C_T)(r_U/r_S)$$

in which 0.8 is the relative response factor for fexofenadine related compound B relative to fexofenadine; C_S is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response for fexofenadine related compound B obtained from the *Test solution;* and r_S is the peak response for fexofenadine obtained from the *Standard solution:* not more than ~~0.1%~~

■0.2%■2S (*USP30*)
is found.

Change to read:

Related compounds—

Phosphate–perchlorate buffer, Diluting solution, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Reference solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay stock preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution,* the *Standard solution,* the *Reference solution,* and *Mobile phase* (used as the blank) into the chromatograph; record the chromatograms; and measure the peak areas, excluding the peaks corresponding to those obtained from the *Mobile phase*. Calculate the percentage of fexofenadine related compound A in the portion of Fexofenadine Hydrochloride taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Fexofenadine Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* and r_U and r_S are the peak responses for fexofenadine related compound A obtained from the *Test solution* and the *Standard solution,* respectively. Calculate the percentage of decarboxylated degradant [(+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene], with a relative

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retention time of 3.2, in the portion of Fexofenadine Hydrochloride taken by the formula:

$$(100/1.1)(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response of the decarboxylated degradant obtained from the *Test solution;* r_S is the peak response of fexofenadine obtained from the *Standard solution;* and 1.1 is the relative response factor for the decarboxylated degradant relative to fexofenadine. Calculate the percentage of other impurities in the portion of Fexofenadine Hydrochloride taken by the formula:

$$100(C_S/C_T)(r_i/r_S)$$

in which C_S is the concentration, in mg per mL, of fexofenadine in the *Reference solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_i is the peak response for any other impurity obtained from the *Test solution;* and r_S is the peak response of fexofenadine obtained from the *Reference solution:* not more than ~~0.18%~~

■0.2%■2S (*USP30*)
of fexofenadine related compound A is found, not more than 0.15% of decarboxylated degradant is found, not more than 0.1% of any other unknown impurity is found, and not more than ~~0.30%~~

■0.5%■2S (*USP30*)
of total impurities is found.

BRIEFING

Fexofenadine Hydrochloride Capsules, *USP 29* page 906—See briefing under *Fexofenadine Hydrochloride.* On the basis of comments received and because the water range allows for use of different hydrate forms of the drug substance, it is proposed to revise the limits for the test for *Water* and also to revise the limits for impurities provided in the test for *Related compounds* in order to match the limits provided for an approved product.

(MD-PS: D. Bempong) RTS—C42474

Change to read:

Water, *Method I* ⟨921⟩**:** ~~between 3.5% and~~

■not more than■2S (*USP30*)
8.0%, the titration being performed at 50° and the titration vessel being kept in a heated water jacket.

Change to read:

Related compounds—

Phosphate–perchlorate buffer, Diluting solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay* under *Fexofenadine Hydrochloride*.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay* under *Fexofenadine Hydrochloride*.

Reference solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay stock preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of fexofenadine related compound A in the portion of Capsules taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Fexofenadine Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* and r_U and r_S are the peak responses of fexofenadine related compound A obtained from the *Test solution* and the *Standard solution,* respectively. Calculate the percentage of decarboxylated degradant [(+)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-isopropylbenzene], with a relative retention time of 3.2, in the portion of Fexofenadine Hydrochloride taken by the formula:

$$(100/1.1)(C_S/C_T)(r_U/r_S)$$

in which 1.1 is the relative response factor for the decarboxylated degradant relative to fexofenadine; C_S is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the *Standard solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response of the decarboxylated degradant obtained from the *Test solution;* and r_S is the peak response of fexofenadine obtained from the *Standard solution*. Calculate the percentage of other impurities in the portion of Fexofenadine Hydrochloride taken by the formula:

$$100(C_R/C_T)(r_U/r_R)$$

in which C_R is the concentration, in mg per mL, of fexofenadine in the *Reference solution;* C_T is the concentration, in mg per mL, of fexofenadine in the *Test solution;* r_U is the peak response for any other impurity obtained from the *Test solution;* and r_R is the peak response of fexofenadine obtained from the *Reference solution.* ~~Not more than 0.3% of fexofenadine related compound A, not more than 0.2% of decarboxylated degradant, and less than 0.1% of any other unknown impurity is found; not more than 0.2% total other unknown impurities, and not more than 0.5% of total impurities is found.~~

■Not more than 0.4% of fexofenadine related compound A, not more than 0.2% of decarboxylated degradant, and less than 0.2% of any other unknown impurity is found; and not more than 0.5% of total impurities is found.■2S (*USP30*)

BRIEFING

Fluvoxamine Maleate, *USP 29* page 964 and page 344 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to widen the limits in the Definition from "not less than 99.0 percent and not more than 101.0 percent" to "not less than 98.0 percent and not more than 102.0 percent". The original acceptance criterion is appropriate for titration assay, whereas the proposed criterion is appropriate for HPLC assay.

(MD-PP: R. Ravichandran) RTS—C46418

In-Process Revision

Change to read:

» Fluvoxamine Maleate contains not less than ~~99.0 percent and not more than 101.0~~

■98.0 percent and not more than 102.0■2S (*USP30*) percent of $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$, calculated on the dried basis.

Delete the following:

~~■**Maleic acid**—Transfer about 800.0 mg of Fluvoxamine Maleate, accurately weighed, to a 250-mL conical flask containing 50 mL of water. Titrate with 0.1 N sodium hydroxide VS, using 0.5 mL of phenolphthalein TS as the indicator. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N sodium hydroxide VS is equivalent to 5.805 mg of maleic acid ($C_4H_4O_4$). Between 26.0% and 27.5% of maleic acid is found.■1S (*USP30*)~~

Change to read:

Assay—

Buffer solution—Dissolve about 5 g of 1-pentanesulfonic acid sodium salt and 0.7 g of monobasic potassium phosphate in 620 mL of water. Adjust with phosphoric acid to a pH of 3.00 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (62 : 38). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Transfer about 6 mg of Fluvoxamine Maleate to a 50-mL volumetric flask. Heat the sample at 120° for 10 minutes. Cool down to room temperature, and add 3.0 mL of 0.1 N hydrochloric acid. Heat the solution in a water bath for 10 minutes. Cool down to room temperature, add 50 mg of Fluvoxamine Maleate, and dissolve in 25 mL of *Mobile phase.* Dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Fluvoxamine Maleate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay stock preparation—Transfer an accurately weighed quantity of about 50 mg of Fluvoxamine Maleate to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer 5.0 mL of the *Assay stock preparation* to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 234-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.7 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.2 for maleic acid, 0.5 for 5-methoxy-1-[4-(trifluoromethyl)-phenyl]-1-pentanone-(*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime, 0.8 for the *Z*-isomer, and 1.0 for fluvoxamine maleate;~~

■■1S (*USP30*)
the resolution, *R,* between the *Z*-isomer and fluvoxamine maleate is not less than 3.0 and not less than 5.0 between 5-methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime and the *Z*-isomer. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

■[NOTE—For the purpose of peak identification, the approximate relative retention times are given in *Table 1.*]■1S (*USP30*)

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the fluvoxamine maleate peaks. Calculate the quantity, in mg, of $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ in the portion of Fluvoxamine Maleate taken by the formula:

$$1000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Fluvoxamine Maleate RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

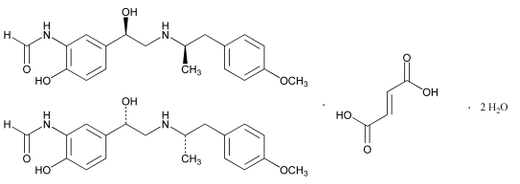
BRIEFING

Formoterol Fumarate, page 106 of *PF* 32(1) [Jan.–Feb. 2006]. The molecular weight and chemical formula have been revised to reflect the dihydrate nature of the salt. The table in the test for *Related compounds* has also been revised to correct the relative response factors. The test for *Content of related compound I (diastereoisomer)* was validated using the Phenomenex ZB-5 brand of G27 column.

(AER: K. Zaidi) RTS—C44367; C43943

Add the following:

■Formoterol Fumarate



$(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$ ~~804.88~~ 840.91

(±)-2′-Hydroxy-5′-[*(R*)*-1-hydroxy-2-[[*(R*)-p*-methoxy-α-methylphenethyl]amino]ethyl]formanilide fumarate (2 : 1) (salt), dihydrate [*43229-80-7*].

» Formoterol Fumarate contains not less than 98.0 percent and not more than 102.0 percent of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$, calculated on the anhydrous basis.

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Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Formoterol Fumarate RS. USP Formoterol Fumarate System Suitability Mixture RS. USP Formoterol Related Compound I RS.*

Identification, *Infrared Absorption* ⟨197K⟩**.**

Specific rotation ⟨781S⟩**:** between –0.10° and +0.10°.

Test solution: 10 mg per mL, in methanol.

pH ⟨791⟩**:** between 5.5 and 6.5, in a solution in water containing 1 mg per mL.

Water, *Method I* ⟨921⟩**:** ~~not more than 5.0%~~ between 4.0% and 5.0%.

Residue on ignition ⟨281⟩**:** not more than 0.1%, determined on 1 g.

Heavy metals, *Method II* ⟨231⟩**:** not more than 0.002%.

Related compounds—

Solution A—Dissolve 3.73 g of sodium dihydrogen phosphate monohydrate and 0.35 g of phosphoric acid in water, dilute with water to 1000 mL, and mix. The pH of this solution is 3.1 ± 0.1.

Solution B—Use acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solution C—Transfer 6.10 g of sodium dihydrogen phosphate monohydrate and 1.03 g of disodium hydrogen phosphate dihydrate to a 1000-mL volumetric flask, add 500 mL of water, and dissolve. Dilute with water to volume, and mix. The pH is 6.0 ± 0.1.

Diluent—Prepare a filtered and degassed mixture of *Solution C* and acetonitrile (84 : 16, v/v).

System suitability solution—Transfer about 5 mg of USP Formoterol Fumarate System Suitability Mixture RS (containing formoterol fumarate, and formoterol related compounds A, B, C, D, E, F, G, and H), accurately weighed, to a 25-mL volumetric flask, add 10 mL of *Diluent,* and sonicate to dissolve. Dilute with *Diluent* to volume, and mix.

Test solution—Transfer about 20.0 mg of Formoterol Fumarate, accurately weighed, to a 100-mL volumetric flask, add 50 mL of *Diluent,* and sonicate to dissolve. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	84	16	equilibration
0–10	84	16	isocratic
10–37	84→30	16→70	linear gradient
37–40	30→84	70→16	linear gradient
40–55	84	16	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between formoterol related compound G and formoterol related compound A is not less than 1.5; the peak-to-valley ratio (H_P / H_V) of formoterol related compound C and formoterol fumarate is not less than 2.5, where H_P is the height above the baseline of the peak due to formoterol related compound C and H_V is the height above the baseline of the lowest point of the curve separating this peak from the peak due to formoterol fumarate; and the relative retention times and limits are as provided in *Table 1* below.

Procedure—Separately inject equal volumes (about 20 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Disregard any peak representing less than 0.05%. Calculate the percentage of each formoterol related compound in the portion of Formoterol Fumarate taken by the formula:

Table 1

Related Compound	Related Compound Chemical Name	Relative Retention Time	Relative Response Factor (*F*)	Limit (%)
G	(2*RS*)-1-(4-methoxyphenyl)propan-2-amine	0.4	~~1.00~~ 2.64	0.1
A	1-(3-amino-4-hydroxyphenyl)-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethanol	0.5	1.75	0.3
B	*N*-[2-hydroxy-5-[(1*RS*)-1-hydroxy-2-[[2-(4-methoxyphenyl)ethyl]amino]ethyl]phenyl]-formamide	0.7	1.00	0.2
C	*N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]-acetamide	1.2	~~1.00~~ 1.10	0.2
D	*N*-[2-hydroxy-5-[1-hydroxy-2-[methyl[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-phenyl]formamide	1.3	~~1.00~~ 1.12	0.2
E	*N*-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-3-methylphenyl)-1-methylethyl]amino]ethyl]-phenyl]formamide	1.8	~~1.00~~ 0.67	0.1
F	*N*-[2-hydroxy-5-[1-[[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]-ethyl]phenyl]amino]-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide	2.0	1.00	0.2
H	*N*-[5-[(1*RS*)-2-[benzyl[(1*RS*)-2-(4-methoxyphenyl)-1-methylethyl]amino]-1-hydroxyethyl]-2-hydroxyphenyl]formamide (monobenzyl analogue)	2.2	~~1.00~~ 1.24	0.1
	Any other individual impurity			0.1
	Total impurities			0.5

$$100F(r_i / r_s)$$

in which *F* is the relative response factor for each formoterol related compound according to *Table 1*; r_i is the peak response for each formoterol related compound; and r_s is the sum of the responses for all the peaks.

Content of related compound I *(diastereoisomer)*—

Standard solution—Dissolve 10 mg of USP Formoterol Related Compound I RS in 1 mL of dimethylformamide. Add 100 µL of *N*-(trimethylsilyl)imidazole, and mix.

Test solution—Dissolve 10 mg of Formoterol Fumarate in 1 mL of dimethylformamide. Add 100 µL of *N*-(trimethylsilyl)imidazole, and mix.

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Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica capillary column coated with a 0.25-µm film of stationary phase G27, and a split injection system. The carrier gas is helium, flowing at a rate of about 2 mL per minute and a split ratio of about 75 : 1. The injection port and the detector temperatures are maintained at about 280° and 300°, respectively. The column temperature is programmed as follows. Initially the column temperature is equilibrated at 220° for 5 minutes, then the temperature is increased at a rate of 1° per minute to 250°, and maintained at 250° for 20 minutes. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between formoterol related compound I and formoterol fumarate is not less than 2.0.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for formoterol related compound I and formoterol fumarate. Disregard all other peaks. Calculate the percentage of formoterol related compound I in the portion of Formoterol Fumarate taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for formoterol related compound I, and r_s is the sum of the responses of both formoterol fumarate and formoterol related compound I peaks: not more than 0.3% of formoterol related compound I is found.

Assay—Transfer about 350 mg of Formoterol Fumarate, accurately weighed, to a titration vessel, dissolve in 50 mL of anhydrous acetic acid, and titrate with 0.1 M perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 M perchloric acid is equivalent to 40.24 mg of $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4$. ■2S *(USP30)*

BRIEFING

Glipizide, *USP 29* page 1002. Comments were received that the currently official HPLC method for the test for *Related compounds* does not have sufficient specificity. It is proposed to designate the currently official method as *Test 1,* and to add a new method that is able to separate glipizide related compounds A and B, as *Test 2*. It is also proposed to use this new liquid chromatographic method for the *Assay.* The procedure is based on analyses performed with the Phenomenex Curosil-PFP brand of L43 column. The typical retention time for the glipizide peak is about 21 minutes. Alternatively, Supelco Discovery HS FS brand of L43 column can be used, with the typical retention times for the glipizide peak of about 14 minutes. In addition, it is proposed to change the format of the formula in *Test 1,* as recommended in the Stimuli article *Common Pharmacopeial Calculations in USP Monographs,* published on page 626 of *PF* 31(2).

(MD-GRE: E. Gonikberg) RTS—C42755

Change to read:

USP Reference standards ⟨11⟩—*USP Glipizide RS. USP Glipizide Related Compound A RS.*

■*USP Glipizide Related Compound B RS. USP Glipizide Related Compound C RS.* ■2S *(USP30)*

Change to read:

Related compounds—[NOTE—Use low-actinic glassware ~~in this procedure~~

■for solutions containing glipizide.]

TEST 1 (limit of methyl-*N*-4-[2-(5-methylpyrazine-2-carboxamido)ethyl] benzenesulfonyl carbamate)—■2S *(USP30)*

Buffer solution—Add 4.0 mL of *n*-butylamine to 1000 mL of water. Adjust with phosphoric acid to a pH of 3.00 ± 0.05.

Diluent—Prepare a mixture of water, acetonitrile, and methanol (3 : 1 : 1).

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* acetonitrile, and methanol (3 : 1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Prepare a solution of USP Glipizide RS in methanol containing about 0.1 mg per mL.

Standard solution—Prepare a solution of USP Glipizide Related Compound A RS in methanol containing about 0.1 mg per mL. Pipet 2.0 mL of this solution into a 100-mL volumetric flask, add 2.0 mL of the *Standard stock solution,* dilute with *Diluent* to volume, and mix. This solution contains about ~~2 µg~~

■0.002 mg■2S *(USP30)*
of USP Glipizide RS and about ~~2 µg~~

■0.002 mg■2S *(USP30)*
of USP Glipizide Related Compound A RS per mL.

Test solution—Transfer about 25 mg of Glipizide, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Pipet 4.0 mL of this solution into a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 30°. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* ~~the retention time of the~~

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~~glipizide peak is about 45 minutes; the relative retention times for glipizide related compound A and glipizide are about 0.12 and 1.0, respectively; the relative retention time of another known impurity, methyl *N*-4-[2-(5-methylpyrazine-2-carboxamido)ethyl] benzenesulfonyl carbamate, is about 0.18; and~~

■■2S (*USP30*)
the relative standard deviation for replicate injections is not more than 5.0% for each peak.

■[NOTE—The retention time of the glipizide peak is about 45 minutes; for the purpose of identification, the relative retention times for glipizide related compound A and glipizide are about 0.12 and 1.0, respectively.]■2S (*USP30*)

Procedure—Separately inject equal volumes (about 35 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses.

■In the *Test solution,* identify the peaks that correspond to glipizide related compounds A, B, and C, based on their relative retention times: the relative retention time for glipizide related compound A is given above; glipizide related compound B, if present, elutes immediately after glipizide related compound A, and these two peaks are not resolved by this method; glipizide related compound C elutes at a relative retention time of approximately 1.1. Disregard these impurities when using *Test 1,* as they will be controlled using *Test 2*.

In the *Test solution,* identify the peak that corresponds to methyl-*N*-4-[2-(5-methylpyrazine-2-carboxamido)ethyl] benzenesulfonyl carbamate impurity, based on its relative retention time, which is about 0.18.■2S (*USP30*)

~~Calculate the percentage of glipizide related compound A in the portion of Glipizide taken by the formula:~~

~~$$6.25(C_A/W)(r_A/r_{SA})$$~~

~~in which C_A is the concentration, in µg per mL, of USP Glipizide Related Compound A RS in the *Standard solution; W* is the amount of Glipizide, in mg, taken to prepare the *Test solution;* and r_A and r_{SA} are the peak responses for glipizide related compound A obtained from the *Test solution* and the *Standard solution,* respectively.~~

■■2S (*USP30*)
Calculate the percentage of

■this impurity■2S (*USP30*)
and any other individual impurity in the portion of Glipizide taken by the formula:

~~$$6.25(C_G/W)(r_i/r_{SG})$$~~

$$■100(C_G/C_T)(r_i/r_{SG})■2S\ (USP30)$$

in which C_G is the concentration, ~~in µg per mL,~~

■in mg per mL,■2S (*USP30*)
of glipizide in the *Standard solution;*

■C_T is the concentration, in mg per mL, of Glipizide in the *Test solution;*■2S (*USP30*)
r_i is the peak response for each individual impurity obtained from the *Test solution;* r_{SG} is the glipizide peak response obtained from the *Standard solution.* ~~; and *W* is defined above.~~

■■2S (*USP30*)
Disregard any impurity peak that is less than 0.05%. Not more than 0.5% of any individual impurity is found. ~~; and not more than 1.5% of total impurities is found.~~

■TEST 2 (limit of related compounds A, B, and C)—

0.02 M Phosphate buffer, Mobile phase, Impurity standard stock solution, System suitability solution, Sensitivity solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Impurity standard solution—Accurately transfer 5.0 mL of the *Impurity standard stock solution* into a 100-mL volumetric flask, and dilute with methanol to volume. Accurately transfer 10.0 mL of the solution obtained into another 100-mL volumetric flask containing 20 mL of acetonitrile and 60 mL of *0.02 M Phosphate buffer.* Sonicate the solution for about 5 minutes, dilute with *0.02 M Phosphate buffer* to volume, and mix. This solution contains about 0.0005 mg of each of glipizide related compounds A, B, and C per mL.

Test solution—Use *Assay preparation.*

Procedure—Separately inject equal volumes (about 10 µL) of the *Impurity standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each of the glipizide related compounds A, B, or C in the portion of Glipizide taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of the respective glipizide related compound in the *Impurity standard solution;* C_T is the concentration, in mg per mL, of Glipizide in the *Test solution;* r_U and r_S are the peak responses for the respective glipizide related compound obtained from the *Test solution* and the *Impurity standard solution,*

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respectively. Not more than 0.5% of any individual impurity is found; and not more than 1.5% of total impurities is found, the results for *Test 1* and *Test 2* being combined.■2S *(USP30)*

Change to read:

~~**Assay**— [NOTE—Use low-actinic glassware in this procedure.]~~

~~*Buffer*— Dissolve 13.8 g of monobasic sodium phosphate in water, and dilute with water to 1000 mL. Adjust with 2.0 N sodium hydroxide to a pH of 6.00 ± 0.05.~~

~~*Mobile phase*— Prepare a filtered and degassed mixture of *Buffer* and methanol (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*— Dissolve an accurately weighed quantity of USP Glipizide RS in methanol, and dilute quantitatively with methanol to obtain a solution having a known concentration of about 0.1 mg per mL. Transfer 25.0 mL of this solution to a 50-mL volumetric flask, dilute with *Buffer* to volume, and mix to obtain a solution having a known concentration of about 0.05 mg per mL.~~

~~*Assay preparation*— Transfer about 20 mg of glipizide, accurately weighed, to a 200-mL volumetric flask, and dissolve in and dilute with methanol to volume. Pipet 25 mL of this solution into a 50-mL volumetric flask, dilute with *Buffer* to volume, and mix to obtain a solution having a known concentration of about 0.05 mg per mL.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩): The liquid chromatograph is equipped with a 225-nm detector and a 15-cm × 3.9-mm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.0%.~~

~~*Procedure*— Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of glipizide ($C_{21}H_{27}N_5O_4S$) in the portion of Glipizide taken by the formula:~~

$$~~400C(r_U/r_S),~~$$

~~in which *C* is the concentration, in mg per mL, of USP Glipizide RS in the *Standard preparation,* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

■[NOTE—Use low-actinic glassware for solutions containing glipizide.]

0.02 M Phosphate buffer—Dissolve 2.84 g of dibasic sodium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 6.00 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *0.02 M Phosphate buffer,* acetonitrile, and methanol (70 : 20 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Transfer accurately weighed amounts of USP Glipizide RS to a suitable volumetric flask, and dissolve in methanol with the aid of sonication for about 5 minutes to obtain a solution having a known concentration of about 1.0 mg of glipizide per mL.

Standard preparation—Accurately transfer 10.0 mL of the *Standard stock preparation* into a 100-mL volumetric flask containing 20 mL of acetonitrile and 60 mL of *0.02 M Phosphate buffer.* Sonicate the solution for about 5 minutes, dilute with *0.02 M Phosphate buffer* to volume, and mix. This solution contains about 0.1 mg of glipizide per mL.

Impurity standard stock solution—Transfer accurately weighed amounts of USP Glipizide Related Compound A RS, USP Glipizide Related Compound B RS, and USP Glipizide Related Compound C RS to a suitable volumetric flask, and dissolve in methanol with the aid of sonication for about 5 minutes to obtain a solution having known concentrations of about 0.1 mg of each of glipizide related compounds A, B, and C per mL. [NOTE—Glipizide related compound A is *N*-{2-[(4-aminosulfonyl)phenyl]ethyl}-5-methyl-pyrazinecarboxamide; glipizide related compound B is 6-methyl-*N*-[2-(4-sulfamoylphenyl)ethyl]pyrazine-2-carboxamide; and glipizide related compound C is 1-cyclohexyl-3-[[4-[2-[[(6-methylpyrazin-2-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]urea.]

System suitability stock solution—Transfer an accurately weighed amount of USP Glipizide RS to a suitable volumetric flask, dissolve in methanol with the aid of sonication for about 5 minutes, and add an accurately measured volume of *Impurity standard stock solution* to obtain a solution containing about 1.0 mg of glipizide and about 0.005 mg of each of glipizide related compounds A, B, and C per mL.

System suitability solution—Accurately transfer 10.0 mL of the *System suitability stock solution* into a 100-mL volumetric flask containing 20 mL of acetonitrile and 60 mL of *0.02 M Phosphate buffer.* Sonicate the solution for about 5 minutes, dilute with *0.02 M Phosphate buffer* to volume, and mix.

Sensitivity solution—Accurately transfer 5.0 mL of the *System suitability solution* into a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Assay stock preparation—Transfer about 100 mg of Glipizide, accurately weighed, to a 100-mL volumetric flask, dissolve in about 50 mL of methanol with the aid of sonication for about 5 minutes, dilute with methanol to volume, and mix.

Assay preparation—Accurately transfer 10.0 mL of the *Assay stock preparation* into a 100-mL volumetric flask containing 20 mL of acetonitrile and 60 mL of *0.02 M Phosphate buffer.* Sonicate the solution for about 5 minutes, dilute with *0.02 M Phosphate buffer* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L43. The column temperature is maintained at 40°. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the elution order is glipizide related compound A, glipizide related compound B, glipizide, and glipizide related compound C; the resolution, *R,* between glipizide related compound A and glipizide related compound B peaks is not less than 1.8, and the resolution, *R,* between glipizide and glipizide related compound C peaks is also not less than 1.8; the tailing factor for the glipizide peak is not more than 2.0; and the relative standard deviation for 5 replicate injections is not more than 1.5% for the glipizide peak and not more than 5.0% for each of the related compounds peaks. Chromatograph the *Sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for each of glipizide related compound A and glipizide related compound B peaks is not less than 15.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of $C_{21}H_{27}N_5O_4S$ in the portion of Glipizide taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of glipizide in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the glipizide peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

BRIEFING

Hydroxyzine Hydrochloride, *USP 29* page 1089 and page 114 of *PF* 32(1) [Jan.–Feb. 2006]. It is proposed to replace the current titration assay with the HPLC method used in the test for *Chromatographic purity.* During the validation it was established that this test can be successfully done with one 25-cm long L3 column instead of the currently required two 10-cm long L3 columns, with some minor modifications. The validation work was performed using the Econosphere brand of Silica column manufactured by Alltech Associates. Hydroxyzine related compound A and hydroxyzine elute around 6.1 and 6.9 minutes, respectively. The definition has been changed to reflect the variability in the HPLC method.

(MD-PP: R. Ravichandran) RTS—C46789

Change to read:

» Hydroxyzine Hydrochloride, contains not less than 98.0 percent and not more than ~~100.5 percent~~

■102.0 percent■2S (*USP30*)
of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$, calculated on the dried basis.

Change to read:

USP Reference standards ⟨11⟩— ~~*USP p-Chlorobenzhydrylpiperazine RS.*~~

▲▲*USP30*
USP Hydroxyzine Hydrochloride RS.

▲*USP Hydroxyzine Related Compound A RS.*▲*USP30*

Change to read:

Chromatographic purity—

~~*Mobile phase*—Prepare a filtered and degassed mixture of acetonitrile and 0.12 N sulfuric acid (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard solution*—Quantitatively dissolve an accurately weighed quantity of USP Hydroxyzine Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 1.8 µg per mL.~~

~~*Resolution solution*—Dissolve suitable quantities of USP Hydroxyzine Hydrochloride RS and USP *p*-Chlorobenzhydrylpiperazine RS~~

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~~★USP Hydroxyzine Related Compound A RS★(USP30)~~
~~in *Mobile phase* to obtain a solution containing 3.6 µg of each per mL.~~

~~*Test solution*—Transfer an accurately weighed quantity of Hydroxyzine Hydrochloride to a suitable volumetric flask, dissolve in and dilute with *Mobile phase* to volume to obtain a solution containing a concentration of about 0.6 mg of specimen per mL, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩): The liquid chromatograph is equipped with a 230-nm detector, and two series-coupled 3-mm × 10-cm columns that contain packing L3. The flow rate is about 0.4 mL per minute. Chromatograph the *Resolution solution* and the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the *p*-chlorobenzhydrylpiperazine~~

~~★hydroxyzine related compound A★(USP30)~~
~~and hydroxyzine peaks is not less than 1.2, and the relative standard deviation for replicate injections of the *Standard solution* is not more than 2.0%.~~

■*Mobile phase, Resolution solution,* and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Quantitatively dilute the *Standard preparation* with *Mobile phase* to obtain a solution having a known concentration of about 1.8 µg per mL of Hydroxyzine Hydrochloride.

Test solution—Use the *Stock Assay preparation*.■2S (USP30)
Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for a total time of not less than 1.8 times the retention time of the hydroxyzine peak, and measure the response for each peak, except for the main hydroxyzine peak in the chromatogram obtained from the *Test solution*. Calculate the ~~apparent~~

■■2S (USP30)
percentage of each impurity in the specimen taken by the formula:

~~$0.1(C_s/C_u)(r_u/r_s)$,~~

■$100(C_S/C_U)(r_U/r_S)$■2S (USP30)

in which C_S is the concentration, in ~~µg~~

■mg■2S (USP30)
per mL, of USP Hydroxyzine Hydrochloride RS in the *Standard solution;* C_U is the concentration, in mg per mL, of specimen in the *Test solution;* r_U is the peak response of a given impurity in the chromatogram obtained from the *Test solution;* and r_S is the peak response of hydroxyzine in the chromatogram obtained from the *Standard solution:* not more than 0.3% of any impurity is found, and the sum of all impurities found is not greater than 1.5%.

Change to read:

Assay—~~Dissolve about 80 mg of Hydroxyzine Hydrochloride, accurately weighed, in 50 mL of a mixture of acetic anhydride and glacial acetic acid (7:3), and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using a glass electrode and a silver-silver chloride electrode containing saturated lithium perchlorate and saturated silver chloride in glacial acetic acid (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 22.39 mg of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$.~~

■*Mobile phase*—Prepare a filtered and degassed mixture of acetonitrile and 0.12 N sulfuric acid (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Hydroxyzine Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.3 mg per mL.

Resolution solution—Dissolve suitable quantities of USP Hydroxyzine Hydrochloride RS and USP Hydroxyzine Related Compound A RS in *Mobile phase* to obtain a solution containing 3.6 µg of each per mL.

Stock assay preparation—Transfer an accurately weighed quantity of Hydroxyzine Hydrochloride to a suitable volumetric flask, dissolve in and dilute with *Mobile phase* to volume to obtain a solution containing a known concentration of about 0.6 mg of Hydroxyzine Hydrochloride per mL, and mix.

Assay preparation—Quantitatively dilute the *Stock assay preparation* with *Mobile phase* to obtain a final known concentration of about 0.3 mg per mL of Hydroxyzine Hydrochloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L3. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution* and the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between hydroxyzine related compound A and hydroxyzine is not less than 1.5; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%. [NOTE—For identification purposes, the relative retention times are about 0.9 for hydroxyzine related compound A and 1.0 for hydroxyzine.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms for a total time of not less than 1.8 times the retention time of the

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hydroxyzine peak, and measure the response for the main hydroxyzine peak in the chromatograms. Calculate the percentage of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$, in the portion of Hydroxyzine Hydrochloride taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Hydroxyzine Hydrochloride RS in the *Standard preparation;* C_U is the concentration, in mg per mL, of Hydroxyzine Hydrochloride in the *Assay preparation;* and r_U and r_S are the peak responses of hydroxyzine in the chromatograms obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

BRIEFING

Lovastatin Tablets, *USP 29* page 1282. It is proposed to update *Identification* test *A* to reflect all tablet strengths. Under *Dissolution,* a new HPLC method featuring a shorter column and thus a reduced run time is being proposed. This method is based on analyses performed with the Apex ODS brand of L1 column. The typical retention time is about 1.5 minutes. Several changes and corrections are also proposed in the *Assay.* The HPLC method in the *Assay* is based on analyses performed with the Hypersil ODS brand of L1 column. The typical retention time is about 7 to 8 minutes.

(MD-GRE: E. Gonikberg) RTS—C44264

Change to read:

Identification—

A: ~~Transfer 1 Tablet to a centrifuge tube, add 1 mL of water and 4.0 mL of acetonitrile, and shake by mechanical means to disintegrate the Tablet. Sonicate for 4 minutes, and centrifuge for 4 minutes to obtain the test solution. Apply separately 5 µL each of the Standard solution and the test solution to the chromatographic plate, and proceed as directed under *Thin-layer Chromatographic Identification Test* ⟨201⟩ using a prepared mixture of cyclohexane, chloroform, and isopropyl alcohol (5 : 2 : 1) as the developing solvent.~~

■*Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution:

FOR TABLETS CONTAINING 10 MG OF LOVASTATIN—Transfer 1 Tablet to a centrifuge tube, add 0.4 mL of water and 1.6 mL of acetonitrile. Mix on a vortex mixer until the tablet disintegrates, and sonicate for 4 minutes. Centrifuge for 4 minutes, and use clear supernatant.

FOR TABLETS CONTAINING 20 MG OR 40 MG OF LOVASTATIN—Transfer 1 Tablet to a centrifuge tube, add 1 mL of water and 4.0 mL of acetonitrile. Mix on a vortex mixer until the tablet disintegrates, and sonicate for 4 minutes. Centrifuge for 4 minutes, and use clear supernatant.

Standard solution—Prepare a solution of USP Lovastatin RS in acetonitrile containing 8 mg per mL.

Application volume: 5 µL of the *Test solution,* 3 µL of the *Standard solution* for 10-mg and 20-mg Tablets, 5 µL of the *Standard solution* for 40-mg Tablets.

Developing solvent solution: a mixture of cyclohexane, chloroform, and isopropyl alcohol (5 : 2 : 1).■2S (*USP30*)

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Change to read:

Dissolution ⟨711⟩—

~~*Buffer solution*~~

■*Medium*■2S (*USP30*)—Dissolve 1.38 g of monobasic sodium phosphate and 20 g of sodium ~~dodecyl~~ ■lauryl■2S (*USP30*) sulfate in 900 mL of water. Adjust with 1 N sodium hydroxide to a pH of 7.0, dilute with water to 1000 mL, and mix; ■900 mL.■2S (*USP30*)

~~*Medium:* Buffer solution; 900 mL.~~

■■2S (*USP30*)

Apparatus 2: 50 rpm.

Time: 30 minutes.

■*Mobile phase*—Proceed as directed in the *Assay.*

Standard solution—Accurately weigh approximately 44 mg of USP Lovastatin RS into a 500-mL volumetric flask, and dissolve in no more than 20 mL of methanol. Dilute with *Medium* to volume, and mix well. Further dilute this solution with *Medium* to obtain a solution containing *L*/900 mg per mL, with *L* being the tablet label claim, in mg.

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Test solution—Pass the solution under test through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 5-cm column that contains 5-µm packing L1. The flow rate is about 2.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is greater than 2.0; the tailing factor is less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.■2S (*USP30*)

Procedure— ~~Determine the amount of Lovastatin dissolved using the method given under *Assay*, making any necessary volumetric adjustments.~~

■Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of lovastatin dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is concentration, in mg per mL, of the *Standard solution;* 900 is the volume, in mL, of *Medium;* and *LC* is the tablet label claim, in mg.■2S (*USP30*)

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{36}O_5$ is dissolved in 30 minutes.

Change to read:

Assay—

Buffer solution—Dissolve 3.45 g of monobasic sodium phosphate in 900 mL of water, adjust with phosphoric acid to a pH of 4.0, dilute with water to 1000 mL, and mix.

Dissolving solvent—Add 3.0 mL of glacial acetic acid to 900 mL of water contained in a 1 L beaker, adjust to a pH of 4.0, determined electrometrically, by the addition of a solution of sodium hydroxide (20%), and mix. Transfer the contents of the beaker to a 1000-mL volumetric flask, dilute with water to volume, and mix. Prepare a mixture of acetonitrile and the resultant solution (80 : 20).

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, *Buffer solution,* and methanol (5 : 3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Lovastatin RS in *Dissolving solvent* to obtain a solution having a known concentration of about 40 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg of lovastatin, to a 200-mL volumetric flask. Add about 150 mL of *Dissolving solvent*, and sonicate for 20 minutes. ~~Cool, dilute with *Dissolving solvent* to volume, and mix. Transfer 20.0 mL to a 100-mL volumetric flask, dilute with *Dissolving solvent* to volume, and mix. Centrifuge a portion of this solution.~~

■Cool to room temperature, and allow the solution to stand for 30 minutes. Dilute with *Dissolving solvent* to volume, and mix. Centrifuge a portion of this solution, transfer 5.0 mL of a clear supernatant to a 25-mL volumetric flask, dilute with *Dissolving solvent* to volume, and mix.■2S (*USP30*)

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a ~~4.5-mm~~

■4.6-mm■2S (*USP30*)
× 25-cm column that contains packing L1 and is maintained at 45°. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is ~~not less~~

■greater■2S (*USP30*)
than 3000 theoretical plates, ~~the capacity factor, k', is not less than 3.5,~~

■■2S (*USP30*)
the tailing factor is ~~not greater~~

■less■2S (*USP30*)
than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the ~~quantity, in mg,~~

■percentage of the labeled amount■2S (*USP30*)
of $C_{24}H_{36}O_5$ in the portion of Tablets taken by the formula:

~~$C(r_U/r_S)$~~

$$■100(C_S/C_U)(r_U/r_S)■2S\ (USP30)$$

in which ~~C~~

■C_S■2S (*USP30*)
is the concentration, in µg per mL, of USP Lovastatin RS in the *Standard preparation;*

■C_U is the concentration of lovastatin, in µg per mL, in the *Assay preparation,* based on the label claim;■2S (*USP30*)
and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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BRIEFING

Meloxicam Tablets. Because there is no *USP* monograph for this dosage form, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with a Kromasil C18 brand of L1 column. The typical retention time for meloxicam is about 4.0 minutes.

(MD-CCA: C. Anthony) RTS—C41830

Add the following:

■Meloxicam Tablets

» Meloxicam Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of meloxicam ($C_{14}H_{13}N_3O_4S_2$).

Packaging and storage—Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Meloxicam RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

0.1 N Methanolic sodium hydroxide—Dilute 100 mL of 1 N sodium hydroxide with methanol to 1000 mL.

Test solution—Transfer a portion of finely powdered Tablets, equivalent to about 50 mg of meloxicam, to a suitable flask. Add 5 mL of *0.1 N Methanolic sodium hydroxide,* and mix. Add 20 mL of methanol, and stir for about 15 minutes. Filter the mixture to remove insoluble material, and use the filtrate.

Standard solution—Transfer about 20 mg of USP Meloxicam RS, accurately weighed, to a 10-mL volumetric flask, dissolve in 2 mL of *0.1 N Methanolic sodium hydroxide,* dilute with methanol to volume, and mix.

Developing solvent system—Prepare a mixture of chloroform, methanol, and ammonia water (25%) (80 : 20 : 1).

Procedure—Proceed as directed in the chapter.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩**:** [To come.]

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Solution A, Solution B, and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution—Use the *Standard preparation* from the *Assay.*

System sensitivity solution—Transfer 4 mL of the *Standard solution* to a 100-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 5 mL of the resulting solution to a 50-mL volumetric flask, add 5 mL of 1 N sodium hydroxide, and dilute with methanol to volume.

Test solution—Use the *Assay preparation* from the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to chromatograph the *Standard solution* and the *System sensitivity solution:* the tailing factor for the meloxicam peak is not more than 2.0; the relative standard deviation for replicate injections of the *Standard solution* is not more than 2.0%; and the signal-to-noise ratio of the meloxicam peak in the chromatogram of the *System sensitivity solution* is not less than 10.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Determine the relative retention times for the impurity peaks relative to that of the meloxicam peak. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$(5000/3)(1/F)(C/W)(A/L)(r_i/r_S)$$

in which F is the relative response factor for each impurity and is equal to 2.7 for the impurity with a relative retention time of about 0.5 (meloxicam related compound B [2-amino-

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5-methylthiazole]) and 1.0 for all other impurities; *C* is the concentration, in mg per mL, of USP Meloxicam RS in the *Standard solution; W* is the weight, in mg, of powdered Tablets taken to prepare the *Test solution; A* is the average weight of a Tablet; *L* is the labeled amount, in mg, of meloxicam in each Tablet; r_i is the peak response obtained for each impurity in the *Test solution;* and r_S is the peak response for meloxicam in the *Standard solution:* not more than 0.15% of meloxicam related compound B is found; not more than 0.2% of any individual unknown impurity is found; and not more than 0.5% of total impurities is found.

Assay—

Solution A—Dissolve 2.0 g of dibasic ammonium phosphate in 1 L of water, and adjust with phosphoric acid to a pH of 7.0 ± 0.1.

Solution B—Mix 650 mL of methanol and 100 mL of isopropyl alcohol.

Mobile phase—Prepare a filtered and degassed mixture of *Solution A* and *Solution B* (63 : 37). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—[NOTE—The *Standard stock preparation* is prepared so that the final concentration of meloxicam, in mg per mL, is approximately equivalent to the concentration of the *Assay stock preparation.*] Transfer a suitable quantity of USP Meloxicam RS, accurately weighed, to a 50-mL volumetric flask, dissolve in 1 mL of 1 N sodium hydroxide and 30 mL of methanol, and dilute with methanol to volume. Transfer 10 mL of the resulting solution to a 100-mL volumetric flask, add 10 mL of 1 N sodium hydroxide, and dilute with methanol to volume.

Standard preparation—Transfer 15 mL of the *Standard stock preparation* to a 25-mL volumetric flask, and dilute with water to volume.

Assay stock preparation—Transfer 10 Tablets to a 1000-mL volumetric flask, add about 100 mL of 1 N sodium hydroxide, shake to disperse the Tablets, and add 800 mL of methanol. Sonicate the solution for about 15 minutes, then stir for 30 minutes. Dilute with methanol to volume, and mix. Filter the resulting solution, and use the filtrate.

Assay preparation—Transfer 15 mL of the *Assay stock preparation* to a 25-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector, a guard column that contains packing L1, and a 4-mm × 10-cm column that contains packing L1. The flow rate is about 0.8 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the meloxicam peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* to the chromatograph, record the chromatograms, and measure the responses for the meloxicam peak. Calculate the quantity, in mg, of meloxicam ($C_{14}H_{13}N_3O_4S_2$) in the portion of Tablets taken by the formula:

$$5000(C/3)(r_U/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Meloxicam RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP30*)

In-Process Revision

BRIEFING

Naratriptan Hydrochloride, *USP 29* page 1487. It is proposed to rename the *Resolution solution* in the *Assay* to *System suitability preparation* to eliminate confusion between its use and preparation in the *Chromatographic purity* test and in the *Assay.* It is also proposed to revise the *System suitability preparation* in the *Assay* to reflect the true nature of the USP Naratriptan Resolution Mixture RS, which is a mixture of naratriptan, naratriptan related compound A, and naratriptan related compound B; and to increase the concentration of the *System suitability preparation* to enhance the ability to see the peaks due to both naratriptan related compounds A and B.

(MD-PP: R. Ravichandran) RTS—C46788

Change to read:

Assay—

0.01 M Triethylamine phosphate buffer—Dilute 0.6 mL of phosphoric acid with water to 900 mL, and adjust with triethylamine to a pH of 2.5.

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Triethylamine phosphate buffer* and isopropyl alcohol (9 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Resolution solution*—Dissolve accurately weighed quantities of USP Naratriptan Hydrochloride RS and USP Naratriptan Resolution Mixture RS in *Mobile phase* to obtain a solution having known concentrations of about 0.11 mg per mL and 0.11 µg per mL, respectively.~~

■*System suitability preparation*—Dissolve an accurately weighed quantity of USP Naratriptan Resolution Mixture RS in *Mobile phase* to obtain a solution having a concentration of about 0.7 mg per mL.■2S (*USP30*)

Standard preparation—Dissolve an accurately weighed quantity of USP Naratriptan Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.11 mg per mL.

Assay preparation—Transfer about 11 mg of Naratriptan Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 282-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L11. The column temperature is maintained at 35°. The flow rate is about 1.5 mL per minute. Chromatograph the ~~*Resolution solution,*~~

■*System suitability preparation,*■2S (*USP30*) and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.9 for 3-(1-methylpiperidin-4-yl)-1*H*-indole (naratriptan related compound A), 1.0 for naratriptan, and 1.1 for naratriptan related compound B; and~~

■■2S (*USP30*) the resolution, *R,* between naratriptan related compound A and naraptriptan and between naratriptan related compound B and naratriptan is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

■[NOTE—For identification purposes, the approximate relative retention times are about 0.9 for naratriptan related compound A, 1.0 for naratriptan, and 1.1 for naratriptan related compound B.]■2S (*USP30*)

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{17}H_{25}N_3O_2S \cdot HCl$ in the portion of Naratriptan Hydrochloride taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Naratriptan Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Nefazodone Hydrochloride, page 3733 of the *Second Supplement* and the *Fifth Interim Revision Announcement* in this number of *PF.* In the newly implemented test for *Related compounds,* it is proposed to combine the currently required two different stock solutions of nefazodone related compound A and nefazodone related compound B into one solution, *Impurities stock solution,* and to specify the final concentration of the components in this solution. Because of this proposed revision, the *Resolution solution* and the *Standard solution* used in the *Related compounds* test now reflect the final concentration.

(MD-PP: R. Ravichandran) RTS—C47315

Add the following:

•**Related compounds—**

Diluent—Prepare a solution of water and acetonitrile (50 : 50).

Solution A—Dissolve 0.77 g of ammonium acetate in about 950 mL of water. Adjust with triethylamine to a pH of 7.10 ± 0.05. Dilute with water to 1 L. Filter and degas.

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed amount of USP Nefazodone Hydrochloride RS in *Diluent* to obtain a solution containing 0.1 mg per mL of nefazodone hydrochloride.

~~*Nefazodone related compound A stock solution* and *Nefazodone related compound B stock solution*—Transfer about 20 mg of each USP Nefazodone Related Compound A RS and USP Nefazodone Related Compound B RS, accurately weighed, into separate 200-mL volumetric flasks. Dissolve in and dilute with *Diluent* to volume.~~

■*Impurities stock solution*—Dissolve accurately weighed quantities of USP Nefazodone Related Compound A RS and USP Nefazodone Related Compound B RS in *Diluent* to obtain a final solution having a known concentration of about 0.1 mg per mL of each compound.■2S (*USP30*)

Resolution solution—~~Pipet 5.0 mL of *Nefazodone related compound A stock solution* and 5.0 mL of *Nefazodone related compound B stock solution* into a 100-mL volumetric flask. Dilute with *Standard stock solution* to volume, and mix. This solution contains about 90 µg per mL of nefazodone hydrochloride, and about 5 µg per mL each of nefazodone related compound A and B.~~

In-Process Revision

■Dilute a suitable volume of the *Impurities stock solution* with the *Standard stock solution* to obtain a solution having a concentration of about 5 µg per mL each of nefazodone related compounds A and B.■2S (*USP30*)

Standard solution—~~Pipet 2.0 mL each of the *Standard stock solution, Nefazodone related compound A stock solution,* and *Nefazodone related compound B stock solution* into a 200-mL volumetric flask. Dilute with *Diluent* to volume, and mix well to obtain a final concentration of 1 µg per mL each of nefazodone hydrochloride, nefazodone related compound A, and nefazodone related compound B.~~

■Dilute accurately measured volumes of the *Impurities stock solution* and the *Standard stock solution* quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1 µg per mL each of nefazodone hydrochloride, nefazodone related compound A, and nefazodone related compound B.■2S (*USP30*)

Test solution—Transfer about 100 mg of Nefazodone Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 250-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.7 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	50	50	equilbration
0–10	50→45	50→55	linear gradient
10–16	45→35	55→65	linear gradient
16–25	35	65	isocratic
25–26	35→50	65→50	linear gradient
26–35	50	50	re-equilbration

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between nefazodone related compound A and nefazodone hydrochloride is not less than 4.0 and is not less than 1.5 between nefazodone hydrochloride and nefazodone related compound B. Chromatograph the *Standard solution,* and measure the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0% for nefazodone related compound A and nefazodone related compound B. [NOTE—For identification purposes, the relative retention times are about 1.2 for nefazodone related compound A, 1.0 for nefazodone hydrochloride, and 0.94 for nefazodone related compound B.]

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each nefazodone related compound in the portion of Nefazodone Hydrochloride taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of the relevant USP Reference Standard in the *Standard solution;* C_T is the concentration of Nefazodone Hydrochloride, in mg per mL, in the *Test solution;* and r_U and r_S are the peak areas of the corresponding nefazodone related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.2% of nefazodone related compound A is found; not more than 0.2% of nefazodone related compound B is found; not more than 0.1% of any unknown impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Use the peak area for nefazodone hydrochloride in the *Standard solution* as r_S to calculate any unknown impurity.]●5

BRIEFING

Ondansetron Orally Disintegrating Tablets, page 3736 of the *Second Supplement.* It is proposed to make a correction in the formula used to calculate the amount of drug dissolved in the *Dissolution* test.

(BPC: M. Marques) RTS— C40143; C41613; C44228

Change to read:

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 500 mL, deaerated.
Apparatus 2: 50 rpm.
Time: 10 minutes.

Standard solution—Accurately weigh an amount of USP Ondansetron RS, and dilute with *Medium* to obtain a solution having a final concentration of 0.01 mg per mL for Tablets labeled to contain 4 mg, and a final concentration of 0.02 mg per mL for Tablets labeled to contain 8 mg.

Test solution—Pass a portion of the solution under test through a filter.

Procedure—Determine the amount of $C_{18}H_{19}N_3O$ dissolved by UV absorption at the wavelength of maximum absorbance at about 310 nm on portions of the *Test solution* in comparison with the *Standard solution,* using a 1-cm cell. Calculate the amount, in percentage, of ondansetron released by the formula:

$$\cancel{\frac{A_U \times W_S \times 500 \times MW_1 \times P \times 100}{A_S \times D \times L \times MW_2}}$$

■$$\frac{A_U \times W_S \times 500 \times P \times 100}{A_S \times D \times L}$$■2S (*USP30*)

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; W_S is the weight, in mg, of USP Ondansetron RS taken; 500 is the volume, in mL, of *Medium;* ~~*MW_1,* is the molecular weight of ondansetron (293.4); *P* is the purity, expressed in decimal, of USP Ondansetron RS;~~

■■2S (*USP30*)
100 is the conversion factor to percentage; *D* is the dilution factor of the *Standard solution;*

■and■2S (*USP30*)
L is the Tablet label claim, in mg. ~~and *MW_2* is the molecular weight of ondansetron hydrochloride dihydrate (365.9).~~

■■2S (*USP30*)
Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{18}H_{19}N_3O$ is dissolved in 10 minutes.

In-Process Revision

BRIEFING

Oxandrolone Tablets, *USP 29* page 1592 and page 3573 of the *First Supplement*. In *Dissolution Test 1* it is proposed to add instructions on how to prepare the *Working standard solution* according to the tablet label claim. In *Dissolution Test 2* it is proposed to correct the type of detector and to specify the temperatures of the column and the detector.

(BPC: M. Marques) RTS—C44276

Change to read:

Dissolution ⟨711⟩—

■TEST 1—■1S (*USP29*)

Medium: a solution of water and isopropanol (7 : 3); 500 mL.

Apparatus 2: 100 rpm.

Time: 60 minutes.

Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Internal standard solution—Dissolve accurately weighed quantities of 17α-methyltestosterone, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.2 mg per mL (for Tablets with a 2.5-mg label claim) and about 0.8 mg per mL (for Tablets with a 10-mg label claim).

Standard solution—Dissolve an accurately weighed quantity of USP Oxandrolone RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 1 mg per mL.

Working standard solution—~~Combine 100 µL of the *Standard solution,* 400 µL of the *Internal standard solution,* and 1500 µL of acetonitrile.~~

■For Tablets labeled to contain 2.5 mg: combine 100 µL of the *Standard solution,* 400 µL of the *Internal standard solution,* and 1500 µL of acetonitrile. For Tablets labeled to contain 10 mg: combine 100 µL of the *Standard solution,* 100 µL of the *Internal standard solution,* and 1800 µL of acetonitrile.■2S (*USP30*)

Test solution—Withdraw 25 mL of the solution under test from the vessel. Pass through a 0.45-µm polytef filter. Transfer 20 mL of the filtrate to a separatory funnel, add 400 µL of the *Internal standard solution,* 40 mL of a 10% potassium chloride solution, and 8 mL of chloroform. In separate separatory funnels, prepare an extraction blank and an internal standard blank in a similar manner using 20 mL of filtered *Medium* in place of the solution under test and excluding the *Internal standard solution* from the extraction blank. Shake each funnel, and allow the layers to separate. Collect the lower chloroform layer. Repeat the extraction procedure one more time. Evaporate the solvents under a stream of nitrogen at 45° until just dry. Reconstitute the dried residue with 2 mL of acetonitrile (for Tablets with a 2.5-mg label claim) or with 8 mL of acetonitrile (for Tablets with a 10-mg label claim), and sonicate for 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m column coated with a 0.5-µm phase G27. The carrier gas is helium, flowing at a rate of about 16.8 mL per minute. The injection port and detector temperatures are maintained at 190° and 320°, respectively. The chromatograph is programmed as follows. Upon injection, the column temperature is increased at a rate of 25° per minute to 280°, and maintained at 280° for 3 minutes. Then the column temperature is increased at a rate of 10° per minute to 320°, and maintained at 320° for 3 minutes. Chromatograph the acetonitrile, the extraction blank, and the internal standard blank, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5. Make two injections of the *Working standard solution,* and record the peak responses. The average oxandrolone/*Internal standard solution* peak area percent comparison is between 98.0% and 102.0%. The resolution, *R,* between the oxandrolone peak and the nearest eluting peak is equal to or greater than 1.5.

Procedure—Separately inject equal volumes (0.5 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{19}H_{30}O_3$ released by the formula:

$$\frac{C_S \times \text{sample ratio} \times V_{UF} \times 500 \times 100}{\text{Standard ratio} \times V_{UI} \times LC}$$

in which C_S is the concentration, in mg per mL, of oxandrolone in the *Standard solution;* sample ratio is the area ratio of oxandrolone to 17α-methyltestosterone in the sample injection for each *Test solution;* V_{UF} is the final volume, in mL, of the sample after reconstitution of the dry residue; 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; standard ratio is the mean area ratio of oxandrolone to 17α-methyltestosterone in all injections of the *Standard solution;* V_{UI} is the initial sample volume, in mL, used in the extraction; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of oxandrolone ($C_{19}H_{30}O_3$) is dissolved in 60 minutes.

■TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 1% polysorbate 80 in water; 500 mL, deaerated.

Apparatus 2: 100 rpm.

Time: 120 minutes.

Determine the amount of $C_{19}H_{30}O_3$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (55 : 45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 20 mg of USP Oxandrolone RS, accurately weighed, to a 200-mL volumetric flask. Add about 20 mL of acetonitrile, and sonicate to dissolve. Dilute with *Medium* to volume, and mix.

Working standard solution—Quantitatively dilute the *Standard stock solution* with *Medium* to obtain a solution having a final concentration of about 5 µg per mL for Tablets with a label claim of 2.5 mg, or a final concentration of about 20 µg per mL for Tablets with a label claim of 10 mg.

Test solution—Withdraw about 10 mL of the solution under test from the vessel. Centrifuge in a glass tube at 2000 rpm for 10 minutes.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~reflective~~ ■refractive■2S (*USP30*) index detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1.

■The column is maintained at 30°, and the detector is maintained at 50°.■2S (*USP30*)

The flow rate is about 1.5 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the column efficiency is not less than 4000 theoretical plates; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{19}H_{30}O_3$ released by the formula:

$$\frac{r_U \times C_S \times D \times 500 \times 100}{r_S \times LC}$$

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in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Working standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution; D* is the dilution factor of the *Test solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim, in mg.

Tolerances—Not less than 65% *(Q)* of the labeled amount of $C_{19}H_{30}O_3$ is dissolved in 120 minutes.■1S (*USP29*)

BRIEFING

Pamidronate Disodium for Injection, page 3739 of the *Second Supplement.* In the *Packaging and storage* section, it is proposed to delete the reference to Type III glass. It is also proposed to correct the limit in the test for *Bacterial endotoxins*. The revised limit is based on the maximum single dosage for the Pamidronate Disodium Injection.

(MD-GRE: E. Gonikberg; MSA: R. Tirumalai) RTS—C46748; C46749

Change to read:

Packaging and storage—Preserve in *Containers for Sterile Solids,* as described under *Injections* ⟨1⟩. ~~, preferably of Type III glass.~~

■■2S (*USP30*)
Store at controlled room temperature.

Change to read:

Bacterial endotoxins ⟨85⟩—It contains not more than ~~2~~

■3.88■2S (*USP30*)
USP Endotoxin Units per mg of anhydrous pamidronate disodium.

BRIEFING

Pyrantel Pamoate, *USP 29* page 1864. In the test for *Limit of iron,* the *Test Preparation* is provided in the monograph; however, the method procedure and the *Standard Preparation* are not specified. Because this test is based on the general chapter *Iron* ⟨241⟩, it is proposed to clarify the procedure by cross referencing the test to the general chapter.

(MD-AA: B. Davani) RTS—C44729

Change to read:

Limit of iron

■⟨241⟩■2S (*USP30*)
—To the residue obtained in the test for *Residue on ignition* add 3 mL of hydrochloric acid and 2 mL of nitric acid, and evaporate on a steam bath to dryness. Dissolve the residue in 2 mL of hydrochloric acid with the aid of gentle heat. Add 18 mL of hydrochloric acid, dilute with water to 50 mL, and mix. Dilute 5 mL of this solution with water to 47 mL: the limit is 0.0075%.

BRIEFING

Sodium Bicarbonate, *USP 29* page 1970 and page 3581 of the *First Supplement*. It is proposed to address the following comments:

1. In the test for *Normal carbonate,* a solubility problem is still encountered when the test is performed without agitation, even after the temperature has been changed from 5° to 15°. It is proposed to allow a "very gentle swirling" in order to get the material into solution. This is consistent with the current industry practice and with the monograph for Sodium Bicarbonate in the *Japanese Pharmacopoeia,* XIV Edition.
2. In the test for *Limit of ammonia,* the procedure does not allow to calculate or verify the percentage of ammonia in the sample. It is proposed to delete the numeric limit in the test and merely state that the material meets the requirement of this test if no blue color develops.

(MD-GRE: E. Gonikberg) RTS—C46744

Change to read:

Normal carbonate—Add 2.0 mL of 0.10 N hydrochloric acid and 2 drops of phenolphthalein TS to 1.0 g of Sodium Bicarbonate, previously dissolved ~~without agitation~~

■with very gentle swirling■2S (*USP30*)
in 20 mL of water at a temperature not exceeding ■15°:■1S (*USP29*) the solution does not assume more than a faint pink color immediately.

Change to read:

Limit of ammonia—

■*Sodium hypochlorite solution*—Use a commercially available solution that contains 4.0% to 6.0% of sodium hypochlorite.

Oxidizing solution—[NOTE—Prepare on the day of use.] Prepare a mixture of alkaline sodium citrate TS and *Sodium hypochlorite solution* (4 : 1).

Diluted sodium nitroferricyanide solution—Prepare a mixture of water and sodium nitroferricyanide TS (10 : 1).

Test solution—Transfer 2.5 g of Sodium Bicarbonate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Procedure—[NOTE—Carefully follow the order of addition stated below.] To 4.0 mL of the *Test solution,* add 0.4 mL of phenol TS, 0.4 mL of *Diluted sodium nitroferricyanide solution,* and 1.0 mL of *Oxidizing solution*. Dilute with water to 10 mL, mix, and allow to stand for 1 hour: no blue color develops. ~~(0.002%).~~

■■2S (*USP30*)
■1S (*USP29*)

BRIEFING

Sodium Fluoride, *USP 29* page 1980. It is proposed to replace the current fluoride-selective electrode procedure in the *Assay* with a simple titration procedure employed in the monograph for Sodium Fluoride in *European Pharmacopoeia* 5.5. The proposed method provides more reproducible assay results, and is also simpler and more time-efficient to perform.

(MD-GRE: E. Gonikberg) RTS—C46326

Change to read:

Assay—~~[NOTE—Store all solutions, except the *Buffer solution*, in plastic containers.]~~

~~*Buffer solution* and *Standard preparations*—Prepare as directed in the *Assay* under *Sodium Fluoride Oral Solution*.~~

~~*Assay preparation*—Transfer about 100 mg of Sodium Fluoride, accurately weighed, to a 250-mL volumetric flask. Add 50 mL of water, mix for 5 minutes, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with water to volume, and mix.~~

~~*Procedure*—Proceed as directed for *Procedure* in the *Assay* under *Sodium Fluoride Oral Solution*. Calculate the quantity, in mg, of NaF in the portion of Sodium Fluoride taken by the formula:~~

~~$(41.99/18.998)(1.25C)$,~~

~~in which 41.99 is the molecular weight of sodium fluoride; 18.998 is the atomic weight of fluorine; and *C* is the determined concentration of fluoride, in µg per mL, in the *Assay preparation*.~~

■To 80.0 mg of Sodium Fluoride add a mixture of 5 mL of acetic anhydride and 20 mL of glacial acetic acid, and heat to dissolve. Allow to cool, and add 20 mL of dioxane. Add 1 drop of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a green endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 4.199 mg of NaF.■2S (*USP30*)

BRIEFING

Sodium Fluoride Oral Solution, *USP 29* page 1981. It is proposed to clarify that a suitable reference electrode could be used in the *Assay* procedure.

(MD-GRE: E. Gonikberg) RTS—C46845

Change to read:

Assay—[NOTE—Store all solutions, except the *Buffer solution,* in plastic containers.]

Buffer solution—Dissolve 57 mL of glacial acetic acid, 58 g of sodium chloride, and 4 g of (1,2-cyclohexylenedinitrilo)tetraacetic acid in 500 mL of water. Adjust with 5 N sodium hydroxide to a pH of 5.25 ± 0.25, dilute with water to 1000 mL, and mix.

Standard preparations—Quantitatively dissolve an accurately weighed quantity of USP Sodium Fluoride RS in water to obtain a solution containing 420 µg per mL. Each mL of this solution (*Standard preparation A*) contains 190 µg of fluoride ion (10^{-2} M). Transfer 25.0 mL of *Standard preparation A* to a 250-mL volumetric flask, dilute with water to volume, and mix. This solution (*Standard preparation B*) contains 19 µg of fluoride ion per mL (10^{-3} M). Transfer 25.0 mL of *Standard preparation B* to a 250-mL volumetric flask, dilute with water to volume, and mix. This solution (*Standard preparation C*) contains 1.9 µg of fluoride ion per mL (10^{-4} M).

Assay preparation—Transfer an accurately measured volume of Oral Solution, equivalent to about 10 mg of fluoride, to a 500-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Pipet 20 mL of each *Standard preparation* and of the *Assay preparation* into separate plastic beakers each containing a plastic-coated stirring bar. Pipet 20 mL of *Buffer solution* into each beaker. Concomitantly measure the potentials (see *pH* ⟨791⟩), in mV, of the solutions from the *Standard preparations* and of the solution from the *Assay preparation,* with a pH meter capable of a minimum reproducibility of ±0.2 mV and equipped with a fluoride-specific ion-indicating electrode and a ~~calomel~~

■suitable■2S (*USP30*) reference electrode. [NOTE—When taking measurements, immerse the electrodes in the solution, stir on a magnetic stirrer having an insulated top until equilibrium is attained (1 to 2 minutes), and record the potential. Rinse and dry the electrodes between measurements, taking care to avoid damaging the crystal of the specific-ion electrode.] Plot the logarithms of the fluoride-ion concentrations, in µg per mL, of the *Standard preparations* versus potential, in mV. From the measured potential of the *Assay preparation* and the standard response line, determine the concentration, *C,* in µg per mL, of fluoride ion in the *Assay preparation*. Calculate the quantity, in mg, of fluoride ion in each mL of the Oral Solution taken by the formula:

$$0.5(C/V)$$

in which *C* is the determined concentration of fluoride, in µg per mL, in the *Assay preparation;* and *V* is the volume, in mL, of Oral Solution taken. Multiply the quantity of fluoride ion by 2.21 to obtain the quantity of NaF.

In-Process Revision

BRIEFING

Streptomycin Sulfate, *USP 29* page 2008. It is proposed to correct the HPLC column designation in the *Assay* test.

(HDQ: M. Marques) RTS—C44411

Change to read:

Assay—

Mobile phase—Use 70 mM sodium hydroxide. During use, store in a plastic bottle flushed with a blanket of helium above the liquid surface. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Streptomycin Sulfate RS in water, and quantitatively dilute with water to obtain a solution having a known concentration of about 0.03 mg per mL. Sonicate for 1 minute, and mix.

Assay preparation—Transfer about 30 mg of Streptomycin Sulfate, accurately weighed, to a 100-mL volumetric flask, dilute with water to volume, sonicate for 1 minute, and mix. Transfer 10.0 mL of this solution to a second 100-mL volumetric flask, dilute with water to volume, and mix.

System suitability solution—Heat about 10 mL of the *Standard preparation* at 75° for 1 hour. Allow to cool.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with an electrochemical detector, a gold working electrode, a pH silver–silver chloride reference electrode, a 4-mm × 5-cm guard column that contains packing ~~L48~~ ■L46,■2S (*USP30*) and a 4-mm × 25-cm analytical column that contains packing ~~L48.~~ ■L46.■2S (*USP30*) The electrochemical detector is used in the integrated amperometric mode with a range of 300 nC, an output of 1 V full scale, and a rise time of 0.5 second, positive polarity. The potential is programmed as follows.

Step	Time (seconds)	Potential (V)	Integration
1	0.00	+0.1	
2	0.20	+0.1	begins
3	0.40	+0.1	ends
4	0.41	–2.0	
5	0.42	–2.0	
6	0.43	+0.6	
7	0.44	–0.1	
8	0.50	–0.1	

The flow rate is about 0.5 mL per minute. Chromatograph the *System suitability solution*, and measure the peak areas as directed for *Procedure:* the relative retention times are about 0.5 for the main degradation product and 1.0 for streptomycin; and the resolution, *R,* between the two peaks is not less than 3. Chromatograph the *Standard preparation,* and measure the peak areas as directed for *Procedure:* the tailing factor is not more than 2; the column efficiency is not less than 1000 theoretical plates; and the relative standard deviation for replicate injections is not more than 5%. [NOTE—If variation of retention time or increase of tailing occurs, clean the columns with 0.2 M sodium hydroxide. Carefully maintain the working and reference electrodes.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in µg, of streptomycin ($C_{21}H_{39}N_7O_{12}$) in each mg of Streptomycin Sulfate taken by the formula:

$$1000(CP/W_U)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Streptomycin Sulfate RS in the *Standard preparation; P* is the designated streptomycin content, in µg per mg, of streptomycin ($C_{21}H_{39}N_7O_{12}$) in USP Streptomycin Sulfate RS; W_U is the weight, in mg, of Streptomycin Sulfate taken to prepare the *Assay preparation;* and r_U and r_S are the streptomycin peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Thalidomide, *USP 29* page 2106 and page 146 of *PF* 32(1) [Jan.–Feb. 2005]. On the basis of comments received, it is proposed to revise the test for *Microbial limits* by removing the requirement for the absence of *Escherichia coli* and placing it in the monograph *Thalidomide Capsules,* proposed revisions for which appear in *In-Process Revision* in this issue.

(MD-OOD: F. Mao; MSA: R. Tirumalai) RTS—C45469

Change to read:

Microbial limits ⟨61⟩~~— meets the requirements.~~

■The total aerobic microbial count using the *Plate Method* is not more than 1000 cfu per g, and the total combined molds and yeasts count is not more than 100 cfu per g. ~~It meets the requirements of the tests for absence of *Escherichia coli.*~~■2S (*USP30*)

Change to read:

Chromatographic purity—

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (95 : 5 : 0.1).

Solution B—Prepare a filtered and degassed mixture of water, acetonitrile, and phosphoric acid (85 : 15 : 0.1).

Diluent—Prepare a mixture of water, acetonitrile, and phosphoric acid (50 : 50 : 0.1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Phthalic acid stock solution—Transfer about 100 mg of phthalic acid to a 100-mL volumetric flask, dissolve in a mixture of acetonitrile and water (80 : 5), and dilute with acetonitrile to volume. Mix, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a concentration of about 0.1 mg per mL.

Standard stock solution—Dissolve, with the aid of sonication, an accurately weighed quantity of USP Thalidomide RS in acetonitrile to obtain a solution having a known concentration of about 1 mg per mL.

Standard solution—Pipet 2.0 mL of *Standard stock solution* and 2.0 mL of *Phthalic acid stock solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, add 10.0 mL of phosphoric acid solution (1 in 100), dilute with water to volume, and mix to obtain a solution having a known concentration of about 0.0002 mg of phthalic acid per mL.

Test solution—Transfer about 100 mg of Thalidomide, accurately weighed, to a 50-mL volumetric flask, and dissolve, with the aid of sonication, in 40 mL of a mixture of water, acetonitrile, and phosphoric acid (50 : 50 : 0.1). Dilute with *Diluent* to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, add 10.0 mL of phosphoric acid solution (1 in 100), dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 3.9-mm × 15-cm column that contains 4-µm packing L1. The flow rate is about 2 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–15	100→50	0→50	linear gradient
15–20	50→100	50→0	linear gradient
20–30	100	0	isocratic

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.35 for phthalic acid and about 1.0 for thalidomide; the tailing factor for the phthalic acid and thalidomide peaks is not more than 2.0; and the relative standard deviation for replicate injections, determined from the phthalic acid peak, is not more than 2.0%.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the percentage of each impurity in ~~the portion of~~

▲▲*USP30*
Thalidomide ~~taken~~

▲▲*USP30*
by the formula:

$$▲50{,}000(C_P / W)(r_i / r_P)▲_{USP29}$$

in which C_P is the concentration, in mg per mL, of phthalic acid in the *Standard solution; W* is the amount, in mg, of Thalidomide taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_P is the phthalic acid peak response obtained from the *Standard solution:* not more than 0.1% of any individual impurity is found; and not more than 0.3% of total impurities is found.

BRIEFING

Thalidomide Capsules, *USP 29* page 2108. On the basis of comments received, it is proposed to add requirements for *Microbial limits.*

(MD-OOD: F. Mao; MSA: R. Tirumalai) RTS—C45959

Add the following:

■**Microbial limits** ⟨61⟩—The total aerobic microbial count using the *Plate Method* is not more than 1000 cfu per g, and the total combined molds and yeasts count is not more than 100 cfu per g. It meets the requirements of the test for absence of *Escherichia coli.*■2S (*USP30*)

BRIEFING

Tiagabine Hydrochloride, *USP 29* page 2141. To eliminate possible interference by the presence of water in the test article, it is proposed to revise *Identification* test *A* to include a *Test specimen* preparation under *Infrared Absorption* ⟨197K⟩. Also, in the table of relative response factors under *Chromatographic purity,* it is proposed to clarify the terms "*x*" and "*y*" for the related compound that has a relative retention time of about 1.13.

(MD-PP: R. Ravichandran) RTS—C44408; C42389

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

■*Test specimen*—Transfer about 5 mg of Tiagabine Hydrochloride to a test tube, add 4 mL of 2-propanol, and sonicate if necessary for complete dissolution. Evaporate the solvent under inert atmosphere at 50° using a nitrogen evaporator for 2 hours.

Standard specimen—A similar preparation of USP Tiagabine Hydrochloride RS.■2S (*USP30*)

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

In-Process Revision

Change to read:

Chromatographic purity—

Solution A—Use a filtered and degassed solution of water adjusted with phosphoric acid to a pH of 2.3.

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Tiagabine Hydrochloride RS in water to obtain a solution having a known concentration of about 1 mg per mL.

Standard solution—Dilute a portion of the *Standard stock solution* quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.001 mg per mL.

Resolution solution—Dissolve an accurately weighed quantity of USP Tiagabine Related Compound A RS in water to obtain a solution having a known concentration of about 1 mg per mL. Transfer 1.0 mL of this solution and 1.0 mL of the *Standard stock solution* to a 10-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer about 100 mg of Tiagabine Hydrochloride, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	75	25	equilibration
0–30	75→45	25→55	linear gradient
30–40	45→10	55→90	linear gradient
40–45	10	90	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between tiagabine hydrochloride and tiagabine related compound A is not less than 9.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Interference check—Inject water as the blank: no interfering peaks are observed.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Tiagabine Hydrochloride taken by the formula:

$$100F(r_i/r_s)$$

in which F is the relative response factor (see the accompanying table for values) for each impurity; r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the sum of the responses of all the peaks, excluding the solvent peaks. (See the accompanying table for limits of individual impurities.) Not more than 1.0% of total impurities is found.

Relative Response Factors

▲Compound Name▲*USP29*	Relative Retention Time ▲(approximated)▲*USP29*	*F*	Limit (%)
▲(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3,4-dihydroxybutyl]-3-piperidinecarboxylic acid▲*USP29*	0.51	0.75	0.2
▲(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-oxybutyl]-3-piperidinecarboxylic acid▲*USP29*	0.79	0.63	0.1
▲(*R*)-1-[4-(3-Methyl-2-thienyl)-4-(2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid▲*USP29*	0.93	1.00	0.1
▲Tiagabine	1.0▲*USP29*	—	—
▲(*R*)-Methyl 1-[[4-(*x*-methyl-2-thienyl)-4-(*y*-methyl-2-thienyl)]-3-butenyl]-3-piperidinecarboxylic acid▲*USP29*	1.13	1.00	0.6
■*■2S (*USP30*)			
▲(*R*)-Methyl 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate▲*USP29*	1.32	1.01	0.2
▲Tiagabine related compound A▲*USP29*	1.39	1.04	0.2
▲4,4-Bis(3-methyl-2-thienyl)-3-buten-1-ol▲*USP29*	1.98	0.97	0.2
▲Bis(3-methyl-2-thienyl)methanone▲*USP29*	2.27	0.39	0.1
▲4,4-Bis(3-methyl-2-thienyl)-3-buten-1-ol, methanesulfonate▲*USP29*	2.33	0.96	0.1
▲2,2-Bis(3-methyl-2-thienyl)tetrahydrofuran▲*USP29*	2.54	0.94	0.1
▲Any unknown impurity▲*USP29*	—	1.00	0.1

■
* Where possible *x,y* combinations include (3,4), (4,3), (4,4), (5,5), (4,5), (5,4), (3,5), and (5,3).■2S (*USP30*)

In-Process Revision

BRIEFING

Vinblastine Sulfate, *USP 29* page 2252; **Vinblastine Sulfate for Injection,** *USP 29* page 2253. On the basis of comments received, it is proposed to revise the *Note* in the *USP Reference standards* section for clarification. A *Loss on drying* determination is not needed only for USP Vincristine Sulfate RS because of its qualitative use in determining system suitability.

(MD-OOD: F. Mao) RTS—C46868

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Vinblastine Sulfate RS. USP Vincristine Sulfate RS.* [NOTE—No *Loss on drying* determination is needed

■for USP Vincristine Sulfate RS.]■2S (*USP30*)

BRIEFING

Vinblastine Sulfate for Injection, *USP 29* page 2253—See briefing under *Vinblastine Sulfate*.

(MD-OOD: F. Mao) RTS—C46869

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Vinblastine Sulfate RS. USP Vincristine Sulfate RS.* [NOTE—No *Loss on drying* determination is needed

■for USP Vincristine Sulfate RS.]■2S (*USP30*)

BRIEFING

Vincristine Sulfate, *USP 29* page 2254; **Vincristine Sulfate Injection,** *USP 29* page 2255; **Vincristine Sulfate for Injection,** *USP 29* page 2255. On the basis of comments received, it is proposed to revise the name of the vinblastine Reference Standard and to clarify that the *Note* in the *USP Reference standards* section refers only to USP Vinblastine Sulfate RS. The *Loss on drying* determination is not needed for USP Vinblastine Sulfate RS because it is used only qualitatively in determining system suitability.

(MD-OOD: F. Mao) RTS—C46870

Change to read:

USP Reference standards ⟨11⟩—*USP Vincristine Sulfate RS. USP Vinblastine*

■*Sulfate*■2S (*USP30*)
RS. [NOTE—No *Loss on drying* determination is needed

■for USP Vinblastine Sulfate RS.]■2S (*USP30*)

BRIEFING

Vincristine Sulfate Injection, *USP 29* page 2255—See briefing under *Vincristine Sulfate*.

(MD-OOD: F. Mao) RTS—C46872

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Vinblastine Sulfate RS. USP Vincristine Sulfate RS.* [NOTE—No *Loss on drying* determination is needed

■for USP Vinblastine Sulfate RS.]■2S (*USP30*)

BRIEFING

Vincristine Sulfate for Injection, *USP 29* page 2255—See briefing under *Vincristine Sulfate*.

(MD-OOD: F. Mao) RTS—C46871

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Vinblastine Sulfate RS. USP Vincristine Sulfate RS.* [NOTE—No *Loss on drying* determination is needed

■for USP Vinblastine Sulfate RS.]■2S (*USP30*)

BRIEFING

Vinorelbine Injection, *USP 29* page 2257, page 3586 of the *First Supplement,* and the *Fifth Interim Revision Announcement* in this number of *PF*—See briefing under *Vinorelbine Tartrate.* Proposed revisions in the tests for *Related compounds* and in the *Assay* are consistent with the changes proposed for the *Vinorelbine Tartrate* monograph. It is also proposed to revise the *Chromatographic system* section in the *Assay* to clarify the system suitability requirement.

(MD-OOD: F. Mao) RTS—C45968

Change to read:

Related compounds—

■*Mobile phase* and *System suitability solution*—Proceed as directed in the *Assay* under *Vinorelbine Tartrate.*■2S (*USP30*)
~~*Mobile phase, System suitability solution,*~~

■■2S (*USP30*)
Standard solution and *Diluted standard solution*—Proceed as directed in the test for *Related compounds* under *Vinorelbine Tartrate.*

Chromatographic system—Proceed as directed in the *Assay.*

Test solution—Dilute a portion of Injection with *Mobile phase* to obtain a solution containing 1.0 mg of vinorelbine per mL.

Procedure—Proceed as directed for *Procedure* in the test for *Related compounds* under *Vinorelbine Tartrate*. Not more than 1.0% of the photodegradation product is found; not more than 0.3% of vinorelbine related compound A is found; not more than 0.2% of any other individual impurity is found; and the sum of all impurities, excluding any peaks that are below the limit of quantitation (0.02%), is not more than 2.0%.

Change to read:

■**Assay—**

Phosphate buffer, Mobile phase, and *System suitability solution*—Proceed as directed in the ~~test for *Related compounds*~~

■*Assay*■2S (*USP30*)
under *Vinorelbine Tartrate.*

Standard preparation—Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in water to obtain a solution having a known concentration of about •0.14 $mg_{•5}$ per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 10 mg of vinorelbine, to a 100-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a diode-array detector and a 3.9-mm × 15-cm column that contains packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.8 for the photodegradation product, 1.0 for vinorelbine, and about 1.2 for vinorelbine related compound A; and~~

■■2S (*USP30*)
the relative retention, ~~is~~

■$r_{■2S}$ (*USP30*)
between vinorelbine tartrate and vinorelbine related compound A is not less than 1.1.

■[NOTE—For peak identification purposes, the relative retention times are about 0.8 for the photodegradation product, 1.0 for vinorelbine, and 1.2 for vinorelbine related compound A.]■2S (*USP30*)

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the vinorelbine peaks, using a diode-array detector. Calculate the quantity, in mg, of vinorelbine ($C_{45}H_{54}N_4O_8$) in each mL of the Injection taken by the formula:

$$•(778.93/1079.11)C(L/D)(r_U/r_S)$$

in which 778.93 and 1079.11 are the molecular weights of vinorelbine and vinorelbine tartrate, respectively;$_{•5}$ C is the concentration, in mg per mL, of USP Vinorelbine Tartrate RS in the *Standard preparation;* L is the labeled quantity, in mg, of vinorelbine in each mL of Injection taken; D is the concentration, in mg per mL, of vinorelbine in the *Assay preparation;* and r_U and r_S are the peak responses at 267 nm obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP29*)

BRIEFING

Vinorelbine Tartrate, *USP 29* page 2256; **Vinorelbine Injection,** *USP 29* page 2257, page 3586 of the *First Supplement,* and the *Fifth Interim Revision Announcement* in this number of *PF.* It is proposed to replace the titration procedure in the *Assay* with a stability-indicating HPLC procedure. The HPLC procedure is based on the test for *Related compounds*. The *Phosphate buffer, Mobile phase, System suitability solution, Standard solution, Test solution,* and *Chromatographic system* in the test for *Related compounds* are identical to those in the proposed test for *Assay;* therefore, these sections are deleted and referenced to the *Assay* section according to USP style. The relative standard deviation criterion is added in the *Chromatographic system* in the *Assay.*

(MD-OOD: F. Mao) RTS—C45964

Change to read:

Related compounds—

~~*Phosphate buffer*—Dissolve 6.9 g of monobasic sodium phosphate in 900 mL of water. Adjust with phosphoric acid to a pH of 4.2, dilute with water to 1000 mL, and mix.~~

~~*Mobile phase*—Dissolve 1.22 g of sodium 1-decanesulfonate in 620 mL of methanol. Add 380 mL of *Phosphate buffer*, mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*System suitability solution*—Dissolve accurately weighed quantities of USP Vinorelbine Tartrate RS and USP Vinorelbine Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 1.4 mg per mL and 0.01 mg per mL, respectively. Expose a portion of this solution in a suitable xenon lamp apparatus capable of supplying a dose of 1600 KJ/m² between 310 and 800 nm at a power of 500 W/m² for about one hour, in order to generate an additional degradation product (3′,4′,7,8-tetradehydro-3,4′-dideoxy-3,6-epoxy-6,7-dihydro-C′-norvincaleukoblastine) having a relative retention time of about 0.8.~~

In-Process Revision

■*Phosphate buffer, Mobile phase, System suitability solution,* and *Chromatographic system*—Proceed as directed in the *Assay.* ■2S (*USP30*)

Standard solution—~~Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in *Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.4 mg per mL.~~

■Use the *Standard preparation,* prepared as directed in the *Assay.* ■2S (*USP30*)

Diluted standard solution—Transfer 1.0 mL of the *Standard solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume. Pipet 1.0 mL of this solution into a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—~~Transfer about 35 mg of Vinorelbine Tartrate, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.~~

■Use the *Assay preparation.* ■2S (*USP30*)

~~*Chromatographic system* (see *Chromatography* ⟨621⟩): The liquid chromatograph is equipped with a 267-nm detector and a 3.9-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the retention time for vinorelbine is about 13.5 minutes; and the relative retention times are about 0.8 for the photodegradation product, 1.0 for vinorelbine, and 1.2 for vinorelbine related compound A. The relative retention, α, between vinorelbine tartrate and vinorelbine related compound A is not less than 1.1.~~

■ ■2S (*USP30*)

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Diluted standard solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Record the chromatograms for three times the retention time of the vinorelbine peak. Disregard any peaks with an area less than or equal to one-half of the area of the peak obtained for vinorelbine in the *Diluted standard solution.* Calculate the percentage of each impurity in the portion of Vinorelbine Tartrate taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the sum of the responses of all the peaks: not more than 0.3% of the photodegradation product is found; not more than 0.2% of any individual impurity or coeluted impurities comprising an individual peak is found; and not more than 0.7% of total impurities, excluding the photodegradation product, is found.

Change to read:

Assay—~~Dissolve about 350 mg of Vinorelbine Tartrate, accurately weighed, in 40.0 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using suitable electrodes. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid is equivalent to 53.96 mg of $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$.~~

■*Phosphate buffer*—Dissolve 6.9 g of monobasic sodium phosphate in 900 mL of water. Adjust with phosphoric acid to a pH of 4.2, dilute with water to 1000 mL, and mix.

Mobile phase—Dissolve 1.22 g of sodium 1-decanesulfonate in 620 mL of methanol. Add 380 mL of *Phosphate buffer,* mix, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Vinorelbine Tartrate RS and USP Vinorelbine Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 1.4 mg per mL and 0.01 mg per mL, respectively. Expose a portion of this solution in a suitable xenon lamp apparatus capable of supplying a dose of 1600 KJ/m^2 between 310 and 800 nm at a power of 500 W/m^2 for about 1 hour, in order to generate an additional degradation product (3′,4′,7,8-tetradehydro-3,4′-dideoxy-3,6-epoxy-6,7-dihydro-C′-norvincaleukoblastine) having a relative retention time of about 0.8.

Standard preparation—Dissolve an accurately weighed quantity of USP Vinorelbine Tartrate RS in *Mobile phase* to obtain a solution having a known concentration of about 1.4 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Vinorelbine Tartrate in *Mobile phase* to obtain a solution having a known concentration of about 1.4 mg per mL.

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 267-nm detector and a 3.9-mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention, *r,* between vinorelbine tartrate and vinorelbine related compound A is not less than 1.1. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for the replicate injections is not more than 2.0%. [NOTE—For peak identification purposes, the relative retention times are about 0.8 for the photodegradation product, 1.0 for vinorelbine, and 1.2 for vinorelbine related compound A.]

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the vinorelbine tartrate peaks. Calculate the quantity in percent of $C_{45}H_{54}N_4O_8 \cdot 2C_4H_6O_6$ in the portion of Vinorelbine Tartrate taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Vinorelbine Tartrate RS in the *Standard preparation;* C_U is the concentration of Vinorelbine Tartrate in the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP30*)

BRIEFING

Zinc Chloride Injection, *USP 29* page 2288. To be consistent with the validation data and minimize the matrix effect in the *Assay,* it is proposed to revise the sodium chloride concentration in the *Assay preparation* to match that in the *Standard preparations*.

(MD-OOD: F. Mao) RTS—C46731

Change to read:

Assay—[NOTE—The *Standard preparations* and the *Assay preparation* may be diluted quantitatively with water, if necessary, to obtain solutions of suitable concentrations adaptable to the linear or working range of the instrument.]

Sodium chloride solution—Dissolve 450 mg of sodium chloride in water, dilute with water to 500 mL, and mix.

Standard preparations—Transfer 3.11 g of zinc oxide, accurately weighed, to a 250-mL volumetric flask, add 80 mL of 1 N sulfuric acid, warm to dissolve, cool, dilute with water to volume, and mix. This stock solution contains 10.0 mg of zinc per mL. Dilute an accurately measured volume of this solution quantitatively with water to obtain a solution containing 125 µg of zinc per mL. Transfer 2.0, 3.0, and 4.0 mL, respectively, of this solution to three separate 500-mL volumetric flasks, each containing 5 mL of *Sodium chloride solution,* dilute the contents of each flask with water to volume, and mix. These *Standard preparations* contain, respectively, 0.50, 0.75, and 1.0 µg of zinc per mL.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 5 mg of zinc, to a 500-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask. From the labeled amount of sodium chloride, if any, in the Injection, calculate the amount, in mg, of sodium chloride in the 10.0-mL portion, and add sufficient *Sodium chloride solution* to bring the total sodium chloride content of the 100-mL volumetric flask to ~~9 mg~~

■0.9 mg.■2S (*USP30*)

Dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparations* and the *Assay preparation* at the zinc emission line at 213.8 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a zinc hollow-cathode lamp and an air–acetylene flame, using water as the blank. Plot the absorbances of the *Standard preparations* versus the concentration, in µg per mL, of zinc, and draw the straight line best fitting the three plotted points. From the graph so obtained, determine the concentration, in µg per mL, of zinc in the *Assay preparation.* Calculate the quantity, in mg, of zinc in each mL of Injection taken by the formula:

$$5C/V$$

in which C is the concentration, in µg per mL, of zinc in the *Assay preparation;* and V is the volume, in mL, of Injection taken.

DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Minerals Capsules, *USP 29* page 2365; **Minerals Tablets,** *USP 29* page 2367; **Oil and Water-Soluble Vitamins with Minerals Capsules,** *USP 29* page 2396; **Oil and Water-Soluble Vitamins with Minerals Oral Solution,** *USP 29* page 2401; **Oil and Water-Soluble Vitamins with Minerals Tablets,** *USP 29* page 2407; **Water-Soluble Vitamins with Minerals Capsules,** *USP 29* page 2430; **Water-Soluble Vitamins with Minerals Oral Solution,** *USP 29* page 2434; **Water-Soluble Vitamins with Minerals Tablets,** *USP 29* page 2435. The current upper tolerance limit for microminerals in dosage form combinations of minerals and vitamins with minerals is 125.0 percent. This tolerance limit became official on January 1, 2004, after previously being published in *PF* 28(5) [Sept.–Oct. 2002], pages 1543–1548, where the reasons for the change were indicated and included new upper limit recommendations from the Food and Nutrition Board, Institute of Medicine (IOM). During the public comment period, no comments were received. Since becoming official, USP has received comments requesting a revision to this assay tolerance. Some of the comments suggest that because minerals are obtained from mined sources and naturally contain trace amounts of extrinsic minerals which vary greatly from batch to batch, the contribution of minute amounts of minerals from extraneous sources will result in significant overage to the trace mineral content in a formulation. On the basis of data received supporting these comments, the Dietary Supplements Non-Botanical Expert Committee approved for publication in *PF* an upper limit of not more than 160.0 percent of label claim in oral dosage form combinations of minerals and vitamins with minerals. However, the *General Notices* to the current *USP* indicate that where applicable legal requirements for dietary supplements require a minimum tolerance to be higher than the lower monograph tolerance, the upper monograph tolerance shall be increased by the corresponding amount. In this case, the minimum legal requirement of 100.0 percent, effective in the United States, is higher than the monograph lower tolerance of 90.0 percent, thus the upper tolerance contained in the monograph is increased by 10.0 percent. Due to this legal requirement, dietary supplements containing 170.0 percent of the labeled amount of microminerals would therefore be in compliance with the monograph.

(DSN: L. Evans) RTS—C43274

Change to read:

» Minerals Capsules contain two or more minerals derived from substances generally recognized as safe, furnishing two or more of the following elements in ionizable form: calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, and zinc. Capsules contain not less than 90.0 percent and not more than 125.0 percent of the labeled amounts of calcium (Ca), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), phosphorus (P), potassium (K), and zinc (Zn), and not less than 90.0 percent and not more than ~~125.0~~ ▪160.0▪2S (*USP30*) percent of the labeled amounts of chromium (Cr), fluorine (F), iodine (I), molybdenum (Mo), and selenium (Se). They contain no vitamins. They may contain other labeled added substances in amounts that are unobjectionable.

BRIEFING

Minerals Tablets, *USP 29* page 2367—See briefing under *Minerals Capsules.*

(DSN: L. Evans) RTS— C43274

Change to read:

» Minerals Tablets contain two or more minerals derived from substances generally recognized as safe, furnishing two or more of the following elements in ionizable form: calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, and zinc. Tablets contain not less than 90.0 percent and not more than 125.0 percent of the labeled amounts of calcium (Ca), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), phosphorus (P), potassium (K), and zinc (Zn), and not less than 90.0 percent and not more than ~~125.0~~ ▪160.0▪2S (*USP30*) percent of the labeled amounts of chromium (Cr), fluorine (F), iodine (I), molybdenum (Mo), and selenium (Se). They contain no vitamins. They may contain other labeled added substances in amounts that are unobjectionable.

BRIEFING

Oil- and Water-Soluble Vitamins with Minerals Capsules, *USP 29* page 2396—See briefing under *Minerals Capsules.*

(DSN: L. Evans) RTS—C43274

In-Process Revision

Change to read:

» Oil- and Water-Soluble Vitamins with Minerals Capsules contain one or more of the following oil-soluble vitamins: Vitamin A, Vitamin D as Ergocalciferol (Vitamin D_2) or Cholecalciferol (Vitamin D_3), Vitamin E, Phytonadione (Vitamin K_1), and Beta Carotene; one or more of the following water-soluble vitamins: Ascorbic Acid or its equivalent as Calcium Ascorbate or Sodium Ascorbate, Biotin, Cyanocobalamin, Folic Acid, Niacin or Niacinamide, Dexpanthenol or Panthenol, Pantothenic Acid (as Calcium Pantothenate or Racemic Calcium Pantothenate), Pyridoxine Hydrochloride, Riboflavin, and Thiamine Hydrochloride or Thiamine Mononitrate; and one mineral or more, furnishing one or more of the following elements in ionizable form: calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, and zinc, derived from substances generally recognized as safe. Capsules contain not less than 90.0 percent and not more than 165.0 percent of the labeled amounts of vitamin A ($C_{20}H_{30}O$) as retinol or esters of retinol in the form of retinyl acetate ($C_{22}H_{32}O_2$) or retinyl palmitate ($C_{36}H_{60}O_2$), vitamin D as cholecalciferol ($C_{27}H_{44}O$) or ergocalciferol ($C_{28}H_{44}O$), vitamin E as alpha tocopherol ($C_{29}H_{50}O_2$) or alpha tocopheryl acetate ($C_{31}H_{52}O_3$) or alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$), phytonadione ($C_{31}H_{46}O_2$), and beta carotene ($C_{40}H_{56}$); and not less than 90.0 percent and not more than 150.0 percent of the labeled amounts of ascorbic acid ($C_6H_8O_6$) or its salts as calcium ascorbate ($C_{12}H_{14}CaO_{12} \cdot 2H_2O$) or sodium ascorbate ($C_6H_7NaO_6$), biotin ($C_{10}H_{16}N_2O_3S$), cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), folic acid ($C_{19}H_{19}N_7O_6$), niacin ($C_6H_5NO_2$) or niacinamide ($C_6H_6N_2O$), dexpanthenol ($C_9H_{19}NO_4$) or panthenol ($C_9H_{19}NO_4$), calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$), riboflavin ($C_{17}H_{20}N_4O_6$), and thiamine ($C_{12}H_{17}ClN_4OS$) as thiamine hydrochloride or thiamine mononitrate; and not less than 90.0 percent and not more than 125.0 percent of the labeled amount of calcium (Ca), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), phosphorus (P), potassium (K), and zinc (Zn); and not less than 90.0 percent and not more than ~~125.0~~

▪160.0▪2S (*USP30*)
percent of the labeled amounts of chromium (Cr), fluorine (F), iodine (I), molybdenum (Mo), and selenium (Se).

They may contain other labeled added substances that are generally recognized as safe, in amounts that are unobjectionable.

BRIEFING

Oil- and Water-Soluble Vitamins with Minerals Oral Solution, *USP 29* page 2401—See briefing under *Minerals Capsules*.

(DSN: L. Evans) RTS—C43274

Change to read:

» Oil- and Water-Soluble Vitamins with Minerals Oral Solution contains one or more of the following oil-soluble vitamins: Vitamin A, Vitamin D as Ergocalciferol (Vitamin D_2) or Cholecalciferol (Vitamin D_3), and Vitamin E; one or more of the following water-soluble vitamins: Ascorbic Acid or its equivalent as Calcium Ascorbate or Sodium Ascorbate, Biotin, Cyanocobalamin, Niacin or Niacinamide, Dexpanthenol or Panthenol, Pantothenic Acid (as Calcium Pantothenate or Racemic Calcium Pantothenate), Pyridoxine Hydrochloride, Riboflavin or Riboflavin-5′-Phosphate Sodium, and Thiamine Hydrochloride or Thiamine Mononitrate; and one or more minerals derived from substances generally recognized as safe, furnishing one or more of the following elements in ionizable form: chromium, fluorine, iodine, iron, magnesium, manganese, molybdenum, and zinc. It contains not less than 90.0 percent and not more than 200.0 percent of the labeled amounts of vitamin A ($C_{20}H_{30}O$) as retinol or esters of retinol in the form of retinyl acetate ($C_{22}H_{32}O_2$) or retinyl palmitate ($C_{36}H_{60}O_2$), vitamin D as ergocalciferol ($C_{28}H_{44}O$) or cholecalciferol ($C_{27}H_{44}O$), vitamin E as alpha tocopherol ($C_{29}H_{50}O_2$) or alpha tocopheryl acetate ($C_{31}H_{52}O_3$) or alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$), ascorbic acid ($C_6H_8O_6$) or its salts as calcium ascorbate ($C_{12}H_{14}CaO_{12} \cdot 2H_2O$) or sodium ascorbate ($C_6H_7NaO_6$), and thiamine ($C_{12}H_{17}ClN_4OS$) as thiamine hydrochloride or thiamine mononitrate; not less than 90.0 percent and not more than 150.0 percent of the labeled amounts of biotin ($C_{10}H_{16}N_2O_3S$), calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$), dexpanthenol ($C_9H_{19}NO_4$) or panthenol ($C_9H_{19}NO_4$), niacin ($C_6H_5NO_2$) or niacinamide ($C_6H_6N_2O$), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$), riboflavin ($C_{17}H_{20}N_4O_6$) or riboflavin-5′-phosphate sodium ($C_{17}H_{20}N_4NaO_9P$); not less than 90.0 percent and not more than 450.0 percent of the labeled amount of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$);

▪not less than 90.0 percent and not more than 160.0 percent of the labeled amounts of chromium (Cr), fluorine (F), iodine (I), and molybdenum (Mo);▪2S (*USP30*)
and not less than 90.0 percent and not more than 125.0 percent of the labeled amounts of ~~chromium (Cr), fluorine (F), iodine (I),~~

▪▪2S (*USP30*)

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iron (Fe), magnesium (Mg), manganese (Mn), ~~molybdenum (Mo),~~

■■2S (*USP30*)
and zinc (Zn).

magnesium (Mg), phosphorus (P), potassium (K), and zinc (Zn); and not less than 90.0 percent and not more than ~~125.0~~

■160.0■2S (*USP30*)
percent of the labeled amounts of chromium (Cr), fluorine (F), iodine (I), molybdenum (Mo), and selenium (Se).

They may contain other labeled added substances that are generally recognized as safe, in amounts that are unobjectionable.

BRIEFING

Oil- and Water-Soluble Vitamins with Minerals Tablets, *USP 29* page 2407—See briefing under *Minerals Capsules*.

(DSN: L. Evans) RTS— C43274

Change to read:

» Oil- and Water-Soluble Vitamins with Minerals Tablets contain one or more of the following oil-soluble vitamins: Vitamin A, Vitamin D as Ergocalciferol (Vitamin D_2) or Cholecalciferol (Vitamin D_3), Vitamin E, Phytonadione (Vitamin K_1), and Beta Carotene; one or more of the following water-soluble vitamins: Ascorbic Acid or its equivalent as Calcium Ascorbate or Sodium Ascorbate, Biotin, Cyanocobalamin, Folic Acid, Niacin or Niacinamide, Pantothenic Acid (as Calcium Pantothenate or Racemic Calcium Pantothenate), Pyridoxine Hydrochloride, Riboflavin, and Thiamine Hydrochloride or Thiamine Mononitrate; and one or more minerals derived from substances generally recognized as safe, furnishing one or more of the following elements in ionizable form: calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, and zinc. Tablets contain not less than 90.0 percent and not more than 165.0 percent of the labeled amounts of vitamin A ($C_{20}H_{30}O$) as retinol or esters of retinol in the form of retinyl acetate ($C_{22}H_{32}O_2$) or retinyl palmitate ($C_{36}H_{60}O_2$), vitamin D as cholecalciferol ($C_{27}H_{44}O$) or ergocalciferol ($C_{28}H_{44}O$), vitamin E as alpha tocopherol ($C_{29}H_{50}O_2$) or alpha tocopheryl acetate ($C_{31}H_{52}O_3$) or alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$), phytonadione ($C_{31}H_{46}O_2$), and beta carotene ($C_{40}H_{56}$); not less than 90.0 percent and not more than 150.0 percent of the labeled amounts of ascorbic acid ($C_6H_8O_6$) or its salts as calcium ascorbate ($C_{12}H_{14}CaO_{12} \cdot 2H_2O$) or sodium ascorbate ($C_6H_7NaO_6$), biotin ($C_{10}H_{16}N_2O_3S$), cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), folic acid ($C_{19}H_{19}N_7O_6$), niacin ($C_6H_5NO_2$) or niacinamide ($C_6H_6N_2O$), calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$), riboflavin ($C_{17}H_{20}N_4O_6$), and thiamine ($C_{12}H_{17}ClN_4OS$) as thiamine hydrochloride or thiamine mononitrate; not less than 90.0 percent and not more than 125.0 percent of the labeled amounts of calcium (Ca), copper (Cu), iron (Fe), manganese (Mn),

BRIEFING

Water-Soluble Vitamins with Minerals Capsules, *USP 29* page 2430—See briefing under *Minerals Capsules*.

(DSN: L. Evans) RTS—C43274

Change to read:

» Water-Soluble Vitamins with Minerals Capsules contain one or more of the following water-soluble vitamins: Ascorbic Acid or its equivalent as Calcium Ascorbate or Sodium Ascorbate, Biotin, Cyanocobalamin, Folic Acid, Dexpanthenol or Panthenol, Pantothenic Acid (as Calcium Pantothenate or Racemic Calcium Pantothenate), Niacin or Niacinamide, Pyridoxine Hydrochloride, Riboflavin, and Thiamine Hydrochloride or Thiamine Mononitrate; and one mineral or more, furnishing one or more of the following elements in ionizable form: calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, and zinc, derived from substances generally recognized as safe. Capsules contain not less than 90.0 percent and not more than 150.0 percent of the labeled amounts of ascorbic acid ($C_6H_8O_6$) or its salts as calcium ascorbate ($C_{12}H_{14}CaO_{12} \cdot 2H_2O$) or sodium ascorbate ($C_6H_7NaO_6$), biotin ($C_{10}H_{16}N_2O_3S$), cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), folic acid ($C_{19}H_{19}N_7O_6$), dexpanthenol ($C_9H_{19}NO_4$) or panthenol ($C_9H_{19}NO_4$), calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$), niacin ($C_6H_5NO_2$) or niacinamide ($C_6H_6N_2O$), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$), riboflavin ($C_{17}H_{20}N_4O_6$), and thiamine ($C_{12}H_{17}ClN_4OS$) as thiamine hydrochloride or thiamine mononitrate; not less than 90.0 percent and not more than 125.0 percent of the labeled amounts of calcium (Ca), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), phosphorus (P), potassium (K), and zinc (Zn); and not less than 90.0 percent and not more than ~~125.0~~

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▪160.0▪2S (*USP30*)
percent of the labeled amounts of chromium (Cr), fluorine (F), iodine (I), molybdenum (Mo), and selenium (Se).

They do not contain any form of Beta Carotene or Vitamin A, D, E, or K. They may contain other labeled added substances that are generally recognized as safe, in amounts that are unobjectionable.

BRIEFING

Water-Soluble Vitamins with Minerals Oral Solution, *USP 29* page 2434—See briefing under *Minerals Capsules*.

(DSN: L. Evans) RTS—C43274

Change to read:

» Water-Soluble Vitamins with Minerals Oral Solution contains one or more of the following water-soluble vitamins: Cyanocobalamin, Niacin or Niacinamide, Dexpanthenol or Panthenol, Pantothenic Acid (as Calcium Pantothenate or Racemic Calcium Pantothenate), Pyridoxine Hydrochloride, Riboflavin or Riboflavin-5′-Phosphate Sodium, and Thiamine Hydrochloride or Thiamine Mononitrate; and one or more minerals derived from substances generally recognized as safe, furnishing one or more of the following elements in ionizable form: iodine, iron, magnesium, manganese, and zinc. It contains not less than 90.0 percent and not more than 450.0 percent of the labeled amount of cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$); not less than 90.0 percent and not more than 250.0 percent of the labeled amount of thiamine ($C_{12}H_{17}ClN_4OS$) as thiamine hydrochloride or thiamine mononitrate; not less than 90.0 percent and not more than 150.0 percent of the labeled amounts of calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$), dexpanthenol ($C_9H_{19}NO_4$) or panthenol ($C_9H_{19}NO_4$), niacin ($C_6H_5NO_2$) or niacinamide ($C_6H_6N_2O$), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$), and riboflavin ($C_{17}H_{20}N_4O_6$) or riboflavin-5′-phosphate sodium ($C_{17}H_{20}N_4NaO_9P$);

▪not less than 90.0 percent and not more than 160.0 percent of the labeled amount of iodine (I);▪2S (*USP30*) and not less than 90.0 percent and not more than 125.0 percent of the labeled amounts of ~~iodine (I),~~

▪▪2S (*USP30*)
iron (Fe), magnesium (Mg), manganese (Mn), and zinc (Zn).

BRIEFING

Water-Soluble Vitamins with Minerals Tablets, *USP 29* page 2435—See briefing under *Minerals Capsules*.

(DSN: L. Evans) RTS—C44102

Change to read:

» Water-Soluble Vitamins with Minerals Tablets contain one or more of the following water-soluble vitamins: Ascorbic Acid or its equivalent as Calcium Ascorbate or Sodium Ascorbate, Biotin, Cyanocobalamin, Folic Acid, Niacin or Niacinamide, Pantothenic Acid (as Calcium Pantothenate or Racemic Calcium Pantothenate), Pyridoxine Hydrochloride, Riboflavin, and Thiamine Hydrochloride or Thiamine Mononitrate; and one or more minerals derived from substances generally recognized as safe, furnishing one or more of the following elements in ionizable form: calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, and zinc. Tablets contain not less than 90.0 percent and not more than 150.0 percent of the labeled amounts of ascorbic acid ($C_6H_8O_6$) or its salts as calcium ascorbate ($C_{12}H_{14}CaO_{12} \cdot 2H_2O$) or sodium ascorbate ($C_6H_7NaO_6$), biotin ($C_{10}H_{16}N_2O_3S$), cyanocobalamin ($C_{63}H_{88}CoN_{14}O_{14}P$), folic acid ($C_{19}H_{19}N_7O_6$), calcium pantothenate ($C_{18}H_{32}CaN_2O_{10}$), niacin ($C_6H_5NO_2$) or niacinamide ($C_6H_6N_2O$), pyridoxine hydrochloride ($C_8H_{11}NO_3 \cdot HCl$), riboflavin ($C_{17}H_{20}N_4O_6$), and thiamine ($C_{12}H_{17}ClN_4OS$) as thiamine hydrochloride or thiamine mononitrate; not less than 90.0 percent and not more than 125.0 percent of the labeled amounts of calcium (Ca), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), phosphorus (P), potassium (K), and zinc (Zn); and not less than 90.0 percent and not more than ~~125.0~~

▪160.0▪2S (*USP30*)
percent of the labeled amounts of chromium (Cr), fluorine (F), iodine (I), molybdenum (Mo), and selenium (Se).

They do not contain any form of Beta Carotene or Vitamin A, D, E, or K. They may contain other labeled added substances that are generally recognized as safe, in amounts that are unobjectionable.

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 24* page 3257, page 3816 of the *Second Supplement,* and page 1144 of *PF* 32(4) [July–Aug. 2006]. It is proposed to add *Hydroxypropyl Betadex* to the *Sequestering Agent* category and *Palm Kernel Oil* to the *Coating Agent* and *Emulsifying and/or Solubilizing Agent* categories to complement the proposed new monographs for *Hydroxypropyl Betadex* and *Palm Kernel Oil,* respectively, which appear elsewhere in this issue of *PF.*

(EM2) RTS—C44166

Change to read:

Bulking Agent for Freeze-Drying
Creatinine
Mannitol

■Polydextrose■2S (*NF25*)

Change to read:

Coating Agent

■Amino Methacrylate Copolymer■1S (*NF25*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose, Sodium
Cellaburate
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Cellulose Acetate Phthalate (see Cellacefate)

■Coconut Oil■1S (*NF25*)
Copovidone

■Corn Syrup Solids■1S (*NF25*)

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■1S (*NF25*)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Maltodextrin
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose

■Palm Kernel Oil■2S (*NF25*)
Polyethylene Glycol

■Polyvinyl Acetate■1S (*NF25*)
Polyvinyl Acetate Phthalate
Shellac
Starch, Pregelatinized Modified
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Desiccant
Calcium Chloride
Calcium Sulfate

■Polyvinyl Acetate■1S (*NF25*)
Silicon Dioxide

Change to read:

Emollient
Alkyl (C12-15) Benzoate
Hydrogenated Soybean Oil

■Oleyl Oleate■1S (*NF25*)

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Carbomer Copolymer
Carbomer Interpolymer
Cholesterol

■Coconut Oil■1S (*NF25*)
Diethanolamine (Adjunct)
Diethylene Glycol Stearates
Ethylene Glycol Stearates
Glyceryl Distearate
Glyceryl Monolinoleate
Glyceryl Monooleate
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)

■Oleyl Oleate■1S (*NF25*)

■Palm Kernel Oil■2S (*NF25*)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
Polyoxyl Lauryl Ether
Polyoxyl Stearyl Ether
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate
Sodium Cetostearyl Sulfate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Sorbitan Sesquioleate
Sorbitan Trioleate
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:

Humectant

■Corn Syrup Solids■1S (*NF25*)

■Erythritol■1S (*NF25*)
Glycerin
Hexylene Glycol
■Maltitol■2S (*NF24*)

■Polydextrose■2S (*NF25*)
Propylene Glycol
Sorbitol
Sorbitol Sorbitan Solution
■Tagatose■1S (*NF24*)

Change to read:

Polymer Membrane

■Amino Methacrylate Copolymer■1S (*NF25*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Cellaburate
Cellulose Acetate

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■1S (*NF25*)

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)

■Gamma Cyclodextrin■1S (*NF25*)

■Hydroxypropyl Betadex■2S (*NF25*)
Sodium Tartrate

Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol

▲Canola Oil▲*NF25*
Caprylocaproyl Polyoxylglycerides
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
▲Lauroyl Polyoxylglycerides▲*NF24*
Linoleoyl Polyoxylglycerides
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Polyoxylglycerides
Peanut Oil
Polyethylene Glycol
Polyethylene Glycol Monomethyl Ether
Propylene Glycol
Sesame Oil
Stearoyl Polyoxylglycerides
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
Alamic Acid
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carbomer Copolymer
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

■Corn Syrup Solids■1S (*NF25*)
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate
Maltodextrin
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
Starch, Corn
Starch, Potato
Starch, Tapioca
Starch, Wheat
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent
Acesulfame Potassium
Aspartame
Aspartame Acesulfame

■Corn Syrup Solids■1S (*NF25*)
Dextrates
Dextrose
Dextrose Excipient

■Erythritol■1S (*NF25*)

Fructose
Galactose
■Maltitol■2S (*NF24*)
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup
■Tagatose■1S (*NF24*)

Change to read:

Tablet Binder
Acacia
Alginic Acid

■Amino Methacrylate Copolymer■1S (*NF25*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
Copovidone

■Corn Syrup Solids■1S (*NF25*)
Dextrin

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■1S (*NF25*)
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Low-Substituted Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Maltodextrin
Maltose
Methylcellulose
Polyethylene Oxide

■Polyvinyl Acetate■1S (*NF25*)
Povidone
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Syrup

Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered

■Corn Syrup Solids■1S (*NF25*)
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose, Monohydrate
■Maltitol■2S (*NF24*)
Maltodextrin
Maltose
Mannitol
Sorbitol
Starch
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tonicity Agent

■Corn Syrup Solids■1S (*NF25*)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

■Corn Syrup Solids■1S (*NF25*)
Dextrose
Peppermint Water
Sorbitol Solution
Syrup
OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil

▲Canola Oil▲*NF25*
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

In-Process Revision

MONOGRAPHS (NF)

BRIEFING

Carbomer Copolymer, *NF 24* page 3295. On the basis of comments received, it is proposed to make the following changes in the *Chromatographic system* section of the test for *Limit of ethyl acetate and cyclohexane:*

1. To change the measurement method of the flow rate of the carrier gas.
2. To delete the current statement of the relative retention times of the components and to add it to a note later in the paragraph, which also states that the relative retention times are for information purposes only (not part of the system suitability requirements).

(EM2: H. Wang) RTS—C47468

Change to read:

Limit of ethyl acetate and cyclohexane—[NOTE—This test is required only for those Carbomer Copolymers where the labeling indicates that ethyl acetate or a mixture of ethyl acetate and cyclohexane was used in the polymerization process.]

Standard stock solution—Transfer 5.0 mL of methanol to a 10-mL serum vial, insert a rubber septum, and seal with a metal cap. Add 25.0 µL of ethyl acetate and 20.0 µL of cyclohexane through the septum into the vial, and mix.

Standard solution—Transfer 20.0 mL of methanol to a 30-mL serum vial, insert a rubber septum, and seal with a metal cap. Through the rubber septum, add 10 µL of methyl ethyl ketone (internal standard) and 50.0 µL of the *Standard stock solution,* and mix to obtain a solution containing 0.225 mg of ethyl acetate and 0.156 mg of cyclohexane.

Test solution—Transfer about 50 mg of Carbomer Copolymer, accurately weighed, to a 30-mL serum vial, add 20.0 mL of methanol, insert a rubber septum, and seal with a metal cap. Through the rubber septum, add 10 µL of methyl ethyl ketone, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 3-m column packed with 1% liquid phase G25 on 60- to 80-mesh support S12. The carrier gas is helium, ~~flowing at a linear velocity of about 33 cm per minute~~

■flowing at a rate of about 33 mL per minute.■2S (*NF25*)
The column temperature is maintained at 115° for 4 minutes after injection, then the temperature is increased at a rate of 6° per minute to 175°, and maintained at 175° for 5 minutes. The injection port and detector temperatures are maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 0.7 for methyl ethyl ketone, 0.9 for ethyl acetate, and 1.0 for cyclohexane;~~

■■2S (*NF25*)
the resolution, *R,* between ethyl acetate and cyclohexane is not less than 1.0; and the relative standard deviation for replicate injections is not more than 2.5%.

■[NOTE—For information purposes only, the relative retention times are about 0.7 for methyl ethyl ketone, 0.9 for ethyl acetate, and 1.0 for cyclohexane.]■2S (*NF25*)

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentages of ethyl acetate and cyclohexane in the portion of Carbomer Copolymer taken by the formula:

$$100(W_S / W_T)(R_U / R_S)$$

in which W_S is the weight, in mg, of ethyl acetate or cyclohexane in the *Standard solution;* W_T is the weight, in mg, of Carbomer Copolymer taken to prepare the *Test solution;* and R_U and R_S are the peak area ratios of the relevant analyte peak to the methyl ethyl ketone peaks obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% of ethyl acetate and not more than 0.3% of cyclohexane is found.

BRIEFING

Hydroxypropyl Betadex, page 1282 of *PF* 28(4) [July–Aug. 2002]. This new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded with the following changes based on comments received to *In-Process Revision*. In addition, editorial style changes have been made.

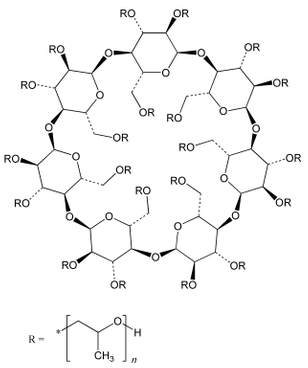
1. The chemical formula is revised and a molecular structure is added.
2. In the Definition, the term "hydroxylpropyl group" is changed to "hydroxypropyl group".
3. A storage statement is included under *Packaging and storage*.
4. The *Labeling* section is changed to include bacterial endotoxin and sterility statements.
5. The USP Reference Standard name is changed from "USP Hydroxypropyl Beta Cyclodextrin RS" to "USP Hydroxypropyl Betadex RS".
6. Clarification is provided in the *IR* Identification test.
7. The specification for the *Microbial limits* test is modified in line with the general requirement for excipients.
8. The *Heavy metals* test is changed from *Method II* to *Method I* for water-soluble material.
9. A test for *Loss on drying* is incorporated into the monograph.
10. The *Test solution* under *Conductivity* is revised to indicate "calculated on the dried basis". Clarification is provided under *Calibration*.
11. An appropriate specification is assigned in the test for *Bacterial endotoxins*. Also, clarification is provided to reflect dosage form requirements.
12. A test for *Sterility* is added to reflect dosage form requirements.
13. The procedure in the test for *Related compounds* is modified based on comments received. A *Note* has been added to indicate that the relative retention times of components are for information purposes only and not as part of the system suitability requirements.
14. For clarification, changes are added to the test for *Molar substitution*.
15. A test for *Limit of propylene oxide* is added. Propylene oxide is a toxic and hazardous substance that is used as a starting material in the manufacture of Hydroxypropyl Betadex. The column used to develop and validate the procedure is a Varian, CP-PoraPLOT Q, Chrompak No. 7550, 10 m × 0.32 mm, 10 µm film thicknes.

(EM2: H. Wang; MSA: R. Tirumalai) RTS—C44146

Add the following:

■Hydroxypropyl Betadex

~~$(C_{26}H_{70-x}O_{35})(C_3H_6O)_x$~~



$C_{42}H_{70}O_{35}(C_3H_6O)_x$ where x = ~~MS 7, MS = Molar Substitution~~ 7MS, MS being Molar Substitution

Beta cyclodextrin, 2-hydroxypropyl ether [*94035-02-6*].

» Hydroxypropyl Betadex is a partially substituted poly(hydroxypropyl) ether of Betadex. The number of ~~hydroxylpropyl~~ hydroxypropyl groups per anhydroglucose unit expressed as molar substitution (MS) is not less than 0.40 and not more than 1.50 and is within 10 percent of the value stated on the label.

Packaging and storage—Preserve in well-closed containers. ~~(Storage conditions to come.)~~ Store at room temperature.

Labeling—Label it to indicate the molar substitution (MS). ~~Where it is intended for use in parenteral dosage forms, it is so labeled.~~ Where Hydroxypropyl Betadex is intended for use in the manufacture of injectable dosage forms, it is so labeled. Where Hydroxypropyl Betadex must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled. Where Hydropropyl Betadex is sterile, it is so labeled.

USP Reference standards ⟨11⟩—~~*USP Hydroxypropyl Beta Cyclodextrin RS.*~~ *USP Hydroxypropyl Betadex RS. USP Beta Cyclodextrin RS. USP Propylene Glycol RS. USP Endotoxin RS.*

Clarity of solution—Dissolve 1.0 g in 2.0 mL of water, and heat: the resulting solution is clear and remains transparent after cooling to room temperature.

Identification—

A: *Infrared Absorption* ⟨197K⟩—The spectrum obtained with Hydroxypropyl Betadex shows the same absorption bands as the spectrum acquired with USP Hydroxypropyl Betadex RS. Due to the difference in the substitution of the substance, the intensity of some absorption bands may vary.

B: It ~~complies with~~ meets the requirements of the test for *Clarity of solution*.

Microbial limits ⟨61⟩—~~It meets the requirements for absence of *Salmonella* species and *Escherichia coli*, and the total aerobic bacterial count does not exceed 1000 per g.~~ The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

Heavy metals, ~~*Method II*~~ *Method I* ⟨231⟩: 20 µg per g.

Loss on drying ⟨731⟩—Dry about 1 g of it at 120° for 2 hours: it loses not more than 10.0% of its weight.

Conductivity—

Test solution—Transfer about 5.0 g of Hydroxypropyl Betadex, accurately weighed and calculated on the dried basis, to a 50-mL volumetric flask, dissolve in and dilute with water ~~, which has been~~ (previously boiled and cooled to room temperature) to volume, and mix.

Apparatus—Use a conductivity meter or resistivity meter that measures the resistance of the column of liquid between the electrodes of the immersed measuring device. The apparatus is supplied with alternating current to avoid the effects of electrode polarization. It is equipped with a temperature compensation device or a precision thermometer.

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Reagents—Prepare three standard solutions of potassium chloride containing 0.7455, 0.0746, and 0.0149 g, respectively, of potassium chloride per 1000.0 g of solution. ~~, using water, which has been previously boiled and cooled to room temperature, whose conductivity does not exceed 2 μS · cm^{-1}.~~ These solutions should be prepared using water, which has been previously boiled and cooled to room temperature and whose conductivity does not exceed 2 μS · cm^{-1}. The conductivity and resistivity of these three solutions at 20° are given below.

Concentration of solution in g/1000.0 g	Conductivity μS · cm^{-1}	Resistivity Ω · cm
0.7455	1330	752
0.0746	133.0	7519
0.0149	26.6	37,594

Calibration—Choose a conductivity cell that is appropriate for the conductivity of the solution to be examined. The higher the expected conductivity, the higher the cell constant that must be chosen. ~~so that the value, *R,* measured is as large as possible for the apparatus used~~ Commonly used conductivity cells have cell constants of the order of 0.1 cm^{-1}, 1 cm^{-1}, and 10 cm^{-1}. Use a Standard solution of potassium chloride that is appropriate for the measurement. The conductivity value of the Standard solution of potassium chloride should be near the expected conductivity value of the *Test solution*. Rinse the cell several times with water, which has been previously boiled and cooled to room temperature, and at least twice with the potassium chloride solution used for the determination of the cell constant of the conductivity cell. Measure the resistance of the conductivity cell using the potassium chloride solution at 20 ± 0.1°. The constant C (in cm^{-1}) of the conductivity cell is given by the expression:

$$C = R_{KCl} \times K_{KCl},$$

in which R_{KCl} is the measured resistance, expressed in megaohms; and K_{KCl} is the conductivity of the standard solution of potassium chloride used, expressed in μS · cm^{-1}. The measured constant, C, of the conductivity cell must be within 5% of the given value.

Procedure—Rinse the conductivity cell several times with water, which has been previously boiled and cooled to room temperature, and at least twice with the *Test solution*. Measure the conductivity of the *Test solution*, while gently stirring with a magnetic stirrer: the conductivity is not more than 200 μS · cm^{-1}.

Bacterial endotoxins ⟨85⟩—~~If intended for use in the manufacturing of parenteral dosage forms, it contains not more than (limit to come).~~ The level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Hydropropyl Betadex is used can be met. Where the label states that Hydroxypropyl Betadex must be subjected to further processing during the preparation of injectable dosage forms, the level of bacterial endotoxins is such that the requirement under the relevant dosage form monograph(s) in which Hydroxypropyl Betadex is used can be met.

Sterility ⟨71⟩—Where the label states that Hydropropyl Betadex is sterile, it meets the requirements for *Sterility* ⟨71⟩ in the relevant dosage form monograph(s) in which Hydropropyl Betadex is used.

Related compounds—

Mobile phase—Use water.

Standard solution A—~~Transfer 75 mg of USP Beta Cyclodextrin RS and 125 mg of USP Propylene Glycol RS, accurately weighed, to a 5-mL volumetric flask, dissolve in and dilute with water to volume, and mix.~~ Dissolve accurately weighed quantities of USP Beta Cyclodextrin RS and USP Propylene Glycol RS in water to make a solution having a known concentration of about 15 mg per mL for beta cyclodextrin, calculated on the anhydrous basis, and about 25 mg per mL for propylene glycol.

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Standard solution B—Pipet 1.0 mL of *Standard solution A* into a ~~5 mL~~ 10-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Dissolve 2.50 g of Hydroxypropyl Betadex, accurately weighed and calculated on the dried basis, in water with the aid of heat. Cool, and dilute with water to 25.0 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a differential refractometer detector and a 3.9-mm × 30-cm column and pre-column that contain packing L11 ~~and that are~~, both maintained at a temperature of 40°. The flow rate is about 1.5 mL per minute. Chromatograph *Standard solution A* and *Standard solution B*, and record the peak responses as directed for *Procedure:* ~~the retention time of propylene glycol is about 2.5 minutes, and the relative retention times with reference to that of propylene glycol are about 4.2 for betadex and about 6 for hydroxypropyl betadex;~~ the resolution, *R*, between the betadex and propylene glycol is not less than 4 for *Standard solution A*; and the relative standard deviation for replicate injections of *Standard solution B* is not more than 2.0%. [NOTE—For information purposes only, the retention time of propylene glycol is about 2.5 minutes, and the relative retention times with reference to that of propylene glycol are about 4.2 for betadex and about 6 for hydroxypropyl betadex; Hydroxypropyl Betadex elutes as a very wide peak or several peaks.]

Procedure—Separately inject equal volumes (about 20 µL) of *Standard solution B* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks, disregarding any peaks eluting before propylene glycol and after the hydroxypropyl betadex peak. The area of the betadex peak in the *Test solution* is not more than the area of the corresponding peak in the chromatogram obtained with *Standard solution B* (1.5%). The area of the propylene glycol peak in the *Test solution* is not more than the area of the corresponding peak in the chromatogram obtained with *Standard solution B* (2.5%). The area obtained from any other single impurity peak is not more than 0.1 times the area of propylene glycol in the chromatogram obtained with *Standard solution B* (0.25%). The total area obtained from all impurity peaks, excluding betadex and propylene glycol, is not more than 0.4 times the area of propylene glycol in the chromatogram obtained with *Standard solution B* (1%). Disregard any peaks that are less than 0.04 times the area of propylene glycol in the chromatogram obtained with *Standard solution B* (0.1%).

Molar substitution (see *Nuclear Magnetic Resonance* ⟨761⟩)—The molar substitution (MS) is calculated from the ratio between the signal from the three protons of the methyl group, contained ~~by~~ in the hydroxypropyl ~~function~~ functional group, and the signal from the proton attached to the carbon C_1 (glycosidic proton) of the anhydroglucose units. Use a Fourier-transform nuclear magnetic resonance (NMR) spectrometer ~~of minimum power 250 MHz~~ having a magnetic field strength of at least 6 Tesla~~, suited to perform a proton spectrum and to carry out quantitative analysis, at a temperature of at least 25°.~~ and that is capable of performing quantitative analysis using proton NMR spectroscopy at a temperature of at least 25°.

Test preparation—~~Introduce not less than the equivalent of 10.0 mg of Hydroxypropyl Betadex (dried) into a 5 mm NMR sinning tube. Add about 0.75 mL of deuterium oxide. Cap the tube, mix thoroughly, and adapt the spinner.~~ Mix not less than the equivalent of 10.0 mg of dried Hydroxypropyl Betadex with 0.75 mL of deuterium oxide thoroughly in an NMR tube. Place the tube into an NMR probe.

Procedure—~~Record the FID, with at least 8 scans, so as to obtain a spectral window comprised, at least, between 0 and 6.2 ppm, referring to the peak of exchangeable protons (solvent) at 4.8 ppm (25°). Make a zero filling of at least 3-fold in size relative to the acquisition data file, and transform the FID to the spectrum without any correction of Gaussian Broadening (GB) factor and with a Line Broadening (LB) factor up to 0.2 maximum (GB = 0 and LB ≤ 0.2). Make sure that the spectrum is phased correctly, and call the integration subroutine after phase corrections. Measure the peak areas of~~

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~~the signal from the methyl of the hydroxypropyl function at 1.2 ppm (A_1), and of the signal of the glycosidic proton between 5 and 5.4 ppm (A_2), after baseline correction between 0.5 and 6.2 ppm.~~ Adjust the spectrometer settings so that a high-resolution proton NMR spectrum can be acquired that will provide quantitative data. Acquire a free induction decay (FID) with at least 8 transients using a spectral window from at least 0 to 6.2 ppm, with the solvent peak located at 4.8 ppm at 25°. Zero fill the spectrum at least 3 times, and Fourier transform the FID with no Gaussian line broadening and no more than 0.2 Hz of Lorenzian line broadening. Determine the peak areas of the doublet from the methyl protons of the hydroxypropyl functional group at 1.2 ppm (A_1) and the peak areas from the glycosidic protons, which are located between 5 and 5.4 ppm (A_2). Calculate the molar substitution by the formula:

$$A_1/(3A_2)$$

in which A_1 is the area of the methyl group of hydroxypropyl; and A_2 is the area of the glycosidic proton. The degree of substitution is the number of hydroxypropyl groups per molecule of betadex and is obtained by multiplying the MS by 7.

Limit of propylene oxide—

Ether stock solution—Add 75 µL of ether to about 30 mL of dimethylacetamide in a 50-mL volumetric flask, dilute with dimethylacetamide to volume, and mix. This solution contains about 1.0 mg per mL of ether.

Internal standard solution—Add 30 µL of *Ether stock solution* to about 70 mL of dimethylacetamide in a 100-mL volumetric flask, dilute with dimethylacetamide to volume, and mix.

Propylene oxide stock solution—[Caution—Propylene oxide is toxic and flammable. Prepare this solution in a well-ventilated fume hood.] Add about 30 mL of dimethylacetamide into a 50-mL volumetric flask. Weigh the flask and contents accurately, add 60 µL of propylene oxide (cooled in a refrigerator) into the flask with a 100-µL cooled microsyringe, weigh again, and calculate the weight of propylene oxide added, by difference. [NOTE—Propylene oxide is a gas at room temperature. It is usually stored in a lecture-type gas cylinder or small metal pressure bomb. Chill the cylinder in a refrigerator before use. Transfer about 5 mL of the liquid propylene oxide to a 100-mL beaker chilled in wet ice. Use a gas-tight syringe that has been chilled in a refrigerator.] Dilute with dimethylacetamide to volume, and mix. This solution contains about 1.0 mg per mL of propylene oxide.

Resolution solution—Add 30 µL of the *Ether stock solution* and 20 µL of *Propylene oxide stock solution* to about 70 mL of dimethylacetamide in a 100-mL volumetric flask, dilute with dimethylacetamide to volume, and mix.

Standard stock solutions—Add about 7 mL of dimethylacetamide into each of four 10-mL volumetric flasks. Transfer the following amount of *Propylene oxide stock solution* into each of the four flask using a microsyringe, with one amount per flask: 40, 100, 200, and 400 µL. Dilute with dimethylacetamide to volume, and mix. The *Standard stock solutions* contain about 4, 10, 20, and 40 µg per mL of propylene oxide, respectively.

Standard solutions—Into each of four 10-mL headspace vials, transfer 200 ± 5 mg of Hydroxypropyl Betadex, calculated on the dried basis. Pipet 1.0 mL of the *Internal standard solution* into each vial, and close the vial with septum and cap. Into each of the vials, add 10 µL of each of *Standard stock solutions* using a 10-µL syringe, respectively. Allow each vial to stand, and gently shake until the sample is dissolved. The *Standard solutions* contain, respectively, about 0.04, 0.1, 0.2, and 0.4 µg per mL of propylene oxide.

Test solution—Transfer 200 ± 5 mg of Hydroxypropyl Betadex, calculated on the dried basis, into a 10-mL headspace autosampler vial. Pipet 1.0 mL of the *Internal standard solution* into the vial, and close the vial with a septum and cap. Add 10 µL of dimethylacetamide using a 10-µL syringe. Allow the vial to stand, and gently shake until the sample is dissolved.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a balanced pressure automatic headspace sampler with a split injection mode of a ratio of 1 : 1, a flame-ionization detector and a 0.32-mm × 10-m fused-silica capillary column coated with a 10-µm layer of stationary phase S3. The column temperature is maintained at 50° for the first 10 minutes after injection, programmed to rise at a rate of 10° per minute to a temperature of 100°, maintained for 10 minutes at 100°, then is increased at a rate of 20° per minute to a temperature of 220°, and maintained at 220° for 4 minutes. The transfer line temperature is maintained at 120°. The detector temperature is maintained at 250° and the injection port temperature is maintained at 120°. The carrier gas is helium, flowing at a rate of about 2.0 mL per minute, corresponding to the linear velocity of 44 cm per second. Chromatograph the *Resolution solution,* and record the peak response as directed for *Procedure:* the resolution, *R,* between ether and propylene oxide is not less than 2.0. [NOTE—For information purposes only, the relative retention times are about 1.0 for propylene oxide and 1.3 for ether.]

Procedure—Separately place the vials containing the *Standard solutions* and the *Test solution* in the automated sampler, and start the sequence so that the vial is heated at a temperature of 100° for 30 minutes before a suitable portion of its headspace is injected into the chromatograph. Using a 2-mL gas syringe preheated in an oven at 110°, separately inject 1.0 mL of the headspace from each vial into the chromatograph. Chromatograph the *Standard solutions* and the *Test solution,* record the chromatograms, and measure the area ratios of the peak responses of propylene oxide and ether as directed for *Procedure*. Determine, based on a retention time comparison, whether propylene oxide is detected in the *Test solution*. Plot the area ratios of the peak responses of propylene oxide and ether of the *Test solution* and the *Standard solutions* versus the content, in µg, of propylene oxide in each vial, as furnished by the *Standard stock solutions,* draw the straight line best fitting the five points, and calculate the correlation coefficient for the line. [NOTE—The *Test solution* should be plotted as if it had a content of added propylene oxide equivalent to 0 µg.] A suitable system is one that yields a line having a correlation coefficient of not less than 0.99. Extrapolate the line until it meets the content axis on the negative side. The distance between this point and the intersection of the axes represents the total amount, T_U, in µg, of propylene oxide in the *Test solution*. Calculate the percentage of propylene oxide in the portion of Hydroxypropyl Betadex taken by the formula:

$$100(T_U / W)$$

in which W is the weight, in µg, of Hydroxypropyl Betadex taken to prepare the *Test solution:* the limit is 0.0001%.■2S (*NF25*)

BRIEFING

Palm Kernel Oil. Because there is no existing *NF* monograph for this article, it is proposed to add a new monograph based on the Palm Kernel Oil monograph in the *Food Chemicals Codex, Fifth Edition,* page 316 and also on the *Cottonseed Oil* monograph in *NF 24,* page 3317.

(EM2: H. Wang; NOM: W. Paul) RTS—C44796

Add the following:

■Palm Kernel Oil

Elaeis guineensis seed oil [*8023-79-8*].

» Palm Kernel Oil is the refined fixed oil obtained from the kernel of the fruit of the oil palm *Elaeis guineensis* Jacq. (Fam. Arecaceae). It may contain suitable antioxidants.

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Packaging and storage—Preserve in well-closed containers. No storage requirements specified.

Labeling—Label it to indicate the name and quantity of any added antioxidants.

Identification—

A: It meets the requirements of the test for *Fatty acid composition*.

B: It meets the requirements of the test for *Melting range*.

Melting range ⟨741⟩**:** between 27° and 29°.

Acid value ⟨401⟩**:** not more than 2.0.

Peroxide value ⟨401⟩**:** not more than 10.0.

Unsaponifiable matter ⟨401⟩**:** not more than 1.5%.

Fatty acid composition—Palm Kernel Oil exhibits the following composition profile of fatty acids, as determined in the section *Fatty Acid Composition* under *Fats and Fixed Oils* ⟨401⟩:

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
6	0	≤1.5
8	0	3–5
10	0	2.5–6
12	0	40–52
14	0	14–18
16	0	7–10
18	0	1–3
20	0	≤1
16	1	≤1
18	1	11–19
18	2	0.5–4

Water, *Method I* ⟨921⟩**:** not more than 0.1%, 50 mL of chloroform being used instead of 35 to 40 mL of methanol as the solvent.

Limit of lead—[NOTE—For this test, use reagent-grade chemicals with as low a lead content as is practicable, as well as high-purity water and gases. Before use in this analysis, rinse all glassware and plasticware twice with diluted nitric acid and twice with diluted hydrochloric acid, and then rinse them thoroughly with *Purified Water*.]

Hydrogen peroxide–nitric acid solution—Dissolve equal volumes of 10% hydrogen peroxide and diluted nitric acid. [NOTE—Use caution.]

Lead nitrate stock solution—Dissolve 159.8 mg of lead nitrate in 100 mL of *Hydrogen peroxide–nitric acid solution*. Dilute with *Hydrogen peroxide–nitric acid solution* to 1000 mL, and mix. Prepare and store this solution in glass containers that are free from lead salts. Each mL of this solution contains the equivalent of 100 µg of lead.

Standard lead solution—On the day of use, dilute 10.0 mL of *Lead nitrate stock solution* with *Hydrogen peroxide–nitric acid solution* to 100.0 mL and mix. Each mL of *Standard lead solution* contains the equivalent of 10 µg of lead.

Butanol–nitric acid solution—Slowly add 50 mL of nitric acid to approximately 500 mL of butanol contained in a 1000-mL volumetric flask. Dilute with butanol to volume, and mix.

Standard solutions—Into five separate 100-mL volumetric flasks, pipet 0.2, 0.5, 1, 2, and 5 mL, respectively, of *Standard lead solution,* dilute with *Butanol–nitric acid solution* to volume, and mix. The *Standard solutions* contain, respectively, 0.02, 0.05, 0.1, 0.2, and 0.5 µg of lead per mL.

Test solution—[Caution—Perform this procedure in a fume hood, and wear safety glasses.] Transfer 1.0 g of Oil, accurately weighed, into a large test tube. Add 1 mL of nitric acid. Place the test tube in a rack in a boiling water bath. As soon as the rusty tint is gone, add 1 mL of 30 percent hydrogen peroxide dropwise to avoid a vigorous reaction, and wait for bubbles to form. Stir with an acid-washed plastic spatula if necessary. Remove the test tube from the water bath, and allow it to cool. Transfer the solution into a 10-mL volumetric flask, and dilute with *Butanol–nitric acid solution* to volume, and mix.

Tungsten solution—Transfer 0.1 g of tungstic acid and 5 g of sodium hydroxide pellets into a 50-mL plastic bottle. Add 5.0 mL of water, and mix. Heat the mixture in a hot water bath until complete solution is achieved. Cool, and store at room temperature.

Procedure—Place the graphite tube in the furnace. Inject a 20-µL aliquot of the *Tungsten solution* into the graphite tube, using an argon flow rate of 300 mL per minute. Maintain the drying temperature at 110° for 20 seconds, the ashing temperature at 700° to 900° for 20 seconds, and with the argon flow stopped, the atomization temperature at 2700° for 10 seconds; repeat this procedure once more using a second 20-µL aliquot of the *Tungsten solution*. Clean the quartz windows. [NOTE—The sample injection technique is the most crucial step in controlling the precision of the analysis; the volume of each of the *Standard solutions* and the *Test solution* must remain constant. Rinse the microliter pipet tip three times with either the *Standard solutions* or the *Test solution* before injection. Use a fresh pipet tip for each injection, and start the atomization process immediately after injecting the *Standard solutions* and the *Test solution*. Between injections, flush the graphite tube of any residual lead by purging at a high temperature as recommended by the manufacturer.]

Concomitantly determine the absorbances of the five *Standard solutions* and the *Test solution*, at the lead emission line at 283.3 nm, with a suitable graphite furnace atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a lead hollow-cathode lamp by atomizing the equal volumes (20 µL) of the solutions with an argon flow rate of 300 mL per minute. Maintain the drying temperature of the furnace at 110° for 30 seconds after a 20-second ramp time and a 10-second hold time; the ashing temperature at 700° for 42 seconds after a 20-second ramp time and a 22-second hold time; and the atomization temperature at 2300° for 7 seconds with the argon flow stopped. Plot the absorbance of each of the *Standard solutions,* compensated for background correction, versus its content of lead, in µg per mL, and draw the best straight line fitting the five points. From this plot, determine the concentration, *C,* in µg per mL, of lead in the *Test solution*. Calculate the quantity, in µg per g, of lead in the Oil taken by the formula:

$$10C / W$$

in which W is the weight, in g, of the Oil taken to prepare the *Test solution*: not more than 0.1 µg of lead per g is found.■2S (*NF25*)

BRIEFING

Polyoxyl 10 Oleyl Ether, *NF 24* page 3400 and page 3629 of the *First Supplement.* On the basis of comments received, it is proposed to revise the specification range for average polymer length in the Definition statement. In addition, it is proposed to revise the test for *Average polymer length* to employ a quantitative analysis and to reflect current practice.

(EM2: H. Wang) RTS—C46394

Change to read:

» Polyoxyl 10 Oleyl Ether is a mixture of the monooleyl ethers of mixed polyoxyethylene diols, the average polymer length being equivalent to not less than ~~8.6~~

■9.1■2S (*NF25*)
and not more than ~~10.4~~

■10.9■2S (*NF25*)
oxyethylene units. It may contain suitable stabilizers.

Change to read:

Average polymer length—If solid material is present, place the Polyoxyl 10 Oleyl Ether in a 60° water bath overnight. Shake vigorously to eliminate any possibility of molecular weight gradients within it. Add about 1 mL of the melt to 1 mL of deuterated chloroform in a test tube, and shake the test tube until dissolution is complete. Transfer about 0.5 mL to an NMR tube, and add ~~5 drops~~

■a small amount■2S (*NF25*)
of tetramethylsilane as an internal reference standard. Cap the tube tightly, and shake thoroughly. Place the tube in the NMR spectrometer

■that is capable of performing quantitative analysis,■2S (*NF25*)

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and record the NMR spectrum ~~at an appropriate RF power level and a sweep time of 250 seconds per 500 Hz (see *Qualitative Scans* under *Nuclear Magnetic Resonance* ⟨761⟩). Adjust the spectrum amplitude so that the signal at 1.1 ppm is at least 80% of full scale. Record the integral areas from 0.4 ppm to 2.35 ppm (A_1), and from 2.35 ppm to 4.9 ppm (A_2) at a sweep time of 50 seconds per 500 Hz at an integral power level such that the integral of the largest peak is at least 80% of full chart height. Do not change the power level during the sweep. Record the integral of each peak several times, and calculate the average integral area.~~

■(see *Quantitative Applications* under *Nuclear Magnetic Resonance* ⟨761⟩). Integrate the areas from 0.4 ppm to 2.35 ppm (A_1), and from 2.35 ppm to 4.9 ppm (A_2).■2S *(NF25)*

Calculate the number of oxyethylene units, n, per molecule taken by the formula:

$$n = (31A_2/A_1 - 3)/4$$

in which 31 is the total number of protons in the molecule not activated by either oxygen or a double bond, 3 is the number of oxygen-activated protons not included in the oxyethylene unit count, and 4 is the number of protons in each oxyethylene unit.

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**11**⟩ **USP Reference Standards,** *USP 29* page 2458, page 3754 of the *Second Supplement,* page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], page 1154 of *PF* 31(4) [July–Aug. 2005], page 1433 of *PF* 31(5) [Sept.–Oct. 2005], page 1680 of *PF* 31(6) [Nov.–Dec. 2005], page 181 of *PF* 32(1) [Jan.–Feb. 2006], page 407 of *PF* 32(2) [Mar.–Apr. 2006], page 829 of *PF* 32(3) [May–June 2006], page 1161 of *PF* 32(4) [July–Aug. 2006].

(HDQ) RTS—C40762; C41770; C42755; C43102; C44146; C44916; C46383; C46788; C47099; C47275

Change to read:

■**USP Benazepril Related Compound D RS** [(3-(1-ethoxycarbonyl-3-cyclohexyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid,■2S (*USP29*)

■monohydrochloride] ($C_{24}H_{34}N_2O_5 \cdot HCl$ ✧ 467.00).■2S (*USP30*)

Add the following:

■**USP Cilostazol Related Compound C RS** ~~[1,6-bis-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)-butoxy]-1*H*-quinolin-2-one]~~[1-(4-(5-cyclohexyl-1*H*-tetrazol-1-yl)butyl)-6-(4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxy)-3,4-dihydroquinolin-2(1*H*)-one] ($C_{31}H_{43}N_9O_3$ ✧ 589.73).■2S (*USP30*)

Add the following:

■**USP Citalopram Related Compound G RS** [1-~~(4-fluorophenyl)~~(4′-fluorophenyl)-1-(3-dimethylaminopropyl)-5-chlorophthalane hydrobromide] ($C_{19}H_{21}$~~ClFNO~~FNOCl · HBr ✧ ~~414.5).~~ 414.74).■2S (*USP30*)

Add the following:

■**USP Citalopram Related Compound H RS** [1-~~4-fluorophenyl~~ (4′-fluorophenyl)-1-(3-dimethylaminopropyl)-5-bromophthalane hydrobromide] ($C_{19}H_{21}$~~Br FNO~~ FNOBr · HBr ✧ 459.1).■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound A RS** [*N*-1,4-benzodioxane-2-carbonyl piperazine] ($C_{13}H_{16}N_2O_3$ ✧ 248.28).■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound B RS** [6,7-dimethoxyquinazoline-2,4-dione] ($C_{10}H_{10}N_2O_4$ ✧ 222.20).■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound C RS** [2-chloro-4-amino-6,7-dimethoxyquinazoline] ($C_{10}H_{10}ClN_3O_2$ ✧ 239.66).■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound D RS** [1,4-benzodioxane-2-carbonic acid] ($C_9H_8O_5$ ✧ 196.16).■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound E RS** [2,4-dichloro-6,7-dimethoxyquinazoline] ($C_{10}H_8Cl_2N_2O_2$ ✧ 259.09).■2S (*USP30*)

Add the following:

■**USP Doxazosin Related Compound F RS** [*N,N′*-bis(1,4-benzodioxane-2-carbonyl)piperazine] ($C_{22}H_{22}N_2O_6$ ✧ 410.42).■2S (*USP30*)

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Add the following:

■**USP Doxepin Related Compound A RS** [5-(4-nitrophenyl)-2-furaldehyde-2-carboxymethyl semicarbazone] ($C_{14}H_{10}O_2$ ✧ 210.23).■2S (*USP30*)

Add the following:

■**USP Doxepin Related Compound B RS** [11(*RS*)-(3-(dimethylamino)propyl)-6,11-dihydrodibenzo-[*b,e*]oxepin-11-ol] ($C_{19}H_{23}NO_2$ ✧ 297.39).■2S (*USP30*)

Add the following:

■**USP Doxepin Related Compound C RS** [(*E,Z*)-3-(dibenzo[*b,e*]oxepin-11(6*H*)-ylidene)-*N*-methylpropan-1-amine] ($C_{18}H_{19}NO \cdot HCl$ ✧ 301.81).■2S (*USP30*)

Add the following:

■**USP Glipizide Related Compound B RS** [6-methyl-*N*-[2-(4-sulfamoylphenyl)ethyl]pyrazine-2-carboxamide] ($C_{14}H_{16}N_4O_3S$ ✧ 320.37).■2S (*USP30*)

Add the following:

■USP Glipizide Related Compound C RS [1-cyclohexyl-3-[[4-[2-[[(6-methylpyrazin-2-yl)carbonyl]amino]ethyl]phenyl]sulfonyl]urea] ($C_{21}H_{27}N_5O_4S$ ✧ 445.54).■2S (*USP30*)

Add the following:

■**USP Hydroxypropyl Betadex RS.**■2S (*USP30*)

Change to read:

USP Naratriptan Resolution Mixture RS—A mixture of naratriptan hydrochloride with approximately ~~1% of~~

■0.1% each of■2S (*USP30*)
naratriptan related compound A [3-(1-methylpiperidin-4-yl)-1*H*-indole hydrochloride] and naratriptan related compound B [2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-5-yl]ethanesulfonic acid methylamide oxalate].

Change to read:

USP Nimodipine Related Compound A RS [(2-methoxyethyl-1-methylethyl-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate] ~~($C_{24}H_{28}N_2O_8$~~

■($C_{21}H_{24}N_2O_7$■2S (*USP30*)
✧416.42).

Add the following:

■**USP Tazobactam Related Compound A RS** [(2*S,3S*)-2-amino-3-methyl-3-sulfino-4-(1*H*-1,2,3-triazol-1-yl)butyric acid] ($C_7H_{12}N_4O_4S$ ✧ 248.26).■2S (*USP30*)

LIMIT TESTS

BRIEFING

⟨**401**⟩ **Fats and Fixed Oils,** *USP 29* page 2568 and page 3766 of the *Second Supplement.* On the basis of comments received, it is proposed to revise the test for *Acid Value (Free Fatty Acids)* to include potassium hydroxide solution as another titrant of choice and to designate the current method as *Method I;* in addition *Method II* is proposed to allow for the use of a different solvent mixture.

(EGC: H. Wang) RTS—C46732

Change to read:

ACID VALUE (FREE FATTY ACIDS)

The acidity of fats and fixed oils in this Pharmacopeia may be expressed as the number of mL of 0.1 N alkali required to neutralize the free acids in 10.0 g of substance. Acidity is frequently expressed as the Acid Value, which is the number of mg of potassium hydroxide required to neutralize the free acids in 1.0 g of the substance.

■Unless otherwise directed in the individual monograph, use *Method I.*■2S (*USP30*)

■**Method I**■2S (*USP30*)

Procedure—Unless otherwise directed, dissolve about 10.0 g of the substance, accurately weighed, in 50 mL of a mixture of equal volumes of alcohol and ether (which has been neutralized to phenolphthalein with

■0.1 N potassium hydroxide or■2S (*USP30*)
0.1 N sodium hydroxide,

■unless otherwise specified)■2S (*USP30*)
contained in a flask. If the test specimen does not dissolve in the cold solvent, connect the flask with a suitable condenser and warm slowly, with frequent shaking, until the specimen dissolves. Add 1 mL of phenolphthalein TS, and titrate with

■0.1 N potassium hydroxide VS or■2S (*USP30*)

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0.1 N sodium hydroxide VS until the solution remains faintly pink after shaking for 30 seconds. Calculate either the Acid Value or the volume of 0.1 N alkali required to neutralize 10.0 g of specimen (free fatty acids), whichever is appropriate. ■Calculate the Acid Value by the formula:

$$56.1V \times N/W$$

in which ~~*V* is the volume, in mL; *N* is the normality, respectively, of the~~

■56.1 is the molecular weight of potassium hydroxide; *V* is the volume, in mL; *N* is the normality, of the potassium hydroxide solution or■2S *(USP30)*
sodium hydroxide solution; and *W* is the weight, in g, of the sample taken.■2S *(USP29)*

If the volume of

■0.1 N potassium hydroxide VS or■2S *(USP30)*
0.1 N sodium hydroxide VS required for the titration is less than 2 mL, a more dilute titrant may be used, or the sample size may be adjusted accordingly. The results may be expressed in terms of the volume of titrant used or in terms of the equivalent volume of

■0.1 N potassium hydroxide or■2S *(USP30)*
0.1 N sodium hydroxide.

If the oil has been saturated with carbon dioxide for the purpose of preservation, gently reflux the alcohol-ether solution for 10 minutes before titration. The oil may be freed from carbon dioxide also by exposing it in a shallow dish in a vacuum desiccator for 24 hours before weighing the test specimens.

■Method II

Procedure—Prepare 125 mL of a solvent mixture consisting of equal volumes of isopropyl alcohol and toluene. Before use, add 2 mL of 1% solution of phenolphthalein in isopropyl alcohol to the 125-mL mixture, and neutralize with alkali to a faint but permanent pink color. Weigh accurately the appropriate amount of well-mixed liquid sample indicated in the table below, and dissolve it in the neutralized solvent mixture. If the test specimen does not dissolve in the cold solvent, connect the flask with a suitable condenser and warm slowly, with frequent shaking, until the specimen dissolves. Shake vigorously while titrating with 0.1 N potassium hydroxide VS or 0.1 N sodium hydroxide VS to the first permanent pink of the same intensity as that of the neutralized solvent before mixture with the sample. Calculate the Acid Value as indicated in *Method I*.

Acid Value	Sample Weight (g)
0–1	20
1–4	10
4–15	2.5
15–74.9	0.5
≥75.0	0.1

■2S *(USP30)*

BRIEFING

⟨**466**⟩ **Ordinary Impurities,** *USP 29* page 2579. Impurites are closely related to integrity and safety, which are matters of principal interest for *USP*. Regulatory agencies participating in the International Conference on Harmonization (ICH) are near to concluding the process for adoption of the guidelines "*Impurities in New Drug Substances (Q3A)*" and "*Impurities in New Drug Products (Q3B)*". Revisions to incorporate the intent of ICH are proposed for the general chapter *Impurities in Official Articles* ⟨1086⟩, published elsewhere in this issue of *PF*. Revisions to this chapter are proposed to maintain consistency with the changes in ⟨1086⟩.

(GC: A. Hernandez-Cardoso) RTS—C46417

Change to read:

~~This test, where called for in the individual monograph, is provided to evaluate the impurity profile of an article. See *Chromatography* ⟨621⟩ for a general discussion of the thin-layer chromatographic technique. Unless otherwise specified in the individual monograph, use the following method.~~

■This test, where called for in the individual monograph, is provided to control ordinary impurities in official articles. Ordinary impurities are defined as those species in drug substances and/or drug products that have no significant, undesirable biological activity in the amounts present. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles. Selections of tests and assays allow for anticipated amounts of impurities that are unobjectionable for the customary use of the article.■2S *(USP30)*

Add the following:

■Reporting and Specifications—The value of 2.0%, unless otherwise specified in the individual monograph, was selected as the general limit on ordinary impurities in monographs where documentation did not support adoption of other values.

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Where a monograph sets limits on concomitant components and/or specified impurities/degradation products, these species are not to be included in the estimation of ordinary impurities unless so stated in the individual monograph.■2S (*USP30*)

Add the following:

■**Methodology**—Unless otherwise specified in an individual monograph, estimation of the amount and number of ordinary impurities is made by relative methods rather than by strict comparison to individual Reference Standards. Nonspecific detection of ordinary impurities is also consistent with this classification.

Typical evaluation methods used for ordinary impurities are thin-layer chromatographic (TLC) techniques. See *Chromatography* ⟨621⟩ for a general discussion of the thin-layer chromatographic technique. Tests for related substances or chromatographic purity may also be used to control the presence of ordinary impurities. Other methods (e.g., HPLC, HPTLC, etc.) may also be used with adequate justification as an alternate method.

Unless otherwise specified in the individual monograph, use the following method.■2S (*USP30*)

Change to read:

Procedure—Use a thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel mixture, and the *Eluant* specified in the monograph. Apply equal volumes (20 µL) of the *Test Solution* and *Standard Solutions* to the plate, using a stream of nitrogen to dry the spots.

Allow the chromatogram to develop in a pre-equilibrated chamber until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, and air-dry. View the plate using the visualization technique(s) specified. Locate any spots other than the principal spot in the chromatogram of the *Test Solution,* and determine their relative intensities by comparison with the chromatograms of the appropriate *Standard Solutions*. ~~The total of any ordinary impurities observed does not exceed 2.0%, unless otherwise specified in the individual monograph.~~

■See discussion with regard to reporting and specifying of ordinary impurities above.■2S (*USP30*)

KEY FOR VISUALIZATION TECHNIQUES

(1) Use UV light at 254 nm and at about 366 nm.
(2) Use Iodoplatinate TS.
(3) *Solution A*—Mix 850 mg of bismuth subnitrate with 40 mL of water and 10 mL of glacial acetic acid.

Solution B—Dissolve 8 g of potassium iodide in 20 mL of water. Mix A and B together to obtain a Stock Solution which can be stored for several months in a dark bottle. Mix 10 mL of the Stock Solution with 20 mL of glacial acetic acid, and dilute with water to make 100 mL, to prepare the spray reagent.
(4) *Ninhydrin Spray*—Dissolve 200 mg of ninhydrin in 100 mL of alcohol. Heat the plate after spraying.
(5) *Acid Spray*—In an ice bath, add slowly and cautiously, with stirring, 10 mL of sulfuric acid to 90 mL of alcohol. Spray the plate, and heat until charred.
(6) *Acid–Dichromate Spray*—Add sufficient potassium dichromate to 100 mL of sulfuric acid to make a saturated solution. Spray the plate, and heat until charred.
(7) *Vanillin*—Dissolve 1 g of vanillin in 100 mL of sulfuric acid.
(8) *Chloramine T–Trichloroacetic Acid*—Mix 10 mL of a 3% aqueous solution of chloramine T with 40 mL of a 25% alcoholic solution of trichloroacetic acid. Prepare immediately before use.
(9) *Folin-C*—Add 10 g of sodium tungstate and 2.5 g of sodium molybdate to 70 mL of water, add 5 mL of 85% phosphoric acid and 10 mL of 36% hydrochloric acid, and reflux this solution for 10 hours.
(10) $KMnO_4$—Dissolve 100 mg of Potassium Permanganate in 100 mL of water.
(11) *DAB*—Mix 1 g of *p*-dimethylaminobenzaldehyde in 100 mL of 0.6 *N* hydrochloric acid.
(12) *DAC*—Mix 100 mg of *p*-dimethylaminocinnamaldehyde in 100 mL of 1 *N* hydrochloric acid.
(13) *Ferricyanide*—Mix equal volumes of a 1% ferric chloride solution and a 1% potassium ferricyanide solution. Use immediately.
(14) *Fast Blue B*—Reagent A—Dissolve 500 mg of Fast Blue B Salt in 100 mL of water.
Reagent B—0.1 N sodium hydroxide.
Spray first with A, then with B.
(15) *Alkaline Ferric Cyanide*—Dilute 1.5 mL of a 1% potassium ferricyanide solution with water to 20 mL, and add 10 mL of 15% sodium hydroxide solution.
(16) *Iodine Spray*—Prepare a 0.5% solution of iodine in chloroform.
(17) Expose the plate for 10 minutes to iodine vapors in a pre-equilibrated closed chamber, on the bottom of which there are iodine crystals.
(18) *Solution A*—Dissolve 0.5 g of potassium iodide in 50 mL of water.
Solution B—Prepare a solution of 0.5 g of soluble starch in 50 mL of hot water.
Just prior to use, mix equal volumes of *Solution A* and *Solution B*.
(19) *PTSS*—Dissolve 20 g of *p*-toluenesulfonic acid in 100 mL of alcohol, spray the plate, dry for 15 minutes at 110°, and view under UV light at 366 nm.
(20) *o-Tolidine Spray*—Dissolve 160 mg of *o*-tolidine in 30 mL of glacial acetic acid, dilute with water to make 500 mL, add 1 g of potassium iodide, and mix until the potassium iodide has dissolved.
(21) Mix 3 mL of chloroplatinic acid solution (1 in 10) with 97 mL of water, followed by the addition of 100 mL of potassium iodide solution (6 in 100) to prepare the spray reagent.
(22) *Iodine–Methanol Spray*—Prepare a mixture of iodine TS and methanol (1 : 1).

BRIEFING

⟨**467**⟩**Residual Solvents,** page 3774 of the *Second Supplement* and page 1011 of *PF* 32(4) [July–Aug. 2006] under *Policies and Announcements*. It was announced in *PF* 32(4) that the new implementation date for this requirement is July 1, 2007. Also, the announcement reflects that the0 implementation date for the change in the title of this general chapter has been modified to July 1, 2007. On the basis of the general concern presented by the industry in stakeholders forums and on comments received regarding several differences between the USP text and ICH Q3C guidelines, this general chapter is being proposed for revision. The changes are intended to

consider and correct many of those differences, harmonizing to the extent possible with the ICH document. Comments received indicate that some problems may exist in performing the analytical procedures for water-insoluble articles. In light of that, it was decided to delete the analytical procedures and allow users to use other validated procedures. In order to correct this deficiency, users are encouraged to send to USP alternative general procedures useful for testing residual solvents Class 1 and Class 2 in water-insoluble articles.

(GC: H. Pappa) RTS—C44705

⟨467⟩ RESIDUAL SOLVENTS

(Chapter under this new title—to become official July 1, 2007)
(Current chapter title is** ⟨467⟩ Organic Volatile Impurities**)

Change to read:

▪INTRODUCTION

This general chapter applies to existing drug substances, excipients, and medicinal products whether or not they are the subject of a monograph of the Pharmacopeia. All substances and products are to be tested for the content of solvents likely to be present in a substance or product.

Where the limits to be applied comply with those given below, tests for residual solvents are not generally mentioned in specific monographs because the solvents employed may vary from one manufacturer to another.

Where a quantitative determination of a residual solvent is carried out and a test for loss on drying is not carried out, the content of residual solvent is taken into account for calculation of the assay content of the article.

The objective of this general chapter is to provide acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. The general chapter recommends the use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.▪2S (*USP30*)

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. This general chapter does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Because residual solvents do not provide therapeutic benefit, they should be removed, to the extent possible, to meet ingredient and product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. ~~Solvents~~

▪Some solvents▪2S (*USP30*)
that are known to cause unacceptable toxicities (Class 1, *Table 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. ~~Solvents~~

▪Some solvents▪2S (*USP30*)
associated with less severe toxicity (Class 2, *Table 2*) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, *Table 3*) should be used where practical. The complete list of solvents included in this general chapter is given in *Appendix 1*. These tables and the list are not exhaustive. ~~Where other solvents have been used, based on approval by the competent regulatory authority, such solvents may be added to the tables and list.~~

▪For the purposes of this Pharmacopeia, when a manufacturer has received approval from a competent regulatory authority for the use of a new solvent not currently listed in this general chapter, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent, the approved residual solvent limit in the article, and the appropriate test procedure for this residual solvent in the article. The USP will then address this topic in the individual monograph. When a new solvent has been approved through the ICH process, this new solvent will be added to the appropriate list in this general chapter. At that time consideration will be given for removal of the specific solvent test requirement in the individual monograph.▪2S (*USP30*)

Testing of drug substances, excipients, and drug products for residual solvents should be performed when production or purification processes are known to result in the presence of such residual solvents. It is only necessary to test for residual solvents that are used or produced in the manufacture or purification ~~processes~~

▪of drug substances, excipients, or drug products.▪2S (*USP30*)

Although manufacturers may choose to test the drug product, a cumulative procedure may be used to calculate the residual solvent levels in the

▪drug▪2S (*USP30*)
product from the levels in ~~its ingredients~~

▪the ingredients used to produce the drug product.▪2S (*USP30*)
If the calculation results in a level equal to or below that ~~recommended~~

▪provided▪2S (*USP30*)
in this general chapter, no testing of the drug product for residual solvents ~~needs to~~

▪need▪2S (*USP30*)
be considered. If, however, the calculated ~~levels are~~

▪level is▪2S (*USP30*)
above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent ~~levels to within acceptable amounts~~

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■level to within the acceptable amount.■2S (*USP30*)
A drug product should also be tested if a residual solvent is used during its manufacture.

■For the purposes of this Pharmacopeia, when a manufacturer has received approval from a competent regulatory authority for a higher level of residual solvent, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent and the approved residual solvent limit in the article. The USP will then address this topic in the individual monograph.■2S (*USP30*)

See *Appendix 2* for additional background information related to residual solvents.

Change to read:

CLASSIFICATION OF RESIDUAL SOLVENTS BY RISK ASSESSMENT

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and the term "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The term "permitted daily exposure" (PDE) is defined as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs of the same substance.

Residual solvents ~~specified~~

■assessed■2S (*USP30*)
in this general chapter are listed in *Appendix 1* by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1	~~Residual Solvents: Solvents to be Avoided~~
■Residual Solvents■2S (*USP30*)	■Solvents to be avoided■2S (*USP30*) Known human carcinogens Strongly suspected human carcinogens Environmental hazards
Class 2	~~Residual Solvents: Solvents to be Limited~~
■Residual Solvents■2S (*USP30*)	■Solvents to be limited■2S (*USP30*) Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.
Class 3	~~Residual Solvents: Solvents with Low Toxic Potential~~
■Residual Solvents■2S (*USP30*)	■Solvents with low toxic potential■2S (*USP30*) Solvents with low toxic potential to humans; no health-based exposure limit is needed. [NOTE—Class 3 residual solvents ~~may have PDEs of up to~~ ■have PDEs of■2S (*USP30*) 50 mg or more per day.]*

* For residual solvents with PDEs of more than 50 mg per day, see the discussion in the section *Class 3* under *Limits of Residual Solvents*.

Change to read:

~~PROCEDURES~~

■METHODS■2S (*USP30*)

FOR ESTABLISHING EXPOSURE LIMITS

The ~~procedure~~ ■method■2S (*USP30*)
used to establish permitted daily exposures for residual solvents is presented in *Appendix 3*.

Change to read:

OPTIONS FOR ~~DETERMINING LEVELS~~

■DESCRIBING LIMITS■2S (*USP30*)

OF CLASS 2 RESIDUAL SOLVENTS

Two options are available ~~to determine levels of~~ ■when setting limits for■2S (*USP30*)
Class 2 residual solvents.

Option 1

The concentration limits in ppm stated in *Table 2* are used. They were calculated using equation (1) below by assuming a product weight of 10 g administered daily.

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}} \quad (1)$$

Here, PDE is given in terms of mg per day, and dose is given in g per day.

These limits are considered acceptable for all drug substances, excipients, and drug products. Therefore, this option may be applied if the daily dose is not known or fixed. If all drug substances and excipients in a formulation meet the limits given in *Option 1,* these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day are to be considered under *Option 2.*

Option 2

It is not necessary for each component of the drug product to comply with the limits given in *Option 1.* The PDE in terms of mg per day as stated in *Table 2* can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in a drug product. Such limits are considered acceptable

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provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process. The limits should also reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the application of *Option 1* and *Option 2* to acetonitrile concentration in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus, the *Option 1* limit is 410 ppm. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Drug product	5.0	728	3.64

Excipient l meets the *Option 1* limit, but the drug substance, excipient 2, and drug product do not meet the *Option 1* limit. Nevertheless, the drug product meets the *Option 2* limit of 4.1 mg per day and thus conforms to the acceptance criteria in this general chapter.

Consider another example using acetonitrile as the residual solvent. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	2000	1.80
Excipient 2	3.8	800	3.04
Drug product	5.0	1016	5.08

In this example, the drug product meets neither the *Option 1* nor the *Option 2* limit

■according to this summation.■2S (*USP30*)
The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced to the allowed limit during formulation, the ~~product fails the requirements of the test.~~

■manufacturer of the drug product should take other steps to reduce the amount of acetonitrile in the drug product, unless the manufacturer has received approval from a competent regulatory authority for such a higher level of residual solvent. If this is the case, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent and the approved residual solvent limit in the article. The USP will then address this topic in the individual monograph.■2S (*USP30*)

Add the following:

■ANALYTICAL PROCEDURES

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this general chapter are to be applied wherever possible. Otherwise, manufacturers may select the most appropriate validated analytical procedure for a particular application. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the results obtained by the procedures given in this general chapter are conclusive (see *General Notices*). If only Class 3 solvents are present, a nonspecific method such as loss on drying may be used.

All methods for residual solvents should be appropriately validated as specified under *Validation of Compendial Procedures* ⟨1225⟩.■2S (*USP30*)

Add the following:

■REPORTING LEVELS OF RESIDUAL SOLVENTS

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in drug substances or excipients in order to meet the criteria of this general chapter. The following statements are given as acceptable examples of the information that could be provided from a supplier of drug substances or excipients to a pharmaceutical manufacturer. The supplier might choose one of the following as appropriate:

- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5%.
- Only Class 2 solvents X, Y, ... are likely to be present. All are below the Option 1 limit. (Here the supplier would name the Class 2 solvents represented by X, Y, ...)

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- Only Class 2 solvents X, Y, ... and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5%.

The phrase "likely to be present" as used in the above examples refers to the solvent used or produced in the final manufacturing step and to solvents that are used or produced in earlier manufacturing steps and not removed consistently by a validated process.

If Class 1 solvents are likely to be present, they should be identified and quantified. If solvents of Class 2 or 3 are present at greater than their Option 1 limits or 0.5%, respectively, they should be identified and quantified.■2S (*USP30*)

Change to read:

LIMITS OF RESIDUAL SOLVENTS

Ethylene Oxide

[NOTE—The test for ethylene oxide is conducted only where specified in the individual monograph.] The standard solution parameters and the procedure for determination are described in the individual monograph. Unless otherwise specified in the individual monograph, the limit is 10 µg per g.

Class 1

■(solvents to be avoided)■2S (*USP30*)

Class 1 residual solvents *(Table 1)* should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if their use in order to produce a medicinal product

■with a significant therapeutic advance■2S (*USP30*)
is unavoidable, their levels should be restricted as shown in *Table 1,* unless otherwise stated in the individual monograph. The solvent 1,1,1-trichloroethane is included in *Table 1* because it is an environmental hazard. The stated limit of 1500 ppm is based on

■a review of■2S (*USP30*)
safety data.

When Class 1 residual solvents are used or produced in the manufacture or purification of a drug substance, excipient, or drug product, these solvents should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this general chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. ~~Such procedure shall be submitted to the USP for evaluation.~~

■■2S (*USP30*)

Table 1. Class 1 Residual Solvents

■(solvents that should be avoided)■2S (*USP30*)

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Class 2

Class 2 residual solvents *(Table 2)* should be limited in drug substances, excipients, and drug products because of the inherent toxicities of the residual solvents. PDEs are given to the nearest 0.1 mg per day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of the determination procedure. Precision should be determined as part of the procedure validation.

If Class 2 residual solvents are present at greater than their *Option 1* limits, they should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this general chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. ~~Such procedure shall be submitted to the USP for evaluation~~

■■2S (*USP30*)

[NOTE—The following Class 2 residual solvents are not readily detected by the headspace injection conditions described in the *Identification, Control, and Quantification of Residual Solvents* section of this general chapter: formamide, 2-ethoxyethanol,2-methoxyethanol, ethylene glycol, *N*-methylpyrrolidone, and sulfolane. Other appropriate validated procedures are to be employed for the quantification of these residual solvents. Such procedures shall be submitted to the USP for review and possible inclusion in the relevant individual monograph.]

Table 2. Class 2 Residual Solvents

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
Methylene chloride	6.0	600
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890

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Table 2. Class 2 Residual Solvents *(Continued)*

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Trichloroethylene	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene

Class 3

Class 3 residual solvents *(Table 3)* may be regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

~~Unless otherwise stated in the individual monograph, Class 3 residual solvents are limited to not more than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*).~~

■It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5% under *Option 1*) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice. For the purposes of this Pharmacopeia, when a manufacturer has received approval from a competent regulatory authority for such a higher level of residual solvent, it is the responsibility of that manufacturer to notify the USP regarding the identity of this solvent and the approved residual solvent limit in the article. The USP will then address this topic in the individual monograph.■2S (*USP30*)

If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day, that residual solvent should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this general chapter, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. ~~Such procedure shall be submitted to the USP for evaluation. USP Reference Standards, where available, should be used in these procedures.~~

■■2S (*USP30*)

Table 3. Class 3 Residual Solvents
(limited by GMP or other quality-based requirements in drug substances, excipients, and drug products)

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone
tert-Butylmethyl ether	Methylisobutylketone
Cumene	2-Methyl-l-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Other Residual Solvents

The residual solvents listed in *Table 4* may also be of interest to manufacturers of drug substances, excipients, or drug products. However, no adequate toxicological data on which to base a PDE was found.

Table 4. Other Residual Solvents
(for which no adequate toxicological data was found)

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Solvent hexane
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

Change to read:

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

■Whenever possible, the substance under test needs to be dissolved to release the residual solvent. As the USP deals with drug products, as well as with active ingredients and excipients, it may be acceptable that in cases, some of the components of the formulation will not dissolve completely. In those cases, the drug product may first need to be pulverized into a fine powder so that any residual solvent that may be present can be released. This operation should be as fast as possible to prevent the loss of volatile solvents during the procedure.■2S (*USP30*)

[NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.]

Class 1 and Class 2 Residual Solvents

~~WATER-SOLUBLE ARTICLES~~

■The following *Procedures* demonstrated that they were appropriate for water-soluble articles. For water-insoluble articles, perform the appropriate modifications to the standard solutions and chromatographic parameters. Otherwise, an appropriate validated procedure is to be employed.■2S (*USP30*)

Procedure A—

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A.* Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B.*

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution,* apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution, Class 1 System Suitability Solution,* and *Class 2 Mixture A Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in the table below) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. ~~If a peak response of any peak in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.~~

■If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions*, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in the *Class 1 Standard Solution*, proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.■2S (*USP30*)

Table 5. Headspace Operating Parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock Solutions, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Class 2 System Suitability Solution—Transfer 1.0 mL of USP Residual Solvent Class 2—Acetonitrile RS and 1.0 mL of USP Residual Solvent Class 2—Trichloroethylene RS to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 0.25-µm layer of phase G16, or a 0.53-mm × 30-m wide-bore column coated with a 0.25-µm layer of phase G16. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second and a split ratio of 1 : 5. The column temperature is maintained at 50° for 20 minutes, then raised at a rate of 6° per minute to 165°, and maintained at 165° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2 System Suitability Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of benzene in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and trichloroethylene in the *Class 2 System Suitability Solution* is not less than 1.0.

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Procedure—Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution,* the *Class 2 Mixture A Standard Solution,* the *Class 2 Mixture B Standard Solution,* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or either of the two *Class 2 Mixture Standard Solutions,* proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock Solution A, Class 2 Mixture A Standard Solution, Test Stock Solution, Test Solution, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Standard Solution—~~[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*]~~

■[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.* For the Class 1 solvents other than 1,1,1-trichloroethane, prepare the first dilution as directed for the first dilution under *Class 1 Standard Stock Solution* in *Procedure A.*]■2S (*USP30*)
Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of the *Standard Solution,* apply the stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—[NOTE—If the results of the chromatography from *Procedure A* are found to be inferior to those found with *Procedure B,* the *Chromatographic System* from *Procedure B* may be substituted.] The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1 : 5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution,* the *Class 1 System Suitability Solution,* and the *Class 2 Mixture A Standard Solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R,* between acetonitrile and methylene chloride in the *Class 2 Mixture A Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution,* the *Test Solution,* and the *Spiked Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{ST} - r_U)]$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_{ST} are the peak responses of each residual solvent obtained from the *Test Solution* and the *Spiked Test Solution,* respectively.

~~WATER-INSOLUBLE ARTICLES~~

~~**Procedure A—**~~

~~*Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution,* and *Chromatographic System*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*~~

~~*Class 2 Standard Stock Solution C*—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture C RS to a 100-mL volumetric flask, dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix.~~

~~*Class 2 Mixture C Standard Solution*—[NOTE—This solution is used for the identification and quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer 1.0 mL of *Class 2 Standard Stock Solution C* to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.~~

~~*Test Stock Solution*—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.~~

~~*Test Solution 1*—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of dimethylformamide, apply the stopper, cap, and mix.~~

~~*Test Solution 2*—[NOTE—This solution is used for the identification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix. Transfer 5.0 mL of this solution to an appropriate headspace vial, add 1.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.~~

~~*Procedure*—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution, Test Solution 1,* and *Test Solution 2* (if applicable) into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in *Test Solution 1* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or any of the three *Class 2 Mixture Standard Solutions,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Mixture C Standard Solution,* proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.~~

~~**Procedure B—**~~

~~*Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, Class 2 Standard Stock Solution B, Class 2 Mixture A Standard Solution,* and *Class 2 Mixture B Standard Solution*—Prepare as directed for *Procedure A* under *Water-Soluble Articles.*~~

~~*Class 2 Standard Stock Solution C, Class 2 Mixture C Standard Solution, Test Stock Solution, Test Solution 1,* and *Test Solution 2*—Proceed as directed for *Procedure A.*~~

~~*Class 2 System Suitability Solution* and *Chromatographic System*—Proceed as directed for *Procedure B* under *Water-Soluble Articles.*~~

~~*Procedure*—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Class 2 Mixture C Standard Solution, Test Solution 1,* and/or *Test Solution 2* (if applicable) into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in *Test Solution 1* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or any of the three *Class 2 Mixture Standard Solutions,*~~

In-Process Revision

proceed to *Procedure C* to quantify the peak(s); otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N,N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Mixture Standard Solution, C* proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test.

Procedure C

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, and *Class 2 Mixture A Standard Solution*—Proceed as directed for *Procedure A* under *Water-Soluble Articles.*

Standard Solution 1—[NOTE—Prepare a separate *Standard Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with dimethylformamide to obtain a solution having a final concentration of 1/20 of the value stated in *Table 1* or *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of dimethylformamide, apply the stopper, cap, and mix.

Standard Solution 2—[NOTE—This solution is used for the quantification of dimethylformamide and/or *N,N*-dimethylacetamide in the article under test.] Transfer an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylformamide RS and/or an accurately measured volume of USP Residual Solvent Class 2—*N,N*-Dimethylacetamide RS to a suitable container, and dilute quantitatively, and stepwise if necessary, with 1,3-dimethyl-2-imidazolidinone to obtain a solution having a final concentration of 1/20 of the value stated in *Table 2* (under *Concentration Limit*). Transfer 1.0 mL of this solution to an appropriate headspace vial, add 5.0 mL of 1,3-dimethyl-2-imidazolidinone, apply the stopper, cap, and mix.

Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A.*

Spiked Test Solution 1—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 1,* apply the stopper, cap, and mix.

Spiked Test Solution 2—[NOTE—Prepare a separate *Spiked Test Solution* for each peak identified and verified by *Procedures A* and *B.*] Transfer 5.0 mL of *Test Solution 2* to an appropriate headspace vial, add 1.0 mL of *Standard Solution 2,* apply the stopper, cap, and mix.

Chromatographic System—Proceed as directed for *Procedure C* under *Water-Soluble Articles.*

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution, Test Solution 1* and/or *Test Solution 2,* and *Spiked Test Solution 1* and/or *Spiked Test Solution 2* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$5(C/W)[r_U/(r_{U2} - r_U)]$$

in which *C* is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_{U2} are the peak responses of each residual solvent obtained from *Test Solution 1* or *Test Solution 2* and *Spiked Test Solution 1* or *Spiked Test Solution 2,* respectively.

■■2S (*USP30*)

Class 3 Residual Solvents

If only Class 3 solvents are present, the level of residual solvents ~~is to~~

■may■2S (*USP30*)
be determined as directed under *Loss on Drying* ⟨731⟩. ~~If the loss on drying value is greater than 0.5%, a water determination should be performed on the test sample as directed under *Water-Determination* ⟨921⟩. Determine the water by *Method Ia*, unless otherwise specified in the individual monograph. If~~

■when the monograph for the article under test contains a loss on drying procedure or a specific determination of the solvent may be made. If there is no loss on drying procedure in the monograph for the article under test or if■2S (*USP30*)
a Class 3 solvent limit in an individual monograph is greater than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option 1*), ~~that residual solvent~~

■the individual Class 3 residual solvent or solvents present in the article under test■2S (*USP30*)
should be identified and quantified, and the procedures as described above, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. ~~Such procedures shall be submitted to USP for evaluation.~~

■■2S (*USP30*)
USP Reference Standards, where available, should be used in these procedures. A flow diagram for the application of residual solvent limit tests is shown in *Figure 1*.

In-Process Revision

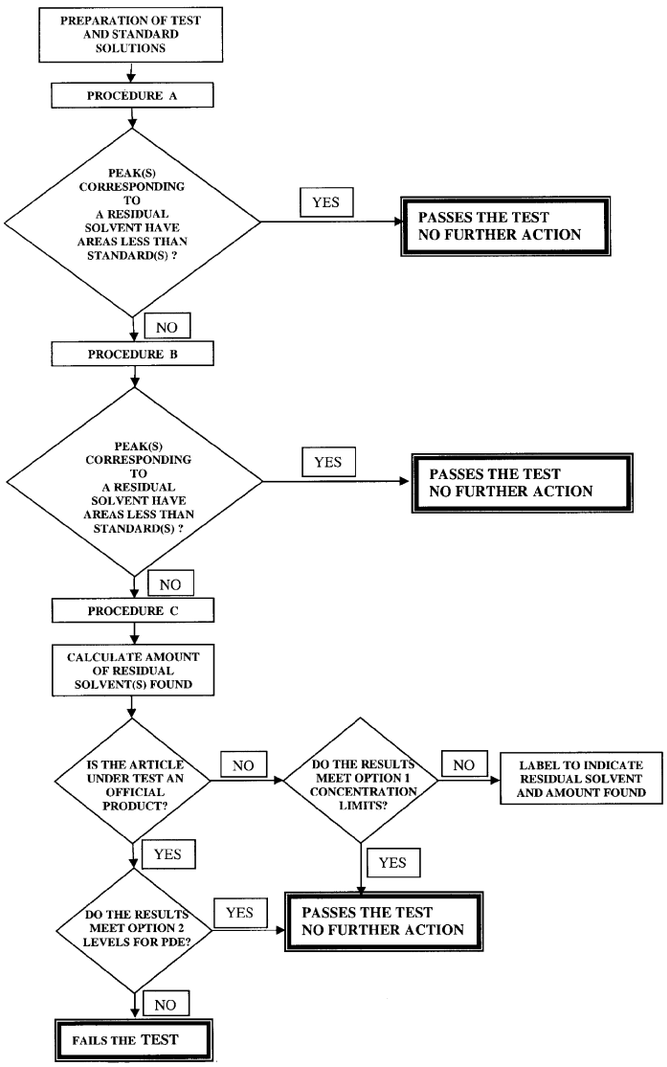

Figure 1. Diagram relating to the identification of residual solvents and the application of limit tests.

Change to read:

GLOSSARY

■*Acceptable daily intake (ADI):* The maximum acceptable intake of toxic chemicals per day. This term is used by the World Health Organization (WHO).■2S (*USP30*)

Genotoxic carcinogens: Carcinogens that produce cancer by affecting genes or chromosomes.

Lowest-observed-effect level (LOEL): The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Modifying factor: A factor determined by professional judgment of a toxicologist and applied to bioassay data so that the data can be safely related to humans.

Neurotoxicity: The ability of a substance to cause adverse effects on the nervous system.

No-observed-effect level (NOEL): The highest dose of a substance at which there are no biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Permitted daily exposure (PDE): The maximum acceptable intake per day of a residual solvent in pharmaceutical products.

Reversible toxicity: The occurrence of harmful effects that are caused by a substance and that disappear after exposure to the substance ends.

Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence of carcinogenesis but for which there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

Teratogenicity: The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

■*Tolerable daily intake (TDI):*Tolerable daily exposure to toxic chemicals. Term used by the International Program on Chemical Safety (IPCS).■2S (*USP30*)

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1005**⟩ **Acoustic Emission.** A new general information chapter for acoustic emission is being proposed. The technique of acoustic emission is based on the detection and analysis of sound produced by a process or system. In terms of pharmaceutical applications, the dependence of the acoustic emission measurement on physical properties such as particle size, mechanical strength, and cohesivity of solid materials allows the technique to be used for the control and endpoint detection of processes such as high shear granulation, fluid bed drying, milling, and micronization. This chapter provides general information on this technique, which may have application in certain cases as a manufacturing real-time control technique.

(GC: G. Ritchie) RTS—C42479

Add the following:

■⟨1005⟩ACOUSTIC EMISSION

INTRODUCTION

Ultrasound techniques can be categorized as two distinct types: acoustic emission (passive mode) and ultrasound spectroscopy (active mode). Both of these techniques have many applications.

The technique of acoustic emission is based on the detection and analysis of sound produced by a process or system. This is essentially equivalent to listening to sounds produced by a process or system, although the sounds are often well above the frequencies that can be detected by the human ear. Generally, frequencies up to about 15 kHz are audible.

In the case of ultrasound spectroscopy, the instrument is designed to generate ultrasound waves across a defined frequency range. These waves travel through the sample and are measured using a receiver. An analogy can be drawn with UV-visible or IR spectroscopy in that the detected ultrasound spectrum reflects changes in velocity or sound attenuation due to the interaction with a sample across a range of frequencies. However, as the scope of this chapter is limited to acoustic emission, ultrasound spectroscopy will not be discussed any further.

Acoustic emission is well-known in the study of fracture mechanics and therefore is used extensively by material scientists. It is also widely used as a nondestructive testing technique and is applied routinely for the inspection of aircraft wings, pressure vessels, and load-bearing structures and components. Acoustic emission is also used in the engineering industry for the monitoring of machine tool wear.

In terms of pharmaceutical applications, the dependence of the acoustic emission measurement on physical properties such as particle size, mechanical strength, and cohesivity of solid materials allows the technique to be used for the control and endpoint detection of processes such as high shear granulation, fluid bed drying, milling, and micronization.

General Principles

Acoustic emissions can propagate by a number of modes. In solids, compressional and shear or transverse modes are important. Compressional modes have the highest velocity and thus reach the acoustic detector (or transducer) first. However, in most process applications of acoustic emission, there are many sources—each producing short bursts of energy—and, consequently, the different modes cannot easily be resolved. The detected signal, for example on the wall of a vessel, is a complex mixture of many overlapping waveforms resulting from many sources and many propagation modes.

At interfaces, depending on the relative acoustic impedance of the two materials, much of the energy is reflected back towards the source. In a fluidized bed, for example, acoustic emissions will only be detected from particles directly impacting the walls of the bed close to the transducer.

A convenient method of studying acoustic emission from processes is to use the "average signal level". A root mean square-to-direct current (RMS-to-DC) converter may be used

to convert the amplitude-modulated (AM) carrier into a more slowly varying DC signal. This is referred to as the average signal level (ASL). The ASL can then be digitally sampled (typically at a sampling frequency of about 50 Hz) and stored electronically for further signal processing.

The simplest way of studying the acoustic data is to examine changes in the ASL. However, other information can be derived from examining the power spectrum of the ASL. The power spectrum is calculated by performing a Fast Fourier Transform (FFT) on the digitized raw data record. Power spectra may be averaged to produce a reliable estimate of power spectral density or to give a ''fingerprint'' of a particular process regime. Interpretation of the power spectrum is complicated by the fact that the acoustic signal originating in the system is distorted by several factors including transmission, reflection, and signal transfer characteristics.

The shape of the power spectrum of the ASL record is a function of the process dynamics. Periodic processes (e.g., mechanical stirring or periodic bubbling of a fluidized bed) show high power at certain discrete frequencies. Random processes show either flicker type properties, where power is inversely proportional to frequency, or white noise type properties in which power is independent of frequency. The amplitude of the power spectrum is also affected by the energy of the acoustic emissions produced by the process. For example, if hard material is being processed, the acoustic emission produced by particle impact will be greater than that produced by soft material.

INSTRUMENTATION

Generally, piezoelectric sensors are used to detect and quantify the acoustic signals produced by a process. Sensors with different resonant frequencies are often used (e.g., 70 and 190 kHz, although higher frequencies may be more appropriate at smaller scales of operation), incorporating various bandpasses. As sound (ultrasound) of the appropriate frequency range reaches these sensors, an electrical signal is generated, the amplitude of which is directly proportional to the energy (amplitude) of the incident sound waves.

These signals are processed through the following:

(1) a pre-amplifier (which incorporates signal filtering),
(2) an RMS-to-DC converter,
(3) a variable gain amplifier, and
(4) a PC-based data acquisition board.

The controlling software is also incorporated into the PC.

Acoustic emission equipment generally allows several sensors to be used simultaneously by incorporating multiple electronic channels into a single instrument.

Signal Processing

The signal from a resonant transducer resembles an AM radio signal. At the resonance frequency of the transducer, the signal consists of a carrier wave that is modulated in amplitude by the process. An RMS-to-DC converter is used to demodulate the signal. The output of this device is the modulation signal or envelope.

The envelope is digitally resampled at a frequency appropriate for the process. For example, 50 Hz is a typical digital sampling rate for a fluid bed drier or high shear granulator.

Qualification and Verification of Acoustic Emission Instruments

A system suitability approach should be taken around instrument performance, establishing optimum measurement configuration, then comparing the instrument performance to the values obtained during routine use to those obtained during installation qualification (IQ).

This approach effectively addresses the issues related to sampling because, unlike other on-line analytical systems, the transducers can be optimally positioned and attached to receive the maximum signal without vessel modification.

Sample rates need to comply with the Nyquist sampling theorem, which states that a signal must be sampled at a rate that is twice the highest frequency component in the signal. A low-pass filter should be used to remove the frequency components greater than half the sampling frequency (Nyquist frequency). Failure to comply with this criterion will result in aliasing.

Owing to the nature of the piezoelectric transducers and because resonant frequencies are natural properties of the crystals, it is not necessary to test the variation (reproducibility) or drift in the frequency domain. If other types of transducers are used, this may be necessary. Any gross change in the frequency domain will be recorded as a drop in the signal intensity at the resonant frequency, and therefore is covered by the signal intensity tests.

The two main areas for instrument performance verification are signal intensity and timings. Any change in the signal intensity will affect the raw signal and the ASL and, therefore, will also affect the power spectrum. Changes in signal intensity can occur as a result of changes in the process (e.g., variation in hardness or moisture in the particles impacting the vessel wall) or changes in the acoustic conduit from the process to transducer.

Reproducibility of the acoustic conduit should be tested using a second transducer to input a pulse or "ping" at the resonant frequency of the receiving sensor. This reproducibility value represents the noise of the signal and can be used in calculations of limit of detection (LOD) and limit of quantitation (LOQ), where LOD is defined as three times the noise of the signal and LOQ is ten times the noise of the signal. The noise value should be calculated from twenty sequential ASL values acquired at the sampling frequency used for normal operation. This test should be repeated in reverse in order to establish that statistically similar intensity values can be obtained on both channels.

Short term reproducibility allows the calculation of noise. However, it does not give a measure of integrity of acoustic conduit over time or, more specifically, changes caused by the process (e.g., variations in adhesive properties with process changes such as heating/cooling). The noise test should be repeated while executing the normal processing parameters (using an empty vessel) and the drift in the ASL should be calculated. This drift will underlay any trend plots (ASL against time), but will not impact chemometric models based purely on endpoint determination. For trend plots, it should be shown that drift is not statistically significant; otherwise, drift correction will need to be applied. Values for noise, drift, and absolute ASL should be recorded and logged, and the tests re-executed if changes are made to the processing equipment or to the acoustic emission system. If no changes are made, then the tests should be re-executed every month. In this way the quality of the acoustic conduit can be shown to be intact and any changes to the signal intensity isolated and attributed to the process itself.

During routine use, it is recommended that the noise test be executed (as above) before each process run, and that signal intensity and noise be calculated. These values should be logged and compared to those generated both during previous use and during installation. Impact of the deviation from previous values will be a function of the prediction model and should be addressed by method validation.

The noise data (from above) can also be used to calculate the time of flight of the pulse. If the pulse activation and signal reception are synchronized, the time taken for the pulse to transmit across the vessel can be measured. This is a good indication of the measurement electronics as well as the overall condition of the acoustic conduit. However, this test should be regarded as a measure of "system" condition and needs to be executed only if changes have been made to the process equipment or the acoustic emission system, or every 6 months. Correlation of the measured timings with the historical ones should be statistically valid. If not, it is an indicator that the acoustic emission system may need requalification by the instrument manufacturer or supplier, or that there are changes in the acoustic conduit.

All these tests require the use of a pulse generated electrically. Failure in any of the above tests could be attributed to the signal generation itself. It is recommended that the electrical pulse generation system be requalified and certified against National Institute of Standards and Technology (NIST) traceable standards every 12 months.

FACTORS AFFECTING MEASUREMENT

The following factors can affect the acoustic data obtained and should be considered when installing an acoustic emission system.

1. As with any other type of sensor, acoustic emission sensors can fail with time or as a result of physical damage. It is important to check the sensor function as part of routine maintenance of the instrument. If multiple sensors are installed on the same vessel, an active signal can be generated from one sensor and this can be used to check the detection on another sensor. This exercise will ensure that the sensors are detecting the acoustic signals generated by the process. A statistically valid ''minimum acceptable acoustic signal'' for the sensor(s) should also be determined and monitored at the start, middle, and end of a process to ensure the performance of the sensor(s) during a process run. This may be established from the routine maintenance signal experiments or based on historical data for the sensors.
2. Sensors are typically installed on the outer wall of the process vessel. Several types of adhesives (temporary or permanent) can be used to attach the sensor to the vessel wall. Through repeated cleaning and vessel movement, it is possible for the bonding between the sensor and vessel to be compromised. Checking the integrity of the installation should be part of routine maintenance. Similar to item *1* above, an active signal can be used to ensure proper bonding between sensor and vessel.
3. The use of high frequencies significantly reduces the contribution of mechanical noise to the acoustic signal detected, especially at smaller scales of operation, although it does not eliminate it completely. Testing the effect of various motor settings, for example, can determine if the acoustic signal detected is a function of mechanical noise. If the effect is significant, using higher frequencies may be necessary. Awareness of the contribution of the mechanical noise, no matter how small, is an important consideration as the motors age or are replaced.
4. Because the sensors are often placed on the outer vessel wall, wall thickness can affect the quality of the signal detected. If the vessel is jacketed, the amplitude of the acoustic signal may be reduced. Adding more sensors on the vessel can improve signal quality. Alternatively, an increase in signal may be obtained by positioning sensor(s) at a location where contact exists between the inner and outer walls, essentially providing a waveguide between the sensor and sound source. Waveguides may also be incorporated into the design of manufacturing equipment to enable utilization of acoustic emission monitoring. Appropriate validation is required to ensure that this does not adversely affect the performance of equipment.
5. During operation, the acoustic signal collected is a summation of various events occurring within the process. For example, the acoustic signal generated as particles hit the wall in a granulator is a function of both the material properties of the granules (i.e., density, size, and porosity), the process-related properties (i.e., force of impact, frequency of impact, and amount of material), and environmental factors (i.e., temperature and humidity). Therefore, significant changes to any of these parameters can affect the acoustic signal and the quality of the ensuing prediction.

The acoustic emission data collected is vessel/equipment specific. It is not advisable to apply a model generated on one piece of equipment to another because the acoustic information can differ as a result of the issues discussed in items *3, 4,* and *5* above.

DATA ANALYSIS

Acoustic emission from granulators and fluid bed driers is known as continuous acoustic emission. Continuous acoustic emission is aphasic (i.e., there are no starts or stops to the signal). This means that it is unnecessary to use signal processing techniques that preserve phase. Power spectral analysis is a useful technique in processing acoustic emission signals. The information in the power spectra, unlike the raw acoustic emission signals, is coherent in the short term, allowing signal averaging to be performed. This provides a better estimate of power spectral density than that provided by a single power spectrum.

To detect endpoints in batch processes (e.g., granulation or drying endpoint), a qualitative multivariate model is appropriate (e.g., PCA or SIMCA). The following sequence of operations is performed:

(1) Training/Calibration—Acoustic emission spectra that are representative of the endpoint condition are obtained.

(2) Modeling—A multivariate model describing the distribution of acoustic emission signals at the endpoint condition is created.

(3) Prediction—Acoustic emission spectra are compared with the model. The fit to the model (usually expressed in terms of a number of standard deviations) is monitored. As the system approaches the endpoint, the fit improves and completion of the process is established once the model fits predefined criteria.

The prediction model is generated from acoustic emission spectra obtained from the process operating under normal conditions. Upsets (e.g., unwanted agglomeration in coaters) are detected by observing statistically valid deviations from the model.

Adaptive modeling has also been proposed for upset detection. This involves generating multivariate models continuously as the acoustic emission signals are acquired. Unusual deviation of the acoustic emission signal indicates the occurrence of a process upset. The advantage of adaptive modeling is that it is not necessary to perform a separate calibration step.

GLOSSARY

Acoustic Emission Transducer—A solid state device usually incorporating a piezoelectric element to convert the acoustic emission wave to an electrical signal.

Acoustic Impedance—Acoustic impedance (Z) is defined as $Z = \rho v$ (where ρ is density and v is the sound velocity). It is an important quantity and gives the proportion of sound energy transmitted from one medium to another and the amount of energy reflected at the interface.

Adaptive Modeling—A method that predicts the state of a process without the use of a previously generated model (i.e., there is no prior training or calibration step).

Aliasing—Spurious low frequency components, appearing in the signal, that are really frequencies above the Nyquist frequency.

Amplitude—The magnitude or strength of a varying waveform.

Average Signal Level (ASL)—A measure of the average power in an acoustic emission signal.

Band-Pass—The range of frequencies within which a component operates.

Compressional Mode—A longitudinal mode of acoustic transmission encountered in solids, liquids, and gases.

Continuous Acoustic Emission—Acoustic emission signals that cannot be separated in time and are typical of pharmaceutical processes such as granulation and fluid bed drying.

Flicker Type Properties—A type of signal associated with many natural processes. The characteristics of flicker noise are that the power of the noise is directly proportional to the signal and has approximately a $1/f$ (f = frequency) spectral density distribution.

Gain—The amplification factor for a component usually expressed in terms of decibels (dB).

Gain in dB = $20 \log_{10} (\text{Voltage}_{out} \text{Voltage}_{in})$.

Piezoelectric—A material which generates an electric field when compressed. Piezoelectric materials are used in the construction of acoustic emission sensors. A common material is PZT (lead zirconium titanate).

Power Spectrum—A power spectrum of a signal is a representation of the signal power as a function of frequency. A power spectrum is calculated from the time domain signal by means of the Fast Fourier Transform (FFT) algorithm. It is useful to study acoustic emission signals in the frequency or spectral domain, as the spectrum is often characteristic of the mechanism. Improvements in signal-to-noise ratio can be obtained by averaging a number of power spectra, as they are coherent.

Power Spectral Density—The measure of acoustic emission power in each resolution element of the power spectrum.

Resonant Frequency—The frequency at which an acoustic emission sensor is most sensitive. Resonant acoustic emission sensors have a clearly defined resonant frequency, but are usually sensitive to other frequencies.

RMS-to-DC Converter—An electronic device that converts an alternating signal to a voltage level proportional to the average power in the signal.

Shear Mode—A transverse mode of acoustic transmission, encountered only in solids.

Signal Filtering—Filtering a signal means attenuating frequencies outside a prescribed range. In acoustic emission work, band-pass filtering is used to improve the signal-to-noise ratio by attenuating noise outside the bandwidth of the sensor. Low pass filtering is used to remove frequencies higher than the Nyquist frequency in order to prevent aliasing.

Transverse Mode—A mode of wave propagation where the displacement of the material is perpendicular to the direction of propagation. These modes are only encountered in solid materials.

White Noise—The characteristic of white noise is a power spectrum of uniform spectral density and is associated with purely random processes.■2S (*USP30*)

BRIEFING

⟨**1086**⟩ **Impurities in Official Articles,** *USP 29* page 2920. Impurites are closely related to integrity and safety, which are matters of principal interest for USP. Regulatory agencies participating in the International Conference on Harmonization (ICH) are near to concluding the process for adoption of the guidelines "*Impurities in New Drug Substances (Q3A)*" and "*Impurities in New Drug Products (Q3B)*". Although this chapter deals with impurities in official articles, as opposed to new drugs, revisions are proposed in order to integrate the intent of the ICH regarding impurities.

(GC: A. Hernandez-Cardoso) RTS—C46417

Change to read:

▪INTRODUCTION

This general information chapter covers impurities or degradation products in drug substances and degradation products in drug products. Impurities or degradation products in drug substances can arise during the manufacturing process or during storage of the drug substance. The degradation products in drug products can arise from drug substances or reaction products of the drug substance with an excipient or an immediate container–closure system. Biological, biotechnological, and radiopharmaceutical products are not covered in this chapter.■2S (*USP30*)

Concepts about purity change with time and are inseparable from developments in analytical chemistry. If a material previously considered to be pure can be resolved into more than one component, that material can be redefined into new terms of purity and impurity. Inorganic, organic, biochemical, isomeric, or polymeric components can all be considered impurities. Microbiological species or strains are sometimes described in similar terms of resolving into more than one component.

Communications about

▪impurities or degradation products in■2S (*USP30*) compendial articles may be improved by including in this Pharmacopeia the definitions of terms and the contexts in which these terms are used. (See *Definitions* below.) There has been much activity and discussion in recent years about term definition. Certain industry-wide concerns about terminology and context deserve widespread publication and ready retrievability and are included here. ~~(See *Industrial Concepts* below.)~~

▪■2S (*USP30*)
See *Foreign Substances and Impurities* in the section *Tests and Assays* under *General Notices and Requirements,* as well as the ~~recently adopted~~

▪■2S (*USP30*)
general chapter *Ordinary Impurities* ⟨466⟩. Some other general chapters added over the years have also addressed topics of purity or impurity as these have come into focus or as analytical methodology has become available. Analytical aspects are enlarged upon in the chapter *Validation of Compendial ~~Methods~~*

In-Process Revision

■*Procedures*■2S (*USP30*)
⟨1225⟩.
Monographs ~~on bulk pharmaceutical chemicals~~

■for drug substances■2S (*USP30*)
usually cite one of three types of purity tests: (1) a chromatographic purity test coupled with a nonspecific assay; (2) a chromatographic purity-indicating method that serves as the assay; or (3) a specific test and limit for a known impurity, an approach that usually requires a Reference Standard for that impurity. Modern separation methods clearly play a dominant role in scientific research today because these methods simultaneously separate and measure components and fulfill the analytical ideal of making measurements only on purified specimens. Nevertheless, the more classical methods based on titrimetry, colorimetry, spectrophotometry, single or multiple partitions, or changes in physical constants (or any other tests or assays) lose none of their previous validities. The *purity profile* of a specimen that is constructed from the results of experiments using a number of analytical methods is the ultimate goal.
Purity or impurity measurements ~~on finished preparations~~

■for drug products■2S (*USP30*)
present a challenge to Pharmacopeial standards-setting. Where degradation of a ~~preparation~~

■drug product■2S (*USP30*)
over time is at issue, the same analytical methods that are stability-indicating are also purity-indicating. Resolution of the active ingredient(s) from the excipients necessary to the preparation presents the same qualitative problem. Thus, many monographs for Pharmacopeial preparations feature chromatographic assays. Where more significant impurities are known, some monographs set forth specific limit tests. In general, however, this Pharmacopeia does not repeat impurity tests in subsequent preparations where these appear in the monographs of ~~bulk pharmaceutical chemicals~~

■drug substances■2S (*USP30*)
and where these impurities are not expected to increase. It is presumed that adequate retention specimens are in storage for the exact batch of ~~bulk chemicals~~

■drug substances■2S (*USP30*)
used in any specific lot of a ~~preparation.~~

■drug product.■2S (*USP30*)
Whenever analysis of an official ~~preparation~~

■article■2S (*USP30*)
raises a question of the official attributes of any of the ~~bulks~~

■drug substances■2S (*USP30*)
used, subsequent analysis of retention specimens is in order.

■Pharmaceutical manufacturers interact with regulatory agencies in developing new drug substances and new drug products, and cooperate with the compendia in writing official monographs for the compendial articles the manufacturers produce. Establishment of impurity limits in drug substances and drug products should proceed on a rational basis so that everyone involved in the development and approval phases can carry on their work in a predictable manner. Although drug development in the United States is the primary focus of this section of the chapter, the subject also has broad applicability across national boundaries.

Manufacturers share with regulatory agencies and with the compendia the goal of making available to the public high-quality products that are both safe and efficacious. This goal continues to be achieved through rational approaches to the complex process of drug development. Tests used at all stages of drug development and marketing should not be interpreted individually but as a whole. Controls on raw materials and on manufacturing as well as those on drug substances, along with toxicological and clinical studies performed, ensure the safety and efficacy of drug products. It is more rational to identify impurities or degradation products and to set limits based on the factors detailed here, relying on the scientific judgments of manufacturers, the compendia, and regulators to arrive at sets of acceptable limits for identified and unidentified impurities or degradation products.

Limits are set for impurity levels or degradation products as one of the steps in ensuring the identity, strength, quality, and chemical purity of drug substances or drug products. The ultimate goal is to produce a final drug product of high quality that is safe and efficacious and remains so throughout its shelf life. The setting of limits for impurities or degradation products in drug substances is a complex process that considers a number of factors:

(1) the toxicology of a drug substance containing typical levels of impurities and/or the toxicology of impurities relative to a drug substance;
(2) the route of administration, e.g., oral, topical, parenteral, or intrathecal;
(3) the daily dose, i.e., frequency and amount (micrograms or grams) administered of a drug substance;
(4) the target population (age and disease state), e.g., neonates, children, or senior citizens;
(5) the pharmacology of an impurity, when appropriate;
(6) the source of a drug substance, e.g., synthetic, natural product, or biotechnology;

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(7) the duration of therapy, i.e., administration over a long period (treatment of chronic conditions) versus administration intended for a short duration (treatment of acute conditions); and

(8) the capability of a manufacturer to produce consistently high-quality material.

Concepts for setting impurity or degradation product limits in drug substances are chemistry and safety concerns. Limits for organic and inorganic impurities and residual solvents should be established for drug substances. The basic tenet for setting limits is that levels of impurities or degradation products in a drug substance must be controlled to ensure its safety and quality throughout its development to use in a drug product.

For drug products the concept for setting degradation product limits are based on sound scientific rationale of the degradation pathways, manufacturing process, and stability studies conducted at the recommended storage conditions. A rationale should be provided for exclusion of those impurities that are not degradation products (e.g., process impurities from drug substance and impurities arising from excipients).

For drug substances and drug products, limits are appropriately set no higher than the level that can be justified (e.g., safety data, literature references, etc.) and no lower than the level achievable by the manufacturing process and analytical capability. Where there is no safety concern, limits should be based on (a) data generated on actual batches of the drug substance or drug product, allowing sufficient latitude to deal with normal process and analytical variation, and (b) stability characteristics.

Documented evidence that the analytical procedure used to evaluate impurities or degradation products is validated and suitable for the detection and quantitation of impurities or degradation products should be established.

The setting of limits on impurities or degradation products is an evolutionary process, beginning in the United States before an investigational new drug (IND) is filed and continuing until well after the approval of a new drug application (NDA). Therefore, it is appropriate to address different stages in drug development as separate issues. There are three points in the drug development process where the setting of limits may be significantly different: (1) at the initial IND application, (2) at the filing of the NDA, and (3) after NDA approval. The filing of an abbreviated new drug application (ANDA) is another activity in which limits are set on impurities or degradation products. Since the approach may vary from that of filing an NDA, it is addressed as a separate issue. The underlying assumption is that the analytical methods used to evaluate impurities or degradation products are suitable for their intended purpose at each stage in the development.■2S (*USP30*)

Change to read:

~~DEFINITIONS~~

~~Foreign Substances~~

~~Foreign substances, which are introduced by contamination or adulteration, are not consequences of the synthesis or preparation of compendial articles and thus cannot be anticipated when monograph tests and assays are selected. The presence of objectionable foreign substances not revealed by monograph tests and assays constitutes a variance from the official standard. Examples of foreign substances include ephedrine in Ipecac or a pesticide in an oral liquid analgesic. Allowance is made in this Pharmacopeia for the detection of foreign substances by unofficial methods. (See *Foreign Substances and Impurities,* in the section *Tests and Assays,* under *General Notices and Requirements*.)~~

~~Residual Solvents~~

~~Residual solvents are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance may enhance the yield or determine characteristics such as crystal form, purity, and solubility and, as such, may be a critical parameter in the synthetic process. Because there is no therapeutic benefit from residual solvents, they should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. A classification of residual solvents by risk assessment is presented in the *Residual Solvents Limits* section of *Organic Volatile Impurities* ⟨467⟩. Class 1 solvents should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment.~~

~~Toxic Impurities~~

~~Toxic impurities have significant undesirable biological activity, even as minor components, and require individual identification and quantitation by specific tests. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles. Based on validation data, individualized tests and specifications are selected. These feature comparison to a Reference Standard of the~~

impurity, if available. It is incumbent on the manufacturer to provide data that would support the classification of such impurities as toxic impurities.

Concomitant Components

Concomitant components are characteristic of many bulk pharmaceutical chemicals and are not considered to be impurities in the Pharmacopeial sense. Limits on contents, or specified ranges, or defined mixtures are set forth for concomitant components in this Pharmacopeia. Examples of concomitant components are geometric and optical isomers (or racemates) and antibiotics that are mixtures. Any component that can be considered a toxic impurity because of significant undesirable biological effect is not considered to be a concomitant component.

Signal Impurities

Signal impurities are distinct from ordinary impurities in that they require individual identification and quantitation by specific tests. Based on validation data, individualized tests and specifications are selected. These feature a comparison to a reference standard of the impurity, if available.

Signal impurities may include some process related impurities or degradation products that provide key information about the process, such as diazotizable substances in thiazides. It is incumbent on the manufacturer to provide data that would support the classification of such impurities as signal impurities rather than ordinary impurities.

Ordinary Impurities

Ordinary impurities are those species in bulk pharmaceutical chemicals that are innocuous by virtue of having no significant, undesirable biological activity in the amounts present. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles. Selections of tests and assays allow for anticipated amounts of impurities that are unobjectionable for the customary use of the article. The presence of ordinary impurities is controlled in monographs in this Pharmacopeia by including tests for *Ordinary Impurities* ⟨466⟩. Tests for *related substances* or *chromatographic purity* may also control the presence of ordinary impurities.

Unless otherwise specified in an individual monograph, estimation of the amount and number of ordinary impurities is made by relative methods rather than by strict comparison to individual Reference Standards. Nonspecific detection of ordinary impurities is also consistent with this classification.

The value of 2.0% was selected as the general limit on ordinary impurities in monographs where documentation did not support adoption of other values. This value represents the maximum allowable impact from this source of variation, when taken with the variation allowed by the composite of other Pharmacopeial tests and assays for both the bulk pharmaceutical chemical and the preparations.

Where a monograph sets limits on concomitant components, signal impurities, and/or toxic impurities, these species are not to be included in the estimation of ordinary impurities unless so stated in the individual monograph.

Related Substances

Related substances are structurally related to a drug substance. These substances may be identified or unidentified degradation products or impurities arising from a manufacturing process or during storage of a material.

Process Contaminants

Process contaminants are identified or unidentified substances (excluding related substances and water), including reagents, inorganics (e.g., heavy metals, chloride, or sulfate), raw materials, and solvents. These substances may be introduced during manufacturing or handling procedures.

INDUSTRIAL CONCEPTS

Pharmaceutical manufacturers interact with regulatory agencies in developing new drug substances and new drug products, and cooperate with the compendia in writing official monographs for the compendial articles the manufacturers produce. Establishment of impurity limits in drug substances should proceed on a rational basis so that everyone involved in the development and approval phases can carry on their work in a predictable fashion. Although drug development in the United States is the primary focus of this section of the chapter, the subject also has broad applicability across national boundaries.

Manufacturers share with regulatory agencies and with the compendia the goal of making available to the public high-quality products that are both safe and efficacious. This goal continues to be achieved through rational approaches to the complex process of drug development. Tests used at all stages of drug development and marketing should not be interpreted individually but as a whole. Controls on raw materials and on manufacturing as well as those on drug substances, along with toxicological and clinical studies performed, ensure the safety and efficacy of drug products. It has been suggested that impurities should be identified when they exceed some set amount, e.g., 0.1, 0.3, or 0.5%. It is more rational to identify impurities and to set limits based on the factors detailed here, relying on the scientific judgments of manufacturers, the compendia, and regulators to arrive at sets of acceptable limits for identified and unidentified impurities.

Limits are set for impurity levels as one of the steps in ensuring the identity, strength, quality, and chemical purity of drug substances. The ultimate goal is to produce a final drug product of high quality and at a reasonable cost that is safe and efficacious and remains so throughout its shelf life. The setting of limits for impurities in bulk drug substances is a complex process that considers a number of factors:

(1) the toxicology of a drug substance containing typical levels of impurities and/or the toxicology of impurities relative to a drug substance;

(2) the route of administration, e.g., oral, topical, parenteral, or intratheceal;

(3) the daily dose, i.e., frequency and amount (micrograms or grams) administered of a drug substance;

(4) the target population (age and disease state), e.g., neonates, children, or senior citizens;

(5) the pharmacology of an impurity, when appropriate;

(6) the source of a drug substance, e.g., synthetic, natural product, or biotechnology;

(7) the duration of therapy, i.e., administration over a long period (treatment of chronic conditions) versus administration intended for a short duration (treatment of acute conditions); and

(8) the capability of a manufacturer to produce high-quality material at a reasonable cost to consumers.

Concepts for setting impurity limits in bulk drug substances are the concerns of the regulatory and compendial agencies as well as the pharmaceutical industry. The basic tenet for setting limits is that levels of impurities in a drug substance must be controlled to ensure its safety and quality throughout its development into and use as a drug product. The concepts are derived from issues and experiences with drug substances from traditional sources and technologies. Issues arising from biotechnologically produced drug substances, e.g., recombinant DNA and hybridomas, are still being defined and so are not necessarily covered by these concepts. However, the concepts can serve as a general foundation to address specific issues arising from biotechnology.

The setting of limits on impurities in drug substances is an evolutionary process, beginning in the United States before an investigational new drug (IND) is filed and continuing until well after the approval of a new drug application (NDA). Therefore, it is appropriate to address different stages in drug development as separate issues.

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~~There are three points in the drug development process where the setting of limits may be significantly different: (1) at the initial IND application, (2) at the filing of the NDA, and (3) after NDA approval. The filing of an abbreviated new drug application (ANDA) is another activity in which limits are set on impurities. Since the approach may vary from that of filing an NDA, it is addressed as a separate issue. The underlying assumption is that the analytical methods used to evaluate impurities in a drug substance are suitable for their intended purpose at each stage in the development.~~

~~An impurity is any component of a drug substance (excluding water) that is not the chemical entity defined as the drug substance. The impurity profile of a drug substance is a description of the impurities present in a typical lot of a drug substance produced by a given manufacturing process. The description includes the identity or some qualitative analytical designation (if unidentified), the range of each impurity observed, and the classification of each identified impurity.~~

~~Following are two more terms that enlarge upon those given under *Definitions*.~~

~~*Related Substances*—Related substances are structurally related to a drug substance. These substances may be identified or unidentified degradation products or impurities arising from a manufacturing process or during storage of a material.~~

~~*Process Contaminants*—Process contaminants are identified or unidentified substances (excluding related substances and water), including reagents, inorganics (e.g., heavy metals, chloride, or sulfate), raw materials, and solvents. These substances may be introduced during manufacturing or handling procedures.~~

~~INITIAL IND FILING~~

~~At the initial IND filing, the chemical nature of a bulk substance has generally been defined. The manufacturing process normally is in an early stage of development, and materials may be produced on a laboratory scale. Usually few batches have been made and, therefore, little historical data are available. The reference materials of a drug substance may be relatively impure. Limits for the purity of a drug substance are set to indicate drug quality. The setting of limits on related substances and process contaminants can be characterized as follows.~~

~~(1) Limits are set on total impurities, and an upper limit may be set on any single impurity. The limit for total impurities should maintain, if possible, a nominal composition material balance.~~

~~(2) Impurity profiles are documented. These are profiles of the lots of drug substances used in clinical studies and in toxicological studies that establish the safety of drug substances. The lots used in these studies should be typical products of the manufacturing process in use at that time.~~

~~(3) Limits for residual solvents are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens.~~

~~(4) General inorganic contaminants are monitored by appropriate tests such as a heavy metals limit test and/or a test for residue on ignition. Traditional compendial limits are applied unless otherwise indicated. Specific metal contaminants that appear during manufacturing should be monitored by appropriate analytical techniques, and limits should be set based on the toxicological properties of these metals.~~

~~(5) Appropriate limits are set for impurities known to be toxic.~~

~~(6) If appropriate, enantiomeric purity is controlled.~~

~~Although water is not classified as an impurity, limits for water content may be needed to ensure the stability or ease of processing a drug substance.~~

~~NDA FILING~~

~~During the IND phases of drug development, the manufacturing process for a drug substance may undergo a number of revisions. Generally, the scale will have changed from laboratory size and will approach or reach full production batch size. A number of batches will normally have been produced, and a historical data base of the results of testing for impurities will exist. When significant changes in a manufacturing process are made, the impurity profile should be reviewed to determine if the toxicological studies are still supportive.~~

~~At the NDA stage a reference standard of defined purity is available, analytical methods have been validated, impurity and degradation profiles are known, and enantiomeric purity has been evaluated. The setting of limits on related substances and process contaminants can be characterized as follows.~~

~~(1) Consistency of the impurity profile of a drug substance has been established.~~

~~(2) IND limits for total and individual impurities (identified and unidentified) are reviewed and adjusted based on manufacturing experience and toxicological data.~~

~~(3) Impurities present in significant amounts are identified and individual limits are set. However, it is not always possible to identify and/or prepare authentic substances for impurities. The labile nature of some impurities precludes this possibility. Limits may be set on these substances based on comparison of lots produced and used in toxicological and clinical studies.~~

~~(4) The impurity profiles of the lots designated for marketing should not be significantly different from those of the lot(s) used for toxicological and clinical studies.~~

~~(5) The composition material balance should be used, if possible, to evaluate the adequacy of the controls.~~

~~(6) Limits for residual solvents are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens.~~

~~(7) Limits are set for inorganic contaminants by appropriate tests such as a heavy metals limit test and/or by a test for residue on ignition. Traditional compendial limits are applied unless otherwise indicated. Based on toxicological properties, limits may be set for specific metal contaminants that appear during manufacturing.~~

~~POST-NDA APPROVAL~~

~~After approval and marketing of a pharmaceutical product, significant changes may be made in manufacturing the bulk drug substance. There may be technological, ecological, economic, or safety reasons for these changes. If they occur, the Pharmacopeial and NDA impurity limits and rationale should be reviewed; the limits should be revised when indicated to ensure similar or improved quality of the drug substance.~~

~~ANDA FILING~~

~~The drug substance for a pharmaceutical product eligible for ANDA status normally is an official article and should be well characterized analytically. Drug substances are typically available from multiple sources, and each source may have a different manufacturing process. Therefore, it is essential that the dosage form manufacturer evaluate each supplier's drug substance impurity profiles. Limits can then be set based on the more detailed concepts described for NDA filing, including review of compendial monographs for appropriateness.~~

▪INITIAL IND FILING

Drug Substances—At the initial IND filing, the chemical nature of a drug substance has generally been defined. The manufacturing process normally is in an early stage of development, and materials may be produced on a laboratory scale. Usually few batches have been made and, therefore, little historical data are available. The reference materials of a drug substance may be relatively impure. Limits for the purity of

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a drug substance are set to indicate drug quality. The setting of limits on related substances and process contaminants can be characterized as follows.

(1) Limits are set on total impurities, and an upper limit may be set on any single impurity. The limit for total impurities should maintain, if possible, a nominal composition material balance.
(2) Impurity profiles are documented. These are profiles of the lots of drug substances used in clinical studies and in toxicological studies that establish the safety of drug substances. The lots used in these studies should be typical products of the manufacturing process in use at that time.
(3) Limits for residual solvents are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens.
(4) General inorganic impurities are monitored by appropriate tests such as a heavy metals limit test and/or a test for residue on ignition. Traditional compendial limits are applied unless otherwise indicated. Specific residual metals that appear during manufacturing should be monitored by appropriate analytical techniques, and limits should be set based on the toxicological properties of these metals.
(5) Appropriate limits are set for impurities known to be toxic.
(6) If appropriate, enantiomeric purity is controlled.

Although water is not classified as an impurity, limits for water content may be needed to ensure the stability or ease of processing a drug substance.

Drug Product—At the initial IND filing, the dosage form of a drug product has been identified, which is appropriate for early clinical studies (and may or may not be representative of the drug product that will eventually be marketed). Usually, few batches have been made and, therefore, little historical data are available.

(1) Qualitative and quantitative limits on degradation products may not be established at this point due to the limited data available. Typically, degradation products will be monitored as part of the stability evaluation of the drug product.
(2) Dating for use of a drug product in clinical studies will be related to the ongoing stabilty data, which are generated. If the data indicate the presence of degradation products, dating and storage conditions are controlled to ensure any degradation products are controlled within industry accepted limits or within limits established through safety assessment studies.
(3) Limits for residual solvents, if appropriate, are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens. When amendments to the IND are filed, limits for impurities in drug substance and degradation products in drug substance or drug product may be updated based on additional data as they become available.

NDA FILING

Drug Substances—During the IND phases of drug development, the manufacturing process for a drug substance may undergo a number of revisions. Generally, the scale will have changed from laboratory size and will approach or reach full production batch size. A number of batches will normally have been produced, and a historical data base of the results of testing for impurities will exist. When significant changes in a manufacturing process are made, the impurity profile should be reviewed to determine if the toxicological studies are still supportive.

At the NDA stage a reference standard of defined purity is available, analytical methods have been validated, impurity and degradation profiles are known, and enantiomeric purity has been evaluated. The setting of limits on related substances and process contaminants can be characterized as follows.

(1) Consistency of the impurity profile of a drug substance has been established.

(2) IND limits for total and individual impurities (identified and unidentified) are reviewed and adjusted based on manufacturing experience and toxicological data.

(3) Impurities present in significant amounts are identified and individual limits are set. However, it is not always possible to identify or prepare authentic substances for impurities. The labile nature of some impurities precludes this possibility. Limits may be set on these substances based on comparison of lots produced and used in toxicological and clinical studies.

(4) The impurity profiles of the lots designated for marketing should not be uniquely different from those of the lot(s) used for toxicological and clinical studies.

(5) The composition material balance should be used, if possible, to evaluate the adequacy of the controls.

(6) Limits for residual solvents are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens.

(7) Limits are set for inorganic impurities by appropriate tests such as a heavy metals limit test and/or by a test for residue on ignition. Traditional compendial limits are applied unless otherwise indicated. Based on toxicological properties, limits may be set for specific residual metals that appear during manufacturing.

Drug Product—Similarly, for the drug product, the dosage form may change, the number or scale of batches may increase and more stability data will have become available. Methods will have been validated.

(1) IND limits for total and individual degradation products (identified and unidentified) are reviewed and adjusted based on manufacturing experience, stability data and toxicological data.

(2) Degradation products present in significant amounts are identified and individual limits are set. However, it is not always possible to identify or prepare authentic substances for degradation products.

(3) The degradation product profiles of the lots designated for marketing should not be uniquely different from those of the lot(s) used for toxicological and clinical studies.

(4) The mass balance should be used, if possible, to evaluate the adequacy of the controls.

(5) Limits for residual solvents, if appropriate, are based on the known toxicology of the solvents and on the manufacturing capabilities and dosing regimens.

POST NDA APPROVAL

After approval and marketing of a pharmaceutical product, significant changes may be made in manufacturing the drug substance. There may be technological, ecological, economic, or safety reasons for these changes. If they occur, the Pharmacopeial and NDA impurity and degradation product limits and rationale should be reviewed; the limits should be revised when indicated to ensure similar or improved quality of the drug substance or drug product.

ANDA FILING

The drug substance for a pharmaceutical product eligible for ANDA status is frequently an official article and should be well characterized analytically. Drug substances are typically available from multiple sources, and each source may have a different manufacturing process. Therefore, it is essential that the dosage form manufacturer evaluate each supplier's drug substance impurity or degradation profiles. Limits can then be set based on the more detailed concepts described for NDA filing, including review of compendial monographs for appropriateness.

DEFINITIONS

Concomitant Components—Concomitant components are characteristic of many drug substances and are not considered to be impurities in the Pharmacopeial sense. Limits on contents, or specified ranges, or defined mixtures are set forth for concomitant components in this Pharmacopeia. Examples of concomitant components are geometric and optical isomers (or racemates) and antibiotics that are mixtures. Any component that can be considered a toxic impurity because of significant undesirable biological effect is not considered to be a concomitant component.

Foreign Substances (Extraneous Contaminants)—Foreign substances (extraneous contaminants), which are introduced by contamination or adulteration, are not consequences of the synthesis or preparation of compendial articles and thus cannot be anticipated when monograph tests and assays are selected. The presence of objectionable foreign substances not revealed by monograph tests and assays constitutes a variance from the official standard. Examples of foreign substances include ephedrine in Ipecac or a pesticide in an oral liquid analgesic. Allowance is made in this Pharmacopeia for the detection of foreign substances by unofficial methods. (See *Foreign Substances and Impurities* in the section *Tests and Assays* under *General Notices and Requirements.*)

Identified Impurities and Identified Degradation Products—Impurities or degradation products for which structural characterizations have been achieved.

Inorganic Impurities—Inorganic impurities can result from the manufacturing process (e.g., residual metals, inorganic salts, filter aids, etc.). Inorganic impurities are typically controlled by tests such as *Heavy Metals* ⟨231⟩ and *Residue On Ignition* ⟨281⟩.

Ordinary Impurities—Some monographs make reference to ordinary impurities and for more details see *Ordinary Impurities* ⟨466⟩.

Process Contaminants—Process contaminants are identified or unidentified substances (excluding related substances and water), including reagents, catalysts, other inorganic impurities (e.g., heavy metals, chloride, or sulfate); and may also include foreign substances (extraneous contaminants). These contaminants may be introduced during manufacturing or handling procedures.

Related Substances—Related substances are structurally related to a drug substance. These substances may be (a) identified or unidentified impurities arising from synthesis manufacturing process such as intermediates or by-products and do not increase on storage or (b) identified or unidentified degradation products that result from drug substance or drug product manufacturing processes or arise during storage of a material.

Residual Solvents—Refer to *Residual Solvents* ⟨467⟩.

Specified Impurities and Specified Degradation Products—Previously referred to as Signal Impurities, specified impurities or specified degradation products are impurities or degradation products that are individually listed and limited with specific acceptance criteria in individual monographs as applicable. Specified impurities or specified degradation products can be identified or unidentified.

Toxic Impurities—Toxic impurities have significant undesirable biological activity, even as minor components, and require individual identification and quantitation by specific tests. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles. Based on validation data, individualized tests and specifications are selected. These feature comparison to a Reference Standard of the impurity, if available. It is incumbent on the manufacturer to provide data that would support the classification of such impurities as toxic impurities.

Unidentified Impurities and Unidentified Degradation Products—Impurities or degradation products for which structural characterizations have not been achieved and that are identified solely by qualitative analytical properties (e.g., chromatographic retention times).

Unspecified Impurities and Unspecified Degradation Products—Impurities or degradation products that are limited by general acceptance criteria but not individually listed with their own specific acceptance criteria in individual monographs.■2S (*USP30*)

BRIEFING

⟨1163⟩ Quality Assurance in Pharmaceutical Compounding. This proposed new general information chapter is intended to provide guidance on developing a good quality assurance program in compounding. This chapter references other USP compounding-related chapters, such as *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩, *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩, and *Good Compounding Practices* ⟨1075⟩. The chapter discusses integral components involved in developing a good quality assurance program, which include standard operating procedures, documentation, verification, and testing. The testing components recommend that a compounder understand the basics in pharmaceutical and microbiological analysis. Also included are testing methods which describe the types of analysis for various dosage forms and the types of equipment required to perform the analysis. Please submit comments and suggestions to Dr. Christina Lee at CHL@usp.org.

(CRX: C. Lee) RTS—C45186

Add the following:

■⟨1163⟩ QUALITY ASSURANCE IN PHARMACEUTICAL COMPOUNDING

INTRODUCTION

A quality assurance program is a system of steps and actions taken to ensure the maintenance of proper standards in compounded preparations, including good documentation of the compounding activities. Although there are numerous *USP* general chapters that may apply to compounding, the need for a quality assurance system is well documented in USP chapters (see *Compounding Controls* under *Good Compounding Practices* ⟨1075⟩; *Quality Control* and *Verification* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩; and *The Quality Assurance Program* under *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩). A quality assurance program for compounding should include at least four separate but integrated components: (1) Standard Operating Procedures, (2) Documentation, (3) Verification, and (4) Testing.

STANDARD OPERATING PROCEDURES

Standard Operating Procedures (SOPs) for pharmaceutical compounding are documents that describe how to perform routine and expected tasks in the compounding environment, including formulation development, purchasing, compounding, testing, maintenance, materials handling and storage, quality assurance, labeling, beyond-use dating, cleaning, safety, and dispensing. SOPs are itemized instructions that describe how a task will be performed, who will do it, why it is done, and any limits.

SOPs must be reviewed regularly and updated as necessary. The SOP should be specific to each device, process, and decision used in compounding. Properly maintained and implemented SOPs should result in quality preparations and fewer compounding errors.

DOCUMENTATION

The purpose of the documentation is to provide a permanent record of all aspects of each compounding operation. Two essential compounding documents, the formulation record and the compounding record, are described in *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩. The compounding record is completed during the compounding process for the preparation being made.

In addition, many SOPs require specific cross-referenced data collection forms (e.g., air temperature and humidity records and balance maintenance and calibration records). Data collection forms required by SOPs are completed during routine tasks directed by the SOPs and may provide blank spaces for data, including logbook entries, data printouts, and reports.

VERIFICATION

Verification involves assurance and documentation that a process, procedure, or piece of equipment is functioning properly and producing the expected results. *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩ states: "The act of verification of a compounding procedure involves checking to ensure that calculations, weighing and measuring, order of mixing, and compounding techniques were appropriate and accurately performed." Verification may require outside laboratory testing. Equipment verification methods are sometimes available from manufacturers of the specific equipment or can be developed in-house. The responsibility for assuring that equipment performance is verified resides with compounding personnel, but may be performed by contractors.

TESTING

A quality assurance program should include testing of finished compounded preparations. It is important for the compounder to have a basic understanding of pharmaceutical analysis to ensure that valid results are obtained when tests are being conducted, whether they are done in-house or outsourced. While it is not practical to test every compounded preparation, it is incumbent on the compounder to know (1) when to test, (2) what to test, (3) what method(s) to use, (4) how to interpret the results, (5) the limits of the test, and (6) the importance of testing in the overall quality program in the compounding facility.

The goal in testing is to produce results as accurately, efficiently and quickly as possible. Any testing method used should have accuracy, speed, reproducibility, and specificity. No single testing method is suited for all drugs. There are a number of factors that determine the validity and reliability of results.

Compounding facilities have two options when testing is required. Some testing methods can easily be performed in-house, but some may need to be outsourced to a contract laboratory. Relatively basic testing methods that can be conducted in-house with proper training and a modest investment in instrumentation include weight and volumetric measurements, pH, density/specific gravity, refractive index, and UV and visible spectroscopy (see *Weights and Balances* ⟨41⟩, *Volumetric Apparatus* ⟨31⟩, *Prescription Balances and Volumetric Apparatus* ⟨1176⟩, *pH* ⟨791⟩, *Specific Gravity* ⟨841⟩, *Refractive Index* ⟨831⟩, and *Spectrophotometry and Light-Scattering* ⟨851⟩). Testing methods often outsourced to a contract laboratory include chromatography (high-pressure liquid chromatography (HPLC) and gas chromatography (GC), see *Chromatography* ⟨621⟩), mass spectroscopy (MS) (see *Mass Spectrometry* ⟨736⟩), hyphenated methods (HPLC-MS and GC-MS), UV and visible spectroscopy (see *Spectrophotometry and Light-Scattering* ⟨851⟩), and other sophisticated methods.

If testing is done in-house, appropriate equipment must be obtained, validated either by the manufacturer or by the compounder upon purchase, maintained, calibrated, and used properly. If testing is outsourced, the compounder needs to determine what to outsource and how to select a laboratory, and should develop ongoing relationships with the laboratories chosen. Contract laboratories should follow USP general chapter standards, as appropriate.

Selection of a Testing Method—One general consideration in testing method selection is the type of information that is needed, such as quantitative (potency, concentration), semi-quantitative (where a tolerance level is involved, as in endotoxin levels), or qualitative (presence/absence type of testing, including substance identification, sterility). Another consideration involves the physical and chemical characteristics of the analyte, including solubility, partition coefficient, dissociation constant (pKa), volatility, binding, and the quantity present.

The degree of quantitative measurement and specificity must be considered in the validation process. The typical analytical characteristics used in method validation include accuracy, precision, specificity, detection limit, quantitation limit,

linearity, range, and ruggedness (see *Validation of Compendial Procedures* ⟨1225⟩). Generally, the greater the level of accuracy, precision, or specificity required, the more sophisticated and expensive the testing methods needed. The methods used are also governed by the types of instrumentation available and the standards available for comparison.

Pharmaceutical analysis decisions include not only method selection but also administrative and economic factors, obtaining a representative sample, storage/shipping of the sample, sample preparation for analysis, the actual analysis, data acquisition, data treatment, and interpretation.

Factors Involved in Methods Selection—The testing method selected depends upon a number of factors, including sample requirements, sample handling/preparation/purification requirements, type of data needed, and levels of specificity and accuracy required.

Sampling Requirements—Prior to collecting samples for testing, the following factors should be considered: the number of samples needed, appropriate methods of obtaining representative samples, the physical state of the samples (solid, liquid, or gas), the type of container required for collection and storage, and possible shipping requirements or restrictions. Storage requirements for samples must be specified, such as type of container, temperature, humidity, and light protection (see *General Notices and Requirements*).

The effect of any substances in the formulation that may interfere or alter the results must be known beforehand. When sending a preparation to a contract laboratory, the compounder should provide the complete formulation so the laboratory can quickly determine if there may be any interfering substances.

Controlled drug substances, dangerous or hazardous chemicals, flammable or caustic substances, and refrigerated or frozen preparations require special handling during shipping.

Data Interpretation Requirements—The collection of raw data from the testing process must be completed accurately. One must ensure that appropriate and valid descriptive statistics are used to analyze the data, and that the operating parameters of the analytical instruments are well established. Reference values, if available, should be provided with the analytical results. A description of the analytical controls used by the laboratory is important for documentation, as well as the source of reference standards used to establish standard curves.

Personnel Requirements and Considerations—If testing is done in-house, personnel involved in this activity must be appropriately trained and evaluated with documentation of the training and evaluation. If testing is outsourced, the compounder must be assured of the credentials, proper training, and continuing competency activities of the personnel in the contract laboratory. The external laboratory should comply with Good Laboratory Practices (see *Good Laboratory Practice for Nonclinical Laboratory Studies,* 21 CFR Part 58 FDA's Good Laboratory Practices www.labcompliance.com/documents/FDA/FDA-GLP/21CFR58.pdf) and Good Compounding Practices (see *Good Compounding Practices* ⟨1075⟩). It is preferable that they be registered with the Food and Drug Administration (FDA). Also, it may be advantageous if the contract laboratory performs testing for pharmaceutical companies.

Testing Methods—Testing methods can be generally divided into physical testing methods, methods that interact with electromagnetic radiation, conductometric techniques, immunoassay methods, separation techniques, and others, as detailed in *Table 1*.

Table 1. Classification of Analytical and Microbiological Methods

Physical Testing Procedures	Interaction of Electromagnetic Radiation	Conductance Methods	Immunoassay	Separation Techniques	Others	Microbiological Methods
Weight	UV/Visible spectroscopy	pH	Radioimmunoassay	High-Performance Liquid Chromatography (HPLC)	Osmolality	Sterility Testing
Volumetric	IR spectroscopy	Ion selective electrodes	Enzyme Multiplied Immunoassay Technique(EMIT)	Gas Chromatography(GC)	—	Endotoxin Testing
Melting point	Fluorescence/Phosphorescence spectroscopy	Polarography	Enzyme Linked Immu noSorbent Assay (ELISA)	Thin-Layer Chromatog raphy (TLC)	—	Preservative Effectiveness Testing
Freezing point	Raman spectroscopy	—	Fluorescent Immunoas say (FIA)	Paper Chromatography (PC)	—	—
Boiling point	X-ray spectroscopy	—	—	Column Chromatogra phy (CC)	—	—
Density	Flame emission and Atomic absorption spectroscopy	—	—	—	—	—
Refractive index	Polarimetry	—	—	—	—	—
Optical rotation (Polarimetry)	Refractometry	—	—	—	—	—
Thermal analysis	Interferometry	—	—	—	—	—
Color change	—	—	—	—	—	—
Precipitate formation	—	—	—	—	—	—
Viscosity change	—	—	—	—	—	—

Table 1. Classification of Analytical and Microbiological Methods *(Continued)*

Physical Testing Procedures	Interaction of Electromagnetic Radiation	Conductance Methods	Immunoassay	Separation Techniques	Others	Microbiological Methods
Particle size	—	—	—	—	—	—
Light scattering	—	—	—	—	—	—
Zeta potential	—	—	—	—	—	—
Light obscuration	—	—	—	—	—	—
Microscopic examination	—	—	—	—	—	—

Nonspecific methods include melting, freezing and boiling points, density, refractive index, polarimetry, UV/visible spectroscopy, and pH. Methods that are somewhat more specific include IR spectroscopy, mass spectroscopy, ion selective electrodes, immunoassay methods, and chromatographic methods (HPLC and GC). Suggested testing methods for different dosage forms are shown in *Table 2*. It is the responsibility of the compounder to implement a program using selected methods for the preparations compounded in the facility.

Table 2. Suggested Analytical Methods for Various Dosage Forms, Depending Upon the Active Drug

	Analytical Method												
Dosage Form	Wt	Vol	pH	Osm	RI	Sp Gr	MP	UV/ Vis	HPLC	GC	IR	Sterile	En- do
Bulk substances	—	—	*	—	*	—	*	*	*	*	*	—	—
Powders	*	—	—	—	—	—	—	—	*	*	—	—	—
Capsules	*	—	—	—	—	—	—	—	*	*	—	—	—
Tablets	*	—	—	—	—	—	—	—	*	*	—	—	—
Lozenges	*	—	—	—	—	—	—	—	*	*	—	—	—
Suppositories	*	—	—	—	—	*	*	—	*	*	—	—	—
Sticks	*	—	—	—	—	*	*	—	*	*	—	—	—
Solutions	*	*	*	*	*	*	—	*	*	*	—	—	—
Suspensions	*	*	*	—	—	*	—	—	*	*	—	—	—
Emulsions	*	*	*	—	—	*	—	—	*	*	—	—	—
Semisolids	*	—	—	—	—	*	*	—	*	*	—	—	—
Gels	*	*	*	—	*	*	—	—	*	*	—	—	—
Ophthalmics, Otics, and Nasals	*	*	*	*	*	*	—	*	*	*	—	*	—
Inhalations	*	*	*	*	*	—	—	*	*	*	—	*	—
Injections	*	*	*	*	*	*	—	*	*	*	—	*	*
Sterile implant gels	*	*	*	*	*	*	—	*	*	*	*	*	*
Sterile implant solids	*	*	—	—	—	—	*	*	*	*	*	*	*

Methods that can be routinely used for testing incoming bulk materials, whether active or excipients, include melting, freezing and boiling points, density, refractive index, UV/Visible spectroscopy, IR spectroscopy, polarimetry, pH, and the separation methods. Final products may generally require a method such as HPLC or GC.

MICROBIOLOGICAL TESTING

Microbiological testing for pharmacy compounding includes sterility and endotoxin testing. Preservative effectiveness may also be considered.

Sterility Testing—Sterility tests can be conducted using commercial kits or by developing and validating USP sterility testing protocols, which are more detailed than the commercial sterility-testing kits. Standards and procedures are explained in *Sterility Tests* ⟨71⟩.

Endotoxin Testing—Endotoxin tests can be conducted using commercially available kits or by purchasing the components separately. Endotoxin testing endpoints can be difficult to interpret and in-house testing should only be done after obtaining training and experience. See *Bacterial Endotoxins Test* ⟨85⟩.

SUMMARY

A sound quality assurance program is important in a compounding pharmacy. It includes detailed SOPs, documentation, verification, and analytical and microbiological testing as appropriate. Analytical and microbiological testing will no doubt become a more important part of pharmaceutical compounding as the public and regulatory agencies demand more documentation on the quality of compounded preparations. Compounders must decide on the types of testing and degree of testing that will be a part of their quality assurance program. A decision must also be made on whether to do testing in-house or outsource it to a contract laboratory. It may be practical for larger compounding facilities to have their own analytical and/or microbiological testing laboratory, analytical chemist, or microbiologist to provide rapid turnaround of testing results.

Analytical and microbiological testing should only be performed by those who are trained and experienced, and who can demonstrate validated performance of their operations.■2S (*USP30*)

BRIEFING

⟨**1178**⟩ **Good Repackaging Practices,** *USP 29* page 3023. This proposed revised general information chapter is intended to provide repackagers with the guidance and references needed to apply good repackaging practices for oral solid drug products. The following proposed changes were based on discussions held by the Packaging and Storage Expert Committee:

1. The sections on *Facilities, Acquisition Process, Repackaging Process, Labeling, Minimum Requirements,* and *Shipping and Distribution* were omitted.
2. References to applicable FDA regulations and *USP* chapters were added to the chapter.
3. The definition of *Beyond-Use-Date* (BUD) was omitted, and its use removed from all text.
4. The definitions for *Repackager, Contract Repackager,* and *Equivalent Container–Closure System* were rewritten.

Other changes were made to clarify the content of the chapter and improve its readability.

(P&S: D. Hunt) RTS—C47502

⟨1178⟩ GOOD REPACKAGING PRACTICES

Change to read:

~~This chapter is intended to provide guidance to those engaged in repackaging of drug products in accordance with 21 CFR 10.90. A pharmacist who repackages under the state law needs to apply (1) the principal information provided in the USP general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩ and (2) other beyond-use date references in the *Expiration Date and Beyond-Use Date* section under *General Notices and Requirements*.~~

~~This chapter provides information to any person who removes drugs from their original manufacturer's container and repacks them into a different container–closure system for resale or for distribution to hospitals or other pharmacies. It does not apply to repackaging of any *radioactive* drug products, including oral solids.~~

~~A repackager referred to here may also be a contract packager or a contract repackager. The words "repackager" and "repacker" are the same in this text and may be used interchangeably. These functions are beyond the regular practice of a pharmacist. A repackager is required to register with the FDA and comply with current Good Manufacturing Practices (cGMPs) regulations in 21 CFR 210 and 211.~~

~~A repackager is expected to meet the requirements of packaging practice under 21 CFR 210 through 226. Because the packaging practice relates to packaging, processing, or holding a drug product intended for administration to humans or animals, the repackager is expected to comply with regulations such as those relating to the sections pertaining to quality control, personnel qualifications, building and facilities, equipment, production and process controls, packaging and labeling controls, laboratory controls, master production record, batch records and reprints, distribution records, storage control records, and complaint files.~~

~~DEFINITIONS~~

~~For the purposes of this chapter, repackager, contract packager, and contract repackager are defined as follows.~~

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A REPACKAGER is one who purchases and removes a drug product from the manufacturer's market container or bulk dosage container and places the product into a different container for distribution for human or animal use. A repackager may or may not take ownership from the manufacturer. A repackager is engaged in the repackaging of drugs (see also *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩ for more definitions of a repackager).

A CONTRACT PACKAGER is one who is contracted by original drug manufacturers to package or repackage their product into a single- or multi-unit container chosen by the manufacturer. These containers should meet all the applicable requirements in this chapter, pertinent sections in general test chapters *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩, and comply with 21 CFR food additive requirements.

AN EQUIVALENT CONTAINER–CLOSURE SYSTEM refers to a container–closure system that yields the same, or better, moisture vapor transmission rate (MVTR), oxygen transmission, and light transmission as the original market container. These values may be determined by the repackager, or they may be obtained from the container–closure vendor for the specific container–closure system under consideration.

BEYOND USE DATE (BUD) AND DISCARD AFTER DATE are equivalent and are assigned using the criteria stated in the relevant section below.

EXPIRATION DATE is determined using stability studies and is not the same as beyond use date or discard after date.

FACILITIES

The facility in which repackaging is practiced should be operated in conformity with cGMPs. The environmental conditions during the packaging and storage operation of the drug product should comply with the *controlled room temperature* (see *General Notices*), storage in a *dry place*, and other requirements as directed by the manufacturer or supplier, especially if the drug requires storage at special temperature and humidity conditions (see *Good Storage and Shipping Practices* ⟨1079⟩).

ACQUISITION PROCESS

The repackager is expected to perform appropriate analytical testing for all pertinent specifications, such as identity and strength of each active ingredient, and any other finished product tests to establish valid analytical data. The repackager is expected to maintain records of such analyses on a batch-by-batch basis for the repackaged product that is either transferred to the repackager by the manufacturer or independently maintained by the repackager.

"Bulk" in this text refers to the quantity of either drug product or dosage form. The following criteria should be considered by the repackager upon receipt of bulk prior to repackaging.

(a) The bulk article should be distributed to the repackager by the manufacturer in accordance with all regulatory requirements and accompanied by appropriate labeling and a valid expiration date. The repackager should also receive Material Safety Data Sheets (MSDS), Certificates of Analysis, and sample market labeling, including inserts from the drug product manufacturer.

(b) The bulk article should be received intact and undamaged and in properly labeled containers with the Certificate of Analysis.

(c) The bulk article should undergo definitive organoleptic evaluations to confirm its identity (e.g., physical appearance, marking, color, and odor) and to confirm the labeling as described by the manufacturer.

(d) Records should be maintained to verify the identity and quantity of each shipment received and to verify the lot number and bar coded information for each article of the bulk shipment received. This record should also include the name of the manufacturer or supplier and its lot numbers and the date of receipt.

(e) The repackager should store and maintain the bulk under storage conditions specified by the manufacturer, and/or as directed under *Controlled Room Temperature* (see *General Notices*).

REPACKAGING PROCESS

The following criteria should be observed.

(a) The repackaging operations should be conducted under conditions that meet specified storage temperature definitions (see *General Notices*). Conditions of operation include maintenance of *controlled room temperature* in the area where the repackaging operation is conducted or other conditions as instructed by the manufacturer.

(b) The manufacturer should include, in the package insert or in other appropriate literature supplied to the repackager, the following information about the packaging: materials of construction of the market package, its MVTR (see *Containers—Permeation* ⟨671⟩), as well as oxygen transmission and light transmission characteristics in order to enable the repackager to properly select an equivalent container–closure system. If the repackager does not use a container–closure system equivalent to the manufacturer's market package, then the repackager must generate stability data for the drug product in the new container–closure system to justify the expiration date assigned.

(c) The repackaging containers are labeled with the same labeling information as the market label that is used by the manufacturer. The conditions on the labeling should meet those required under 21 CFR 201, 211.122, 211.125, and 211.130.

(d) Written procedures should be maintained to ensure that correct labels, labeling, and packaging materials are used for drug products.

(e) All requirements for repackaging of bulk products should meet 21 CFR 211.

(f) The packaging materials should comply with 21 CFR food additives regulations and all applicable requirements in USP general chapters ⟨661⟩, ⟨671⟩, and ⟨1146⟩.

LABELING

A repackager should provide appropriate labeling of the product identical to the manufacturer's approved market container. All repackaged products should be labeled with an appropriate BUD in the absence of stability data, or with an expiration date in cases where suitable stability studies, determined in CFR 211.166 (for recommended conditions see *International Conference on Harmonization ICH Q1A Stability Testing of New Drug Substances and Products*), have been performed on the product using the repackager's container. The expiration date will ensure that the products meet applicable standards of identity, strength, quality, and purity at the time of use.

EXPIRATION DATE/BEYOND USE DATE

Expiration Date

Stability studies are performed on the drug product in the original manufacturer's containers to establish an expiration date. When a drug is repackaged into a different container, the product's expiration date is altered or interrupted.

(a) The repackager may perform stability studies on the repackaged products to establish an expiration date for the product based on scientific evaluation of the drug product in the container–closure system in which it is to be marketed.

(b) A repackager may use the manufacturer's original expiration date without additional stability testing if the drug product is repackaged into an equivalent container–closure system that is at least as protective as, or more protective than, the original system and complies with criteria established for equivalency. Establishment of system equivalency means (1) that the requirements of USP general test chapters ⟨661⟩ and ⟨671⟩ are met and (2) that the specifications such as light transmission, seals, or desiccants associated with the original container–closure system, or special protective materials in which the drug product is marketed, are the same. Comparison of container–closure systems may be done through stress testing of the product after storage under exaggerated conditions of temperature and humidity. If the repackager does not use a container–closure system equivalent to the manu-

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facturer's market package, then the repackager must generate stability data for the drug product in the new container–closure system to justify the expiration date or BUD assigned.

(c) A repackager should not use the equivalency container–closure system criteria to repackage drug products where such products have been identified by the manufacturer to have stability problems or if the manufacturer specifically states that the product should not be repackaged using the equivalency container–closure system criteria. For example, "This product is labile (e.g., moisture sensitive) and therefore should be dispensed only in the original manufacturer's container". In this case, a repackager needs to demonstrate the stability of the drug product in the repackager's container–closure system.

(d) Establishing the expiration date in the case listed in ô) is applicable for unit-dose containers, multiple-unit containers, and unit-of-use container types.

Beyond-Use Date or Discard-After Date

In the absence of stability data, where a repackager repackages a product into a unit-dose or multiple-unit container without conducting appropriate stability studies to support expiration dates used, the period of use of the product is limited by the BUD for the repackaged product, which must be less than the expiration date.

UNIT-DOSE PACKAGING

For unit-dose packaging, the following criteria should be considered.

(1) The original bulk container of the drug product to be used for repackaging has not been previously opened.

(2) The contents of the original bulk drug product to be repackaged are repackaged at one time.

(3) The unit-dose container meets USP general test chapter ⟨671⟩ testing requirements for either Class A or Class B containers.

(4) The unit-dose container meets or exceeds the manufacturer's specification for light resistance.

(5) The conditions of storage meet the storage specifications provided in the *General Notices* and as described in the labeling by the manufacturer of the bulk product. Where no specific storage conditions are specified, the product should be maintained at *controlled room temperature* and in a *dry place* during repackaging.

(6) The BUD used for the repackaged product does not exceed 6 months from the date of repackaging.

(7) The BUD does not exceed the manufacturer's expiration date.

(8) The BUD does not exceed 25% of the time between the date of repackaging and the expiration date shown on the manufacturer's bulk article container of the drug being repackaged.

(9) Documentation should be in place to show that the preceding criteria (items 1–8) are met. Documentation to show the type of packaging material used and the testing for these materials is also kept on file.

(10) The repackager may not repackage if the manufacturer specifically states "Do not repackage." HOwever, the repackager may affix the repackager's labeling if it is in accordance with FDA requirements and in agreement with the manufacturer of the drug product.

(11) The repackager may not use the expiration date and BUD interchangeably because they imply the presence or absence of stability testing, respectively.

MULTIPLE-UNIT PACKAGING

The *General Notices* define multiple-unit packaging as a package that contains more than one single dosage unit. For multiple unit packaging, the following criteria should be considered in assigning a BUD.

(1) The original bulk container of drug product to be used for repackaging has not been previously opened.

(2) The contents of the original bulk drug product to be packaged are repackaged at one time.

(3) The conditions of storage meet the storage specifications in the *General Notices* and as described in the labeling of the manufacturer's bulk product. Where no specific storage conditions are specified, the product should be maintained at *controlled room temperature* and in a *dry place* during repackaging.

(4) The type of container used for repackaging should be the same type used by the manufacturer as the market container, and the product container should comply with the requirements for containers as directed under *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩, as well as the requirements of 21 CFR for food additives, or the container should be composed of an approved food contact substance. For example, if the manufacturer packages in glass, the repackager should repackage in glass of the same type used by the manufacturer or in chemical resistant glass containers.

(5) Where the original container is a material other than glass or high density polyethylene (HDPE), the repackager may use a container demonstrated to be equivalent to, or exceed, the protective properties of the manufacturer's multiple-unit market container when performing the applicable tests as described in USP general test chapters ⟨661⟩ and ⟨671⟩.

(6) Where the original container is polyethylene, the repackager may repackage in a chemical resistant glass container or a polyethylene container. These containers should meet the appropriate tests and specifications in 21 CFR and USP general test chapters ⟨661⟩ and ⟨671⟩.

(7) The container meets or exceeds the test results of the manufacturer's multiple-unit market container for light transmission.

(8) The container meets or exceeds the manufacturer's container in special protective features: methods used to prevent leaching of container materials or the use of desiccants to maintain low moisture content. [NOTE—Desiccants should always be packaged on top of the drug product.]

(9) The container meets or exceeds the manufacturer's container test results for "tight" as provided in USP general test chapters ⟨661⟩ and ⟨671⟩.

(10) For all products, if the repackager uses a container that is equivalent in MVTR to the manufacturer's container or one that has a higher barrier, then the BUD should be 12 months or the manufacturer's expiration date, whichever is less. (See *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩ for a description of low- and high-barrier packaging.)

(11) The repackager may not repackage the original bulk container of the drug product if the manufacturer specifically states "Do not repackage." However, the repackager may affix the repackager's labeling if this is in accordance with FDA requirements or the specifications of the drug product manufacturer.

MINIMUM REQUIREMENTS

The following represents the minimum requirements a repackager must meet in order to engage in repackaging drugs from their original manufacturer's container.

(a) A repackager is expected to comply with cGMPs and 21 CFR 211.170(b) for retained samples of repackaged drug products. Any alteration or manipulation of the repackaging process should be documented in accordance with the requirements in 21 CFR 211.

(b) A repackager is expected to repack penicillins, or products such as penicillins, in facilities separate from those facilities used for drug products as described in 21 CFR 211.42 and 21 CFR 211.46.

SHIPPING AND DISTRIBUTION

For products identified by the manufacturer as moisture- and temperature-sensitive, the repackager must follow the specifications provided by the manufacturer during repackaging, shipping, and distribution.

~~(a) A repackager may not repackage a moisture- and temperature-sensitive product if the manufacturer so instructs, except if the repackager is only altering the labeling in accordance with FDA requirements.~~
~~(b) The repackaging container should show the equivalent of, or be better in protective properties than, the manufacturer's original container. For moisture-sensitive products, a higher-barrier container should be used for repackaging.~~
~~(c) The repackager should have proper documentation in place to show the equivalency in protection of the container used.~~
~~(d) The storage and handling of the drug product should meet the conditions specifically instructed by the manufacturer of the product.~~
~~(e) The repackager should label the container "Contains moisture-sensitive product."~~
~~For all other products, the repackager should follow the same guidelines provided in *Good Storage and Shipping Practices* ⟨1079⟩ that are applicable to a manufacturer.~~

▪INTRODUCTION

This chapter is intended to provide guidance to those engaged in repackaging of oral solid drug products; and the chapter provides information to any person who removes drugs from their original container–closure system (new primary package) and repackages them into a different container–closure system for sale and/or for distribution.

This chapter does not apply to pharmacists engaged in dispensing prescription drugs in accordance with state practice of pharmacy. The pharmacist needs to apply

(1) the principal information provided in the USP general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩ and

(2) other beyond-use date references in the subsection *Expiration Date and Beyond-Use Date* in the *Labeling* section under *General Notices and Requirements*.

DEFINITIONS

The section *Preservation, Packaging, Storage, and Labeling* under *General Notices and Requirements* provides definitions related to repackaging. For the purposes of this chapter, a repackager, a contract packager, and an equivalent container–closure system are defined as follows:

1. **Repackager—**A repackager is an establishment that repackages drugs and sends them to a second location in anticipation of a need. Repackaging firms repackage preparations for distribution (e.g., for resale to distributors, hospitals, or other pharmacies), a function that is beyond the regular practice of a pharmacy. Distribution is not patient-specific in that there are no prescriptions. Unlike dispensers, repackaging firms are required to register with the FDA and to comply with the Current Good Manufacturing Practice Regulations in 21 CFR 210 and 211.
2. **Contract Packager—**A contract packager is an establishment that is contracted to package or repackage a drug product into a single- or multi-unit container. These containers should meet all of the applicable requirements in this chapter. A contract packager does not take ownership from the manufacturer and generally receives the assigned expiration date from the contractor.
3. **Equivalent Container–Closure System—**This term refers to a container–closure system that is at least as protective or more protective than the original container–closure system in terms of moisture vapor transmission rate (MVTR), oxygen transmission, light transmission, and compatibility of the container–closure system with the drug product. System equivalency extends to any special protective materials, such as for light transmission, seals, or desiccants associated with the original container–closure system. These values may be determined by the repackager, or they may be obtained from the container–closure vendor for the specific container–closure system under consideration.

ESTABLISHING EXPIRATION DATE

In the absence of stability data, the following criteria should be considered by repackagers when assigning an expiration date.

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Unit-Dose Packaging

1. The original container–closure system of the drug product to be used for repackaging must be received un-opened and show no outward signs of having been previously opened.
2. The unit-dose container–closure system must meet the testing requirements under *Containers—Performance Testing* ⟨671⟩ for either *Class A* or *Class B* containers.
3. The contents of the original bulk drug product to be repackaged are repackaged at one time unless the repackager has data and/or other scientific information from literature sources demonstrating that the drug product is not sensitive to exposure to moisture, oxygen, or light.
4. The unit-dose container–closure system must meet or exceed the original container's specification for light resistance.
5. The conditions of storage must meet the storage specifications provided in the *USP General Notices* and as described in the labeling of the original container–closure system received for repackaging. Where no specific storage conditions are specified, the product must be maintained at controlled room temperature and in a dry place during the repackaging process, including storage.
6. The expiration dating period used for the repackaged product does not exceed (1) 6 months from the date of repackaging; or (2) the manufacturer's expiration date; or (3) 25% of the time between the date of repackaging and the expiration date shown on the manufacturer's bulk article container of the drug being repackaged, whichever is earlier.
7. Nitroglycerin Sublingual Tablets or any other drug product known to have stability problems should not be repackaged. This would include any drug known to be oxygen-sensitive or one that exhibits extreme moisture or light sensitivity. In deciding whether a particular drug product is suitable for repackaging, the repackager should take into consideration any available information from the manufacturer, published literature, the USP, and the FDA.
8. Documentation must be maintained to demonstrate that the preceding criteria are met.
9. Documentation must be maintained that specifies the container–closure packaging material used in repackaging operations.

Multiple-Unit Packaging

1. A repackager may use the manufacturer's original expiration date without additional stability testing if the drug product is repackaged into an equivalent container–closure system that is at least as protective as, or more protective than, the original system and complies with criteria established for equivalency.
2. The original container–closure system of the drug product to be used for repackaging must be received un-opened and shows no outward signs of having been previously opened.
3. The contents of the original bulk drug product to be repackaged are repackaged at one time unless the repackager has data and/or other scientific information from literature sources demonstrating that the drug product is not sensitive to exposure to moisture, oxygen, or light.
4. The conditions of storage meet the storage specifications in the *General Notices* and as described in the labeling of the original container–closure system received for repackaging. When no specific storage conditions are specified, the product should be maintained at controlled room temperature and in a dry place during repackaging operations.
5. The type of container–closure system used for repackaging must be at least as protective or more protective than the original container–closure system in terms of moisture vapor transmission rate (MVTR), oxygen transmission,

light transmission, and compatibility of the container–closure system with the drug product. System equivalency extends to any special protective materials, such as for light transmission, seals, or desiccants associated with the original container–closure system.

6. The container–closure system must meet or exceed the original container–closure system's results for light transmission.
7. Nitroglycerin Sublingual Tablets or any other drug product known to have stability problems should not be repackaged. This would include any drug known to be oxygen-sensitive or one that exhibits extreme moisture or light sensitivity. In deciding whether a particular drug product is suitable for repackaging, the repackager should take into consideration any available information from the manufacturer, published literature, the USP, and the FDA.
8. Documentation must be maintained to demonstrate that the preceding criteria are met.
9. Documentation must be maintained that specifies the container–closure packaging material used in repackaging operations.

REFERENCES FOR REPACKAGING REGULATIONS AND GUIDANCES

The references listed below are not meant to be all inclusive: specific repackaging operations may have additional requirements.

- **Food, Drug, and Cosmetic Act**
- **Food and Drug Administration Regulations and Guidances**

Enforcement Policy: 21 CFR, Part 7

General Labeling Provisions: 21 CFR, Part 201, Subpart A

Drug Establishment Registration and Listing: 21 CFR, Part 207.20

Current Good Manufacturing Regulations: 21 CFR, Parts 210–211

Special Requirements for Specific Human Drugs: 21 CFR, Part 250

Controlled Substances: CFR, Part 1300

Potable Water: 40 CFR, Part 141

FDA *Compliance Policy Guides,* including the following:

Sub Chapter 430 Labeling and Repackaging

Sub Chapter 460 Pharmacy Issues

Sub Chapter 480 Stability/Expiration Dating

- **Applicable USP Chapters**

⟨660⟩ *Containers—Glass*

⟨661⟩ *Containers—Plastics*

⟨671⟩ *Containers—Performance Testing*

⟨681⟩ *Repackaging into Single-Unit Container and Unit-Dose Container for Nonsterile Solid and Liquid Dosage Forms*

⟨1079⟩ *Good Storage and Shipping Practices*

⟨1146⟩ *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container*■2S (*USP30*)

BRIEFING

⟨**1231**⟩ **Water for Pharmaceutical Purposes,** *USP 29* page 3056. This informational chapter, which became official in the *Second Supplement* to *USP 28,* has a discussion of *Pure Steam* as a "USP monograph to come"; however, the *Pure Steam* monograph became official April 1, 2006 in the *First Supplement* to *USP 29*. In order to better align the ⟨1231⟩ discussion of Pure Steam with the wording and intended uses of this new official article, the Pharmaceutical Waters Expert Committee is proposing the following changes to that section. Please direct comments to Gary Ritchie, liaison to the Pharmaceutical Waters Expert Committee.

(PW: G. Ritchie) RTS—C43049

In-Process Revision

Change to read:

TYPES OF WATER

There are many different grades of water used for pharmaceutical purposes. Several are described in *USP* monographs that specify uses, acceptable methods of preparation, and quality attributes. These waters can be divided into two general types: bulk waters, which are typically produced on site where they are used; and packaged waters, which are produced, packaged, and sterilized to preserve microbial quality throughout their packaged shelf life. There are several specialized types of packaged waters, differing in their designated applications, packaging limitations, and other quality attributes.

There are also other types of water for which there are no monographs. These are all bulk waters, with names given for descriptive purposes only. Many of these waters are used in specific analytical methods. The associated text may not specify or imply certain quality attributes or modes of preparation. These nonmonographed waters may not necessarily adhere strictly to the stated or implied modes of preparation or attributes. Waters produced by other means or controlled by other test attributes may equally satisfy the intended uses for these waters. It is the user's responsibility to ensure that such waters, even if produced and controlled exactly as stated, be suitable for their intended use. Wherever the term "water" is used within this compendia without other descriptive adjectives or clauses, the intent is that water of no less purity than *Purified Water* be used.

What follows is a brief description of the various types of pharmaceutical waters and their significant uses or attributes. *Figure 1* may also be helpful in understanding some of the various types of waters.

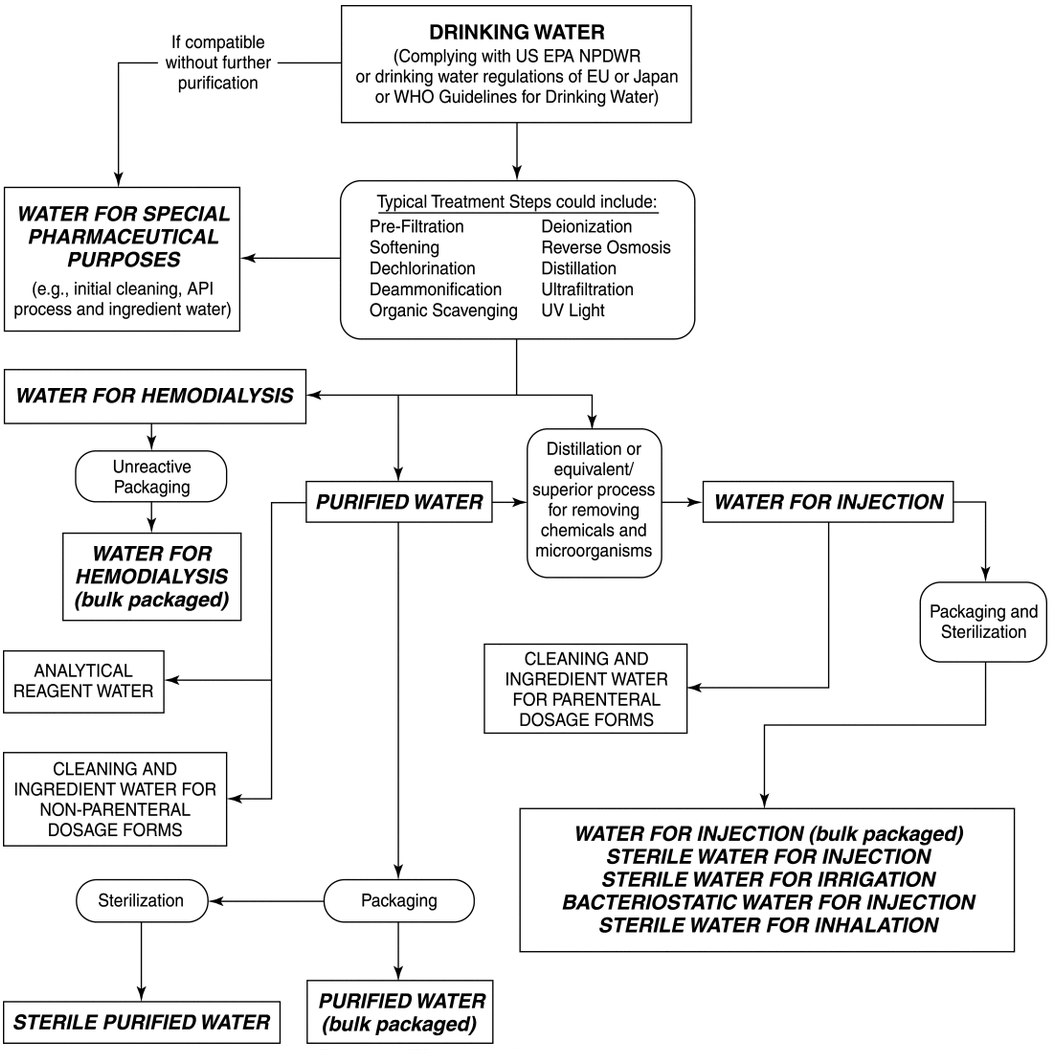

Figure 1. Water for pharmaceutical purposes.

Bulk Monographed Waters and Steam

The following waters are typically produced in large volume by a multiple-unit operation water system and distributed by a piping system for use at the same site. These particular pharmaceutical waters must meet the quality attributes as specified in the related monographs.

Purified Water—*Purified Water* (see *USP* monograph) is used as an excipient in the production of nonparenteral preparations and in other pharmaceutical applications, such as cleaning of certain equipment and nonparenteral product-contact components. Unless otherwise specified, *Purified Water* is also to be used for all tests and assays for which water is indicated (see *General Notices and Requirements*). *Purified Water* is also referenced throughout the *USP–NF*. Regardless of the font and letter case used in its spelling, water complying with the *Purified Water* monograph is intended. *Purified Water* must meet the requirements for ionic and organic chemical purity and must be protected from microbial contamination. The minimal quality of source or feed water for the production of *Purified Water* is Drinking Water. This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse os-

mosis, filtration, or other suitable purification procedures. Purified water systems must be validated to reliably and consistently produce and distribute water of acceptable chemical and microbiological quality. Purified water systems that function under ambient conditions are particularly susceptible to the establishment of tenacious biofilms of microorganisms, which can be the source of undesirable levels of viable microorganisms or endotoxins in the effluent water. These systems require frequent sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at the points of use.

The *Purified Water* monograph also allows bulk packaging for commercial use elsewhere. When this is done, the required specifications are those of the packaged water *Sterile Purified Water*, except for *Sterility* and *Labeling*. There is a potential for microbial contamination and other quality changes of this bulk packaged non-sterile water to occur. Therefore, this form of *Purified Water* should be prepared and stored in such a fashion that limits microbial growth and/or simply used in a timely fashion before microbial proliferation renders it unsuitable for its intended use. Also depending on the material used for packaging, there could be extractable compounds leaching into the water from the packaging. Though this article may meet its required chemical attributes, such extractables may render the water an inappropriate choice for some applications. It is the user's responsibilitiy to assure fitness for use of this packaged article when used in manufacturing, clinical, or analytical applications where the pure bulk form of the water is indicated.

Water for Injection—*Water for Injection* (see *USP* monograph) is used as an excipient in the production of parenteral and other preparations where product endotoxin content must be controlled, and in other pharmaceutical applications, such as cleaning of certain equipment and parenteral product-contact components. The minimum quality of source or feed water for the generation of *Water for Injection* is Drinking Water as defined by the U.S. EPA, EU, Japan, or the WHO. This source water may be pre-treated to render it suitable for subsequent distillation (or whatever other validated process is used according to the monograph). The finished water must meet all of the chemical requirements for *Purified Water* as well as an additional bacterial endotoxin specification. Since endotoxins are produced by the kinds of microorganisms that are prone to inhabit water, the equipment and procedures used by the system to purify, store, and distribute *Water for Injection* must be designed to minimize or prevent microbial contamination as well as remove incoming endotoxin from the starting water. *Water for Injection* systems must be validated to reliably and consistently produce and distribute this quality of water.

The *Water for Injection* monograph also allows it to be packed in bulk for commercial use. Required specifications include the test for *Bacterial endotoxins,* and those of the packaged water *Sterile Purified Water,* except for *Labeling*. Bulk packaged *Water for Injection* is required to be sterile, thus eliminating microbial contamination quality changes. However, packaging extractables may render this water an inappropriate choice for some applications. It is the user's responsibility to ensure fitness for use of this packaged article when used in manufacturing, clinical, or analytical applications where the purer bulk form of the water is indicated.

Water for Hemodialysis—*Water for Hemodialysis* (see *USP* monograph) is used for hemodialysis applications, primarily the dilution of hemodialysis concentrate solutions. It is produced and used on-site and is made from EPA Drinking Water which has been further purified to reduce chemical and microbiological components. It may be packaged and stored in unreactive containers that preclude bacterial entry. The term "unreactive containers" implies that the container, especially its water contact surfaces, are not changed in any way by the water, such as by leaching of container-related compounds into the water or by any chemical reaction or corrosion caused by the water. The water contains no added antimicrobials and is not intended for injection. Its attributes include specifications for *Water conductivity, Total organic* carbon (or oxidizable substances), *Microbial limits,* and *Bacterial endotoxins.* The water conductivity and total organic carbon attributes are identical to those established for *Purified Water* and *Water for Injection;* however, instead of total organic carbon, the organic content may alternatively be measured by the test for *Oxidizable substances*. The *Microbial limits* attribute for this water is unique among the "bulk" water monographs, but is justified on the basis of this water's specific application that has microbial content requirements related to its safe use. The *Bacterial endotoxins* attribute is likewise established at a level related to its safe use.

~~**Pure Steam**—*Pure Steam* is intended for use in steam sterilizing porous loads and equipment and in other processes such as cleaning where condensate would directly contact official articles, containers for these articles, process surfaces that would in turn contact these articles, or materials which are used in analyzing such articles. *Pure Steam* may be used for air humidification in controlled manufacturing areas where official articles or article-contact surfaces are exposed to the resulting conditioned air. The primary intent of using this quality of steam is to ensure that official articles or article-contact surfaces exposed to it are not contaminated by residues within the steam. *Pure Steam* is prepared from suitably pretreated source water, analogous to the pretreatment used for *Purified Water* or *Water for Injection,* vaporized with a suitable mist elimination, and distributed under pressure. The sources of undesirable contaminants within Pure Steam could be derived from entrained source water droplets, anti corrosion steam additives, or particulate matter from the steam production and distribution system itself; therefore, the attributes in the monograph should preclude most of the contaminants that could arise from these sources.~~

■*Pure Steam* (see *USP* monograph) is also sometimes referred to as "clean steam". It is used where the steam or its condensate would directly contact official articles or article-contact surfaces such as during their preparation, sterilization, or cleaning where no subsequent processing step is used to remove any codeposited impurity residues. These *Pure Steam* applications include but are not limited to porous load sterilization processes, to product or cleaning solutions heated by direct steam injection, or in humidification of processes where steam injection is used to control the humidity inside processing vessels where the official articles or their in-process forms are exposed. The primary intent of using this quality of steam is to ensure that official articles or article-contact surfaces exposed to it are not contaminated by residues within the steam.

Pure Steam is prepared from suitably pretreated source water, analogously to either the pretreatment used for *Purified Water* or *Water for Injection*. The water is vaporized with suitable mist elimination, and distributed under pressure. The sources of undesirable contaminants within *Pure Steam* could arise from entrained source water droplets, anti-corrosion steam additives, or residues from the steam production and distribution system itself. The attributes in the *Pure Steam* monograph should detect most of the contaminants that could arise from these sources. If the official article exposed to potential *Pure Steam* residues is intended for parenteral use or

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other applications where the pyrogenic content must be controlled, the *Pure Steam* must additionally meet the specification for *Bacterial Endotoxins* ⟨85⟩.■2S (*USP30*)

These purity attributes are measured on the condensate of the article, rather than the article itself. This, of course, imparts great importance to the cleanliness of the *Pure Steam* condensate generation and collection process because it must not adversely impact the quality of the resulting condensed fluid.

Other steam attributes not detailed in the monograph, in particular, the presence of even small quantities of noncondenseable gases or the existence of a superheated or dry state, may also be important for applications such as sterilization. The large release of energy (latent heat of condensation) as water changes from the gaseous to the liquid state is the key to steam's sterilization efficacy and its efficiency, in general, as a heat transfer agent. If this phase change (condensation) is not allowed to happen because the steam is extremely hot and in a persistent super heated, dry state, then its usefulness could be seriously compromised. Noncondensable gases in steam tend to stratify or collect in certain areas of a steam sterilization chamber or its load. These surfaces would thereby be at least partially insulated from the steam condensation phenomenon, preventing them from experiencing the full energy of the sterilizing conditions. Therefore, control of these kinds of steam attributes, in addition to its chemical purity, may also be important for certain *Pure Steam* applications. However, because these additional attributes are use-specific, they are not mentioned in the *Pure Steam* monograph.

~~Note that less pure plant steam may be used for steam sterilization of nonporous loads, general cleaning and sterilization of nonproduct contact equipment and analytical materials, humidification of air in nonmanufacturing areas, where used as a nonproduct contact heat exchange medium, and in all compatible applications involved in bulk pharmaceutical chemical and API manufacture.~~

■Note that less pure "plant steam" may be used for steam sterilization of nonproduct contact nonporous loads, for general cleaning of nonproduct contact equipment, as a nonproduct contact heat exchange medium, and in all compatible applications involved in bulk pharmaceutical chemical and API manufacture.■2S (*USP30*)

Packaged Monographed Waters

The following monographed waters are packaged forms of either *Purified Water* or *Water for Injection* that have been sterilized to preserve their microbiological properties. These waters may have specific intended uses as indicated by their names and may also have restrictions on packaging configurations related to those uses. In general, these packaged waters may be used in lieu of the bulk form of water from which they were derived. However, the user should take into consideration that the packaging and sterilization processes used for the articles may leach materials from the packaging material into the water over its shelf life, rendering it less pure than the original water placed into the package. The chemical attributes of these waters are still defined primarily by the wet chemistry methods and specifications similar to those formerly used for the bulk pharmaceutical waters prior to their replacement with water conductivity and total organic carbon (TOC). It is the user's responsibility to ensure fitness for use of this article when used in manufacturing, clinical, or analytical applications where the purer bulk form of the water is indicated.

Sterile Purified Water—*Sterile Purified Water* (see *USP* monograph) is *Purified Water*, packaged and rendered sterile. It is used in the preparation of nonparenteral compendial dosage forms or in analytical applications requiring *Purified Water* where access to a validated *Purified Water* system is not practical, where only a relatively small quantity is needed, where sterile *Purified Water* is required, or where bulk packaged *Purified Water* is not suitably microbiologically controlled.

Sterile Water for Injection —*Sterile Water for Injection* (see *USP* monograph) is *Water for Injection* packaged and rendered sterile. It is used for extemporaneous prescription compounding and as a sterile diluent for parenteral products. It may also be used for other applications where bulk *Water for Injection* or *Purified Water* is indicated but where assess to a validated water system is either not practical or where only a relatively small quantity is needed. *Sterile Water for Injection* is packaged in single-dose containers not larger than 1 L in size.

Bacteriostatic Water for Injection —*Bacteriostatic Water for Injection* (see *USP* monograph) is sterile *Water for Injection* to which has been added one or more suitable antimicrobial preservatives. It is intended to be used as a diluent in the preparation of parenteral products, most typically for multi-dose products that require repeated content withdrawals. It may be packaged in single-dose or multiple-dose containers not larger than 30 mL.

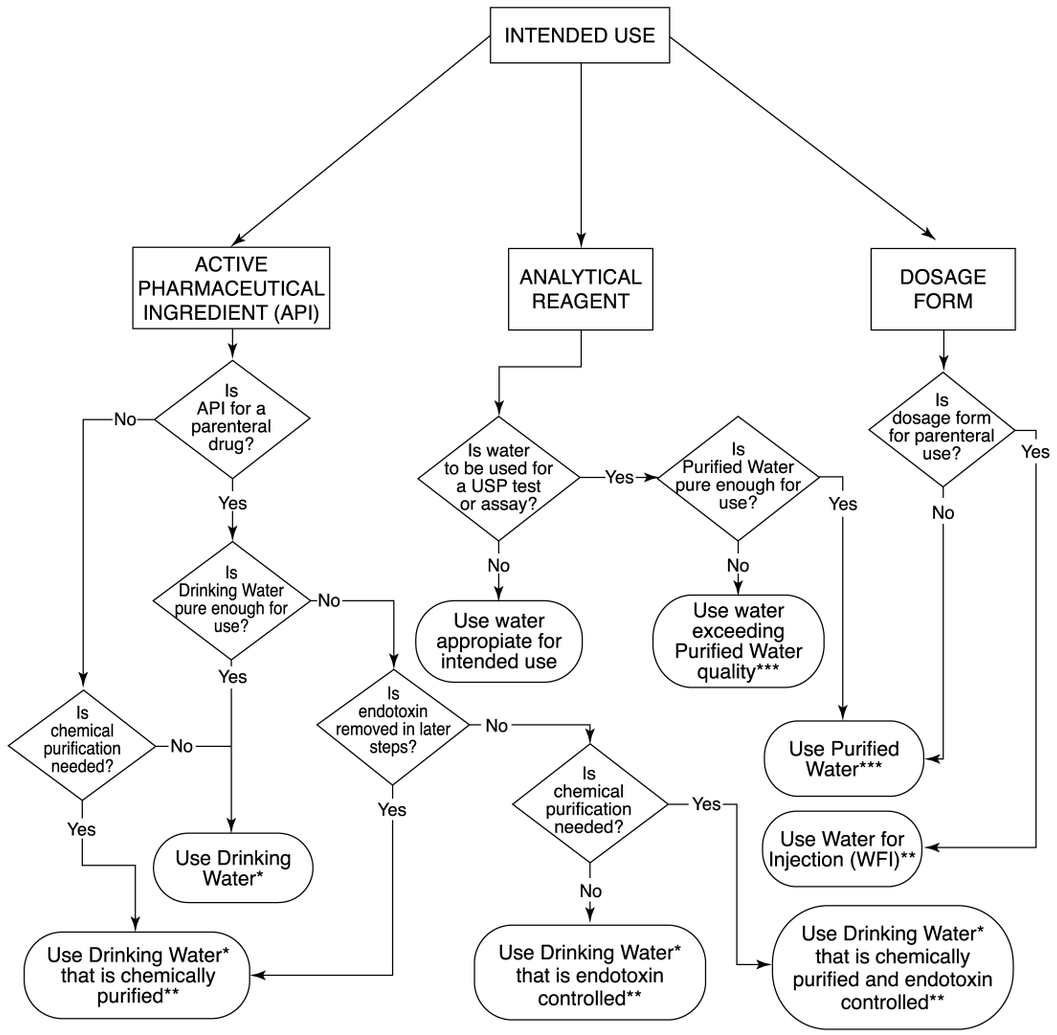
Sterile Water for Irrigation—*Sterile Water for Irrigation* (see *USP* monograph) is *Water for Injection* packaged and sterilized in single-dose containers of larger than 1 L in size that allows rapid delivery of its contents. It need not meet the requirement under small-volume injections in the general test chapter *Particulate Matter in Injections* ⟨788⟩. It may also be used in other applications, which do not have particulate matter specifications, where bulk *Water for Injection* or *Purified Water* is indicated but where access to a validated water system is not practical or where somewhat larger quantities than are provided as *Sterile Water for Injection* are needed.

Sterile Water for Inhalation—*Sterile Water for Inhalation* (see *USP* monograph) is *Water for Injection* that is packaged and rendered sterile and is intended for use in inhalators and in the preparation of inhalation solutions. It carries a less stringent specification for bacterial endotoxins than *Sterile Water for Injection*, and therefore, is not suitable for parenteral applications.

Nonmonographed Manufacturing Waters

In addition to the bulk monographed waters described above, nonmonographed waters can also be used in pharmaceutical processing steps such as cleaning, synthetic steps or as a starting material for further purification. The following is a description of several of these nonmonographed waters as cited in various locations within this compendia.

Drinking Water—This type of water can be referred to as Potable Water (meaning drinkable or fit to drink), National Primary Drinking Water, Primary Drinking Water, or National Drinking Water. Except where a singular drinking water specification is stated (such as the NPDWR [U.S. Environmental Protection Agency's National Primary Drinking Water Regulations as cited in 40 CFR Part 141]), this water must comply with the quality attributes of either the NPDWR, or the drinking water regulations of the European Union or Japan, or the WHO Drinking Water Guidelines. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of these sources. Drinking Water may be used in the early stages of cleaning pharmaceutical manufacturing equipment and product-contact components. Drinking Water is also the minimum quality of water that should be used for the preparation of official substances and other bulk pharmaceutical ingredients. Where compatible with the processes, the allowed contaminant levels in Drinking Water are generally considered safe for use for official substances and other drug substances. Where required by the processing of the materials to achieve their required final purity, higher qualities of water may be needed for these manufacturing steps, perhaps even as pure as *Water for Injection* or *Purified Water*. Such higher purity waters, however, might require only selected attributes to be of higher purity than Drinking Water (see *Figure 2* below). Drinking Water is the prescribed source or feed water for the production of bulk monographed pharmaceutical waters. The use of Drinking Water specifications establishes a reasonable set of maximum allowable levels of chemical and microbiological contaminants with which a water purification system will be challenged. As seasonal variations in the quality attributes of the Drinking Water supply can occur, due consideration to its synthetic and cleaning uses must be given. The processing steps in the production of pharmaceutical waters must be designed to accommodate this variability.



* Drinking Water is water complying with US EPA NPDWR or drinking water regulations of EU or Japan or WHO drinking water guidelines.

** Water for sterile API's or dosage forms must first be rendered sterile if there is not a subsequent sterilization step in the process where used.

*** See guidance in this chapter where waters other than Purified Water are required by some USP tests and assays.

Note: All water systems should be validated with whatever microbial control is needed to suit the intended purposes of the water.

Figure 2. Selection of water for pharmaceutical purposes.

Hot Purified Water—This water is used in the preparation instructions for *USP–NF* articles and is clearly intended to be *Purified Water* that has been heated to an unspecified temperature in order to enhance solubilization of other ingredients. There is no upper temperature limit for the water (other than being less than 100°), but for each monograph there is an implied lower limit below which the desired solubilization effect would not occur.

Nonmonographed Analytical Waters

Both *General Notices and Requirements* and the introductory section to *Reagents, Indicators, and Solutions* clearly state that where the term ''water,'' without qualification or other specification, is indicated for use in analyses, the quality of water shall be *Purified Water*. However, numerous such qualifications do exist. Some of these qualifications involve methods of preparation, ranging from specifying the primary purification step to specifying additional purification. Other qualifications call for specific attributes to be met that might otherwise interfere with analytical processes. In most of these latter cases, the required attribute is not specifically tested. Rather, a further ''purification process'' is specified that ostensibly allows the water to adequately meet this required attribute.

However, preparation instructions for many reagents were carried forward from the innovator's laboratories to the originally introduced monograph for a particular *USP–NF* article or general test chapter. The quality of the reagent water described in these tests may reflect the water quality designation of the innovator's laboratory. These spe-

cific water designations may have originated without the innovator's awareness of the requirement for *Purified Water* in *USP–NF* tests. Regardless of the original reason for the creation of these numerous special analytical waters, it is possible that the attributes of these special waters could now be met by the basic preparation steps and current specifications of *Purified Water*. In some cases, however, some of the cited post-processing steps are still necessary to reliably achieve the required attributes.

Users are not obligated to employ specific and perhaps archaically generated forms of analytical water where alternatives with equal or better quality, availability, or analytical performance may exist. The consistency and reliability for producing these alternative analytical waters should be verified as producing the desired attributes. In addition, any alternative analytical water must be evaluated on an application-by-application basis by the user to ensure its suitability. Following is a summary of the various types of nonmonographed analytical waters that are cited in the *USP–NF.*

Distilled Water—This water is produced by vaporizing liquid water and condensing it in a purer state. It is used primarily as a solvent for reagent preparation, but it is also specified in the execution of other aspects of tests, such as for rinsing an analyte, transferring a test material as a slurry, as a calibration standard or analytical blank, and for test apparatus cleaning. It is also cited as the starting water to be used for making *High Purity Water.* Because none of the cited uses of this water imply a need for a particular purity attribute that can only be derived by distillation, water meeting the requirements for *Purified Water* derived by other means of purification could be equally suitable where *Distilled Water* is specified.

Freshly Distilled Water—Also called "recently distilled water", it is produced in a similar fashion to *Distilled Water* and should be used shortly after its generation. This implies the need to avoid endotoxin contamination as well as any other adventitious forms of contamination from the air or containers that could arise with prolonged storage. It is used for preparing solutions for subcutaneous test animal injections as well as for a reagent solvent in tests for which there appears to be no particularly high water purity needed that could be ascribable to being "freshly distilled". In the "test-animal" use, the term "freshly distilled" and its testing use imply a chemical, endotoxin, and microbiological purity that could be equally satisfied by *Water for Injection* (though no reference is made to these chemical, endotoxin, or microbial attributes or specific protection from recontamination). For nonanimal uses, water meeting the requirements for *Purified Water* derived by other means of purification and/or storage periods could be equally suitable where "recently distilled water" or *Freshly Distilled Water* is specified.

Deionized Water—This water is produced by an ion-exchange process in which the contaminating ions are replaced with either H^+ or OH^- ions. Similarly to *Distilled Water, Deionized Water* is used primarily as a solvent for reagent preparation, but it is also specified in the execution of other aspects of tests, such as for transferring an analyte within a test procedure, as a calibration standard or analytical blank, and for test apparatus cleaning. Also, none of the cited uses of this water imply any needed purity attribute that can only be achieved by deionization. Therefore, water meeting the requirements for *Purified Water* that is derived by other means of purification could be equally suitable where *Deionized Water* is specified.

Freshly Deionized Water—This water is prepared in a similar fashion to *Deionized Water,* though as the name suggests, it is to be used shortly after its production. This implies the need to avoid any adventitious contamination that could occur upon storage. This water is indicated for use as a reagent solvent as well as for cleaning. Due to the nature of the testing, *Purified Water* could be a reasonable alternative for these applications.

Deionized Distilled Water—This water is produced by deionizing (see *Deionized Water*) *Distilled Water.* This water is used as a reagent in a liquid chromatography test that requires a high purity. Because of the importance of this high purity, water that barely meets the requirements for *Purified Water* may not be acceptable. *High Purity Water* (see below) could be a reasonable alternative for this water.

Filtered Distilled or Deionized Water—This water is essentially *Purified Water* produced by distillation or deionization that has been filtered through a 1.2-µm rated membrane. This water is used in particulate matter testing where the presence of particles in the water could bias the test results (see *Particulate Matter in Injections* ⟨788⟩). Because the chemical water purity needed for this test could also be afforded by water purification processes other than distillation or deionization, filtered water meeting the requirements for *Purified Water,* but produced by means other than distillation or deionization could be equally suitable.

Filtered Water—This water is *Purified Water* that has been filtered to remove particles that could interfere with the analysis where the water is used. Where used for preparing samples for particulate matter testing (see *Particulate Matter in Injections* ⟨788⟩), though unspecified in monographs, water filtration should be through a 1.2-µm filter to be consistent with the general test chapter. Where used as a chromatography reagent, monograph-specified filter ratings range from 0.5 µm to unspecified.

High Purity Water—The preparation of this water is defined in *Containers* ⟨661⟩. It is water that is prepared by deionizing previously distilled water, and then filtering it through a 0.45-µm rated membrane. This water must have an in-line conductivity of not greater than 0.15 µS/cm (6.67 Megohm-cm) at 25°. For the sake of purity comparison, the analogous Stage 1 and 2 conductivity requirements for *Purified Water* at the same temperature are 1.3 µS/cm and 2.1 µS/cm, respectively. The preparation specified in *Containers* ⟨661⟩ uses materials that are highly efficient deionizers and that do not contribute copper ions or organics to the water, assuring a very high quality water. If the water of this purity contacts the atmosphere even briefly as it is being used or drawn from its purification system, its conductivity will immediately degrade, by as much as about 1.0 µS/cm, as atmospheric carbon dioxide dissolves in the water and equilibrates to bicarbonate ions. Therefore, if the analytical use requires that water purity remains as high as possible, its use should be protected from atmospheric exposure. This water is used as a reagent, as a solvent for reagent preparation, and for test apparatus cleaning where less pure waters would not perform acceptably. However, if a user's routinely available purified water is filtered and meets or exceeds the conductivity specifications of *High Purity Water,* it could be used in lieu of *High Purity Water.*

Ammonia-Free Water—Functionally, this water must have a negligible ammonia concentration to avoid interference in tests sensitive to ammonia. It has been equated with *High Purity Water* that has a significantly tighter Stage 1 conductivity specification than *Purified Water* because of the latter's allowance for a minimal level of ammonium among other ions. However, if the user's *Purified Water* were filtered and met or exceeded the conductivity specifications of *High Purity Water,* it would contain negligible ammonia or other ions and could be used in lieu of *High Purity Water.*

Carbon Dioxide-Free Water—The introductory portion of the *Reagents, Indicators, and Solutions* section defines this water as *Purified Water* that has been vigorously boiled for at least 5 minutes, then cooled and protected from absorption of atmospheric carbon dioxide. Because the absorption of carbon dioxide tends to drive down the water pH, most of the uses of Carbon Dioxide-Free Water are either associated as a solvent in pH-related or pH- sensitive determinations or as a solvent in carbonate-sensitive reagents or determinations. Another use of this water is for certain optical rotation and color and clarity of solution tests. Though it is possible that this water is indicated for these tests simply because of its purity, it is also possible that the pH effects of carbon dioxide containing water could interfere with the results of these tests. A third plausible reason that this water is indicated is that outgassing air bubbles might interfere with these photometric-type tests. The boiled water preparation approach will also greatly reduced the concentrations of many other dissolved gases along with carbon dioxide. Therefore, in some of the applications for *Carbon Dioxide-Free Water,* it could be the inadvertent deaeration effect that actually renders this water suitable. In addition to boiling, deionization is perhaps an even more efficient process for removing dissolved carbon dioxide (by drawing the dissolved gas equilibrium toward the ionized state with subsequent removal by the ion-exchange resins). If the starting *Purified Water* is prepared by an efficient deionization process and protected after deionization from exposure to atmospheric air, water that is carbon dioxide-free can be effectively made without the application of heat. However this deionization process does not deaerate the water, so if *Purified Water* prepared by deionization is considered as a substitute water in a test requiring Carbon Dioxide-Free Water, the user must verify that it is not actually water akin to *Deaerated Water* (discussed below) that is needed for the test. As indicated in the *High Purity Water,* even brief contact with the atmosphere can allow small amounts of carbon diox-

ide to dissolve, ionize, and significantly degrade the conductivity and lower the pH. If the analytical use requires the water to remain as pH-neutral and as carbon dioxide-free as possible, even the analysis should be protected from atmospheric exposure. However, in most applications, atmospheric exposure during testing does not significantly affect its suitability in the test.

Ammonia- and Carbon Dioxide-Free Water—As implied by the name, this water should be prepared by approaches compatible with those mentioned for both *Ammonia-Free Water* and *Carbon Dioxide-Free Water.* Because the carbon dioxide-free attribute requires post-production protection from the atmosphere, it is appropriate to first render the water ammonia-free using the *High Purity Water* process followed by the boiling and carbon dioxide-protected cooling process. The *High Purity Water* deionization process for creating *Ammonia-Free Water* will also remove the ions generated from dissolved carbon dioxide and ultimately, by forced equilibration to the ionized state, all the dissolved carbon dioxide. Therefore, depending on its use, an acceptable procedure for making *Ammonia- and Carbon Dioxide-Free Water* could be to transfer and collect *High Purity Water* in a carbon dioxide intrusion-protected container.

Deaerated Water—This water is *Purified Water* that has been treated to reduce the content of dissolved air by "suitable means". In the *Reagents* section, approaches for boiling, cooling (similar to *Carbon Dioxide-Free Water* but without the atmospheric carbon dioxide protection), and sonication are given as applicable for test uses other than dissolution and drug release testing. Though *Deaerated Water* is not mentioned by name in *Dissolution* ⟨711⟩*,* suggested methods for deaerating dissolution media (which may be water) include warming to 41°, vacuum filtering through a 0.45-µm rated membrane, and vigorously stirring the filtrate while maintaining the vacuum. This chapter specifically indicates that other validated approaches may be used. In other monographs that also do not mention *Deaerated Water* by name, degassing of water and other reagents is accomplished by sparging with helium. *Deaerated Water* is used in both dissolution testing as well as liquid chromatography applications where outgassing could either interfere with the analysis itself or cause erroneous results due to inaccurate volumetric withdrawals. Applications where ambient temperature water is used for reagent preparation, but the tests are performed at elevated temperatures, are candidates for outgassing effects. If outgassing could interfere with test performance, including, chromatographic flow, colorimetric, or photometric measurements, or volumetric accuracy, then *Deaerated Water* should probably be used, whether called for in the analysis or not. The above deaeration approaches might not render the water "gas-free". At best, they reduce the dissolved gas concentrations so that outgassing caused by temperature changes is not likely.

Recently Boiled Water—This water may include recently or freshly boiled water (with or without mention of cooling in the title), but cooling prior to use is clearly intended. Occasionally it is necessary to use when hot. *Recently Boiled Water* is specified because it is used in a pH-related test or carbonate-sensitive reagent, in an oxygen-sensitive test or reagent, or in a test where outgassing could interfere with the analysis, such as specific gravity or an appearance test.

Oxygen-Free Water—The preparation of this water is not specifically described in the compendia. Neither is there an oxygen specification or analysis mentioned. However, all uses involve analyses of materials that could be sensitive to oxidation by atmospheric oxygen. Procedures for the removal of dissolved oxygen from solvents, though not necessarily water, are mentioned in *Polarography* ⟨801⟩ and *Spectrophotometry and Light-Scattering* ⟨851⟩. These procedures involve simple sparging of the liquid with an inert gas such as nitrogen or helium followed by inert gas blanketing to prevent oxygen reabsorption. The sparging times cited range from 5 to 15 minutes to an unspecified period. Some *Purified Water* and *Water for Injection* systems produce water that is maintained in a hot state and that is inert gas blanketed during its preparation and storage and distribution. Though oxygen is poorly soluble in hot water, such water may not be oxygen-free. Whatever procedure used for removing oxygen should be verified as reliably producing water that is fit for use.

LAL Reagent Water—This water is also referred to as endotoxin-free water. This is usually *Water for Injection,* which may have been sterilized. It is free from a level of endotoxin that would yield any detectable reaction or interference with the Limulus amebocyte lysate reagent used in the *Bacterial Endotoxins Test* ⟨85⟩.

Organic-Free Water—This water is defined by *Organic Volatile Impurities* ⟨467⟩ as producing no significantly interfering gas chromatography peaks. Referenced monographs specify using this water as the solvent for standard and test solution preparation for the *Organic volatile impurities* test

Lead-Free Water—This water is used as a transferring diluent for an analyte in a *Lead* ⟨251⟩ test. Though no specific instructions are given for its preparation, it must not contain any detectable lead. *Purified Water* should be a suitable substitute for this water.

Chloride-Free Water—This water is specified as the solvent for use in an assay that contains a reactant that precipitates in the presence of chloride. Though no specific preparation instructions are given for this water, its rather obvious attribute is having a very low chloride level in order to be unreactive with this chloride sensitive reactant. *Purified Water* could be used for this water but should be tested to assure it is unreactive.

Hot Water—The uses of this water include solvents for achieving or enhancing reagent solubilization, restoring the original volume of boiled or hot solutions, rinsing insoluble analytes free of hot water soluble impurities, solvents for reagent recrystallization, apparatus cleaning, and as a solubility attribute for various *USP–NF* articles. In only one monograph is the temperature of "hot" water specified; so in all the other cases, the water temperature is less important, but should be high enough to achieve the desirable effect. In all cases, the chemical quality of the water is implied to be that of *Purified Water.*

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

***N,N*-Dimethylacetamide,** *USP 29* page 3126 and page 656 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to update the specifications for this reagent to reflect the products currently available on the market.

(HDQ: M. Marques) RTS—47676

Change to read:

***N,N*-Dimethylacetamide,** C_4H_9NO—**87.12**

■[*127-19-5*]■1S (*USP30*)
—Clear, colorless liquid. Miscible with water and with many organic solvents.

~~*Assay*~~ ~~When examined by gas–liquid chromatography, with the use of suitable apparatus and conditions, it shows a purity of not less than 99%.~~

~~*Distilling range*~~ ~~⟨721⟩: between 164.5° and 167.5°.~~

~~*Residue on evaporation*~~ ~~Evaporate 215 mL on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 2 mg (0.001%).~~

~~*pH of 20% solution*~~ ~~Weigh 20 g of it into a 100-mL volumetric flask, and dilute with carbon dioxide–free water to volume: the solution shows a pH between 4.0 and 7.0.~~

~~*Ultraviolet absorbance*~~ ~~Determine its absorbance throughout the range 270 to 400 nm, using a 1-cm cell, a suitable spectrophotometer, and water to set the instrument: the absorbance does not exceed 1.00 at 270 nm, 0.30 at 280 nm, 0.15 at 290 nm, 0.05 at 310 nm, 0.03 at 320 nm, and 0.01 at 360 to 400 nm.~~

~~*Water, Method I*~~ ~~⟨921⟩: not more than 0.05%.~~

■Use a suitable HPLC or spectroscopic grade.■2S (*USP30*)

BRIEFING

2,4-Dinitrophenylhydrazine, *USP 29* page 3128 and page 901 of *PF* 32(3) [May–June 2006]. It is proposed to update the information regarding this reagent to reflect the products currently available on the market.

(HDQ: M. Marques) RTS—C47532

Change to read:

2,4-Dinitrophenylhydrazine, $2,4\text{-}C_6H_3(NO_2)_2NHNH_2$—**198.14**

■[*119-26-6*]■2S (*USP30*)
—Orange-red crystals, which under the microscope appear individually to be lemon-yellow, lath-like needles. Very slightly soluble in water; slightly soluble in alcohol; moderately soluble in dilute inorganic acids.

~~*Melting range*~~ ~~⟨741⟩: between 197° and 200°.~~

~~*Solubility in sulfuric acid*~~ ~~Dissolve 500 mg in a mixture of 25 mL of sulfuric acid and 25 mL of water: the solution is clear or not more than slightly turbid.~~

~~*Residue on ignition*~~ ~~(Reagent test): negligible, from 500 mg.~~

■Use a suitable grade with a content of not less than 97%.■2S (*USP30*)

BRIEFING

Hydrogen Peroxide, 10 Percent. It is proposed to add this new reagent used in the test for *Limit of lead* in the proposed new monograph for *Palm Kernel Oil,* also appearing in this issue of *PF.*

(HDQ: M. Marques) RTS—C47603

Add the following:

■**Hydrogen Peroxide, 10 Percent,** H_2O_2—**34.01**—Dilute 30 mL of 30 percent hydrogen peroxide with water to 100 mL.■2S (*USP30*)

In-Process Revision

BRIEFING

4-Hydroxyisophthalic Acid, *USP 29* page 3134 and page 917 of *PF* 32(3) [May–June 2006]. It is proposed to delete this reagent. It is currently available as USP Salicylic Acid Related Compound B RS.

(HDQ: M. Marques) RTS—C47634

Delete the following:

~~■**4-Hydroxyisophthalic Acid,** $C_8H_8O_4$—**182.13**~~

~~■[*636-46-4*]■1S (*USP30*)~~
~~—Colorless branched needles. Freely soluble in alcohol and in ether.~~
~~*Melting range* ⟨741⟩: between 308° and 310°, with decomposition at 314° to 315°.~~■2S (*USP30*)

BRIEFING

Methyl Green, *USP 29* page 3138. It is proposed to update the information regarding this reagent.

(HDQ: M. Marques) RTS—C47613

Change to read:

Methyl Green,

■*(Methyl Green Zinc Chloride Double Salt; Ethyl Green Zinc Chloride Double Salt; C.I. 42590),*■2S (*USP30*)
~~$C_{28}H_{33}N_3BrCl \cdot ZnCl_2$—**653.24**~~

■$C_{27}H_{35}Cl_2N_3 \cdot ZnCl_2$—**608.78**■2S (*USP30*)
[*7114-03-6*]—Use a suitable grade

■for microscopy.■2S (*USP30*)

BRIEFING

Methyl Iodide, *USP 29* page 3138 and page 929 of *PF* 32(3) [May–June 2006]. It is proposed to update the specifications for this reagent to reflect the products currently available on the market.

(HDQ: M. Marques) RTS—C47646

Change to read:

Methyl Iodide
■(Iodomethane),■2S (*USP30*)
CH_3I—**141.94**

■[*74-88-4*]■2S (*USP30*)
—Colorless, heavy, transparent liquid. Slightly soluble in water. Miscible with alcohol, with ether, and with solvent hexane. Turns brown on exposure to light as a result of liberation of iodine.

~~*Assay*—Add 1 mL to a 100-mL volumetric flask tared with 10 mL of alcohol. Weigh again, add alcohol to volume, and mix. Pipet 20 mL into a glass-stoppered flask, and add 50.0 mL of 0.1 N silver nitrate VS and 2 mL of nitric acid. Insert the stopper immediately, shake frequently during 2 hours, and allow to stand in the dark overnight. Shake again for 2 hours, then add 50 mL of water and 3 mL of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 N ammonium thiocyanate VS. Each mL of 0.1 N silver nitrate is equivalent to 14.19 mg of CH_3I: not less than 98.5% is found.~~

~~*Boiling range* (Reagent test)—Distill 50 mL into a chilled, partly closed receiver: not less than 48 mL distills between 41.5° and 43°.~~

~~*Density:*—between 2.270 and 2.285.~~

~~*Residue on evaporation*—Evaporate 4 mL (10 g) on a steam bath, and dry the residue at 105° for 1 hour: the residue weighs not more than 1 mg (0.01%).~~

~~*Acidity*—Shake 3 mL with 5 mL of water for 30 seconds, and immediately draw off the lower layer: the aqueous layer is neutral to litmus, and when 1 mL of silver nitrate TS is added, it shows not more than a slight opalescence.~~

■Use a suitable grade with a content of not less than 99%.■2S (*USP30*)

In-Process Revision

BRIEFING

***n*-Octadecane.** This proposed reagent is used to prepare the *Internal standard solution* in the test for *Limit of monomers* under *Polydextrose,* a new monograph proposed in *PF* 32(4) [July–Aug. 2006].

(HDQ: M. Marques) RTS—C44166

Add the following:

■***n*-Octadecane,** $CH_3(CH_2)_{16}CH_3$—**254.49**[*593-45-3*]—Use a gas chromatographic standard with a content of not less than 99.5%.■2S (*USP30*)

BRIEFING

Sodium Citrate Dihydrate. It is proposed to add this new reagent.

(HDQ: M. Marques) RTS—C46393

Add the following:

■**Sodium Citrate Dihydrate** *(2-Hydroxy-1,2,3-propanetricarboxylic Acid, Trisodium Salt, Dihydrate),* $Na_3C_6H_5O_7 \cdot 2H_2O$—**294.10**[*6132-04-3*]—Use ACS reagent grade.■2S (*USP30*)

BRIEFING

Pullulan Standards. These proposed reagents are used to prepare the *Standard solution* in the test for *Molecular weight limit* under *Polydextrose,* a new monograph proposed on page 1155 of *PF* 32(4) [July–Aug. 2006].

(HDQ: M. Marques) RTS—C44166

Add the following:

■**5,800, 23,700, and 100,000 Molecular Weight (MW) Pullulan Standards** (a commercial Pullulan Standard set contains standards having several molecular weights: 5,800; 12,000; 24,000; 48,000; 100,000; 186,000; 380,000; and 750,000)—[*9057-02-7*]—Use a suitable grade. Each individual Pullulan Standard with a different molecular weight, such as 5,800, 24,000, or 100,000, is equivalently used.

[NOTE—The standard set is available from Polymer Laboratories (www.polymerlabs.com), Sigma-Aldrich (www.sigma-aldrich.com), and Waters (www.waters.com).]■2S (*USP30*)

BRIEFING

Stachyose Hydrate. It is proposed to add this new reagent used in the test for *Molecular weight limit* under *Polydextrose,* a proposed new monograph appearing on page 1155 of *PF* 32(4) [July–Aug. 2006].

(HDQ:M. Marques) RTS—C44166

Add the following:

■**Stachyose Hydrate,** $C_{24}H_{42}O_{21} \cdot xH_2O$—**666.58** [*10094-58-3*]—Use a suitable grade.■2S (*USP30*)

BRIEFING

Tungstic Acid. It is proposed to add this new reagent used in the test for *Limit of lead* in the monograph for *Palm Kernel Oil,* also appearing in this issue of *PF*.

(HDQ: M. Marques) RTS—C47595

Add the following:

■**Tungstic Acid,** H_2WO_4—**249.85**[*7783-03-1*]—Use a suitable grade with a content of not less than 99%.■2S (*USP30*)

Indicator and Test Papers

BRIEFING

Methyl Green–Iodomercurate Paper. It is proposed to add this new indicator paper used in *Identification* test *B* in the monograph for *Cetrimonium Bromide*.

(HDQ: M. Marques) RTS—C47614

Add the following:

■**Methyl Green–Iodomercurate Paper—**Immerse thin strips of suitable filter paper in a 40 g per L solution of methyl green, and allow to air-dry. Immerse the strips for 1 hour in a solution containing 140 g per L of potassium iodide and 200 g per L of mercuric iodide. Wash with water until the washings are practically colorless, and allow to air-dry. Store protected from light, and use within 48 hours.■2S (*USP30*)

Test Solutions

BRIEFING

Test Solutions, *USP 29* page 3168 and page 3812 of the *Second Supplement.* It is proposed to add two test solutions: Acetic Acid, Strong, TS; and Ammonium Pyrrolidinedithiocarbamate, Saturated, TS. These test solutions are used in the test for *Limit of nickel* in the proposed new monograph *Polydextrose,* which appears elsewhere in this issue of *PF*.

(HDQ: M. Marques) RTS—C44166

Add the following:

■**Acetic Acid, Strong, TS**—Add 300.0 mL of glacial acetic acid, and dilute with water to 1000 mL. This solution contains about 30% (v/v) of CH_3COOH and has a concentration of about 5 N.■2S (*USP30*)

Add the following:

■**Ammonium Pyrrolidinedithiocarbamate, Saturated, TS**—Add about 10 g of ammonium pyrrolidinedithiocarbamate to a 1000-mL volumetric flask, and dilute with water to volume.■2S (*USP30*)

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 29* page 3184, page 3813 of the *Second Supplement,* and page 1299 of *PF* 32(4) [July–Aug. 2006].

(HDQ) RTS—C41830; C46298

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Add the following:	
■Acetaminophen, Chlorpheniramine, and Dextromethorphan Tablets	T■2S (*USP30*)
Add the following:	
▲Benazepril Hydrochloride Tablets	W▲(*USP30*)
Add the following:	
■Capecitabine Tablets	T■2S (*USP30*)
Add the following:	
■Cat's Claw Capsules	T, LR■2S (*USP30*)
Add the following:	
■Cat's Claw Tablets	T, LR■2S (*USP30*)
Add the following:	
■Black Cohosh Tablets	T, LR■2S (*USP30*)
Add the following:	
■Dantrolene Sodium Capsules	T, LR■2S (*USP30*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
▲Desogestrel and Ethinyl Estradiol Tablets	W▲(*USP30*)
Add the following:	
▲Diclofenac Potassium Tablets	T, LR▲(*USP30*)
Add the following:	
■Didanosine Tablets	T■1S (*USP30*)
Add the following:	
■Estradiol Vaginal Tablets	T■1S (*USP30*)
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	W■1S (*USP30*)
Add the following:	
■Fexofenadine Hydrochloride Tablets	W■1S (*USP30*)
Add the following:	
■Fosinopril Sodium Tablets	T■1S (*USP30*)
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	T■1S (*USP30*)
Add the following:	
▲Ginkgo Capsules	T, LR▲(*USP30*)
Add the following:	
▲Ginkgo Tablets	T, LR▲(*USP30*)
Add the following:	
▲Asian Ginseng Capsules	T~~, LR~~▲(*USP30*)
Add the following:	
■Glipizide and Metformin Hydrochloride Tablets	W■1S (*USP30*)

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets	T, LR■2S (*USP30*)
Add the following:	
■Glucosamine and Methylsulfonylmethane Tablets	T, LR■2S (*USP30*)
Add the following:	
■Irbesartan Tablets	W■1S (*USP30*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W■1S (*USP30*)
Add the following:	
■Isosorbide Mononitrate Tablets	T■1S (*USP30*)
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■2S (*USP30*)
Add the following:	
■Ketoprofen Capsules, Extended-Release	T■1S (*USP30*)
Add the following:	
■Meloxicam Tablets	W■2S (*USP30*)
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■1S (*USP30*)
Add the following:	
■Methylsulfonylmethane Tablets	T, LR■1S (*USP30*)
Add the following:	
■Modafinil Tablets	T■1S (*USP30*)
Add the following:	

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
▲Morphine Sulfate Capsules, Extended-Release	T, LR▲(*USP30*)
Add the following:	
■Nefazodone Hydrochloride Tablets	T■1S (*USP30*)
Add the following:	
■Nevirapine Tablets	W■1S (*USP30*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■1S (*USP30*)
Add the following:	
▲Oxybutynin Chloride Tablets, Extended-Release	T▲(*USP30*)
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	T, LR■1S (*USP30*)
Add the following:	
■Pravastatin Sodium Tablets	T■1S (*USP30*)
Add the following:	
■Quinapril Tablets	W■1S (*USP30*)
Add the following:	
■Risperidone Tablets	T, LR■2S (*USP30*)
Add the following:	
▲Tizanidine Tablets	T▲(*USP30*)
Add the following:	
■Valerian Capsules	T, LR■1S (*USP30*)
Add the following:	
■Valganciclovir Tablets	T■1S (*USP30*)
Add the following:	
▲Valsartan and Hydrochlorothiazide Tablets	~~W~~T▲(*USP30*)

In-Process Revision

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 29* page 3191, page 3813 of the *Second Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 2183 of *PF* 30(6) [Nov.–Dec. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], page 1193 of *PF* 31(4) [July–Aug. 2005], page 1491 of *PF* 31(5) [Sept.–Oct. 2005], page 1703 of *PF* 31(6) [Nov.–Dec. 2005], page 188 of *PF* 32(1) [Jan.–Feb. 2006], page 662 of *PF* 32(2) [Mar.–Apr. 2006], page 942 of *PF* 32(3) [May–June 2006], and page 1301 of *PF* 32(4) [July–Aug. 2006].

(HDQ) RTS—C43595; C44146; C44408; C44796

Add the following:

■**Cetirizine Hydrochloride:** White or almost white powder. Freely soluble in water; insoluble in acetone and in methylene chloride.■2S (*USP30*)

Add the following:

■**Hydroxypropyl Betadex:** White or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol. *NF category:* Sequestering agent.■2S (*NF25*)

Add the following:

■**Palm Kernel Oil:** White to yellowish, fatty solid. Insoluble in water. *NF category:* Coating agent; emulsifying and/or solubilizing agent.■2S (*NF25*)

Change to read:

Tiagabine Hydrochloride: White to off-white powder.

■Freely soluble in methanol and in alcohol; soluble in isopropanol;■2S (*USP30*)
very slightly soluble in chloroform; sparingly soluble in water; practically insoluble in *n*-heptane.

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 32(1) through 32(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF.*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
<u>*USP Monographs*</u>			
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetazolamide Oral Solution (new)	32	1	43
Acetazolamide Oral Suspension (new)	32	1	44
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Medical Air—*Definition, Packaging and storage*	31	4	1024
Alprazolam Oral Suspension (new)	32	1	46
Albumin Human—*Definition, Packaging and storage, Expiration date, Labeling, USP Reference standards* (add), *Identification A, B* (add), *Bacterial endotoxins* (add), *Safety* (add), *Sterility* (add), *pH* (add), *Molecular size distribution* (add), *Heat stability* (add), *Incubation* (add) *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add)	31	5	1338
Albuterol Tablets—*Assay*	31	3	726
Allopurinol—*Definition, Packaging and storage, USP Reference standards, Chromatographic purity (delete), Related compounds,* (add), *Assay*	32	2	302
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Aluminum Sulfate and Calcium Acetate Powder for Topical Solution (new)	32	3	755
Amifostine—*Related compounds*	32	3	756
Amifostine for Injection—*Related compounds*	32	3	757

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Amitriptyline Hydrochloride—*USP Reference standards, Identification, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	31	6	1606
Amlodipine Besylate (new)	32	3	757
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Atracurium Besylate—*Chromatographic purity, Assay*	32	2	305
Azathioprine Oral Suspension (new)	32	1	48
Azithromycin—*Labeling, USP Reference standards, Limit of related substances*	32	2	306
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Oral Solution (new)	32	1	49
Baclofen Oral Suspension (new)	32	1	51
Bemotrizinol (new)	32	4	1044
Benazepril Hydrochloride Tablets (new)	32	1	52
Benzonatate Capsules—*Dissolution* (add)	32	1	55
Bethanechol Chloride Oral Solution (new)	32	1	55
Bethanechol Chloride Oral Suspension (new)	32	1	57
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	31	3	741
Bisoctrizole (new)	32	2	309
Bromocriptine Mesylate Capsules—*Dissolution*	32	1	58
Budesonide (new)	30	6	1978
Bupropion Hydrochloride Extended-Release Tablets—*Drug release, Dissolution*	32	4	1047
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butorphanol Tartrate Nasal Solution (new)	32	4	1049
Calcitonin Salmon (new)	32	3	760
Calcitonin Salmon Nasal Solution (new)	32	3	767
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	32	1	58
Calcitriol Injection (new)	32	1	61
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate—*USP Reference standards* (add), *Identification*	31	6	1608
Calcium Lactate Tablets—*Identification*	31	6	1609
Calcium Pantothenate—*USP Reference standards, Ordinary impurities*	32	1	62
Dibasic Calcium Phosphate Dihydrate (harmonization)	32	4	1329
Anhydrous Dibasic Calcium Phosphate (harmonization)	32	4	1332
Camphor—*Water*	31	3	742
Capecitabine (new)	32	4	1052
Capecitabine Tablets (new)	32	4	1054
Captopril Oral Solution (new)	32	1	63
Captopril Oral Suspension (new)	32	1	64
Carbamazepine—*USP Reference standards, Chromatographic purity (Related compounds), Assay*	32	1	65
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium—*Heavy metals*	31	5	1349
Carboxymethylcellulose Sodium Paste—*Heavy metals*	31	5	1349
Carvedilol (new)	32	4	1057
Cefaclor Tablets (new)	32	2	314
Cefadroxil for Oral Suspension—*Dissolution* (add)	32	2	315
Cefepime Hydrochloride—*Limit of N-methylpyrrolidine, Related compounds*	32	2	316
Cefonicid for Injection—*Assay*	32	1	67
Ceftazidime—*USP Reference standards, Assay*	32	1	67
Ceftazidime Injection—*USP Reference standards*	32	1	68
Ceftazidime for Injection—*USP Reference standards*	32	1	68

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Chlorhexidine Gluconate Oral Rinse—*Assay*	32	3	768
Chlorhexidine Gluconate Solution—*Assay*	32	3	768
Chlorophyllin Copper Complex Sodium—*Content of total copper*	32	3	769
Chlorthalidone—*USP Reference standards, Limit of 4'-chloro-3'-sulfamoyl-2-benzophenone carboxylic acid (CCA) (Limit of chlorthalidone related compound A), Assay*	32	1	68
Cholestyramine Resin—*Dialyzable quaternary amines*	32	2	320
Cilostazol (new)	32	1	69
Cimetidine—*Identification, Chromatographic purity*	32	3	769
Cimetidine Tablets—*Dissolution*	32	1	72
Ciprofloxacin—*Chromatographic purity, Assay*	32	2	320
Ciprofloxacin and Dexamethasone Otic Suspension (new)	32	2	321
Ciprofloxacin Hydrochloride—*Chromatographic purity, Assay*	32	2	325
Ciprofloxacin Injection—*Bacterial endotoxins, Limit of ciprofloxacin ethylenediamine analog, Assay*	32	4	1059
Citalopram Hydrobromide—*Labeling* (add), *USP Reference standards, Related compounds*	32	4	1060
Citalopram Tablets—*Identification* (add), *Related compounds, Assay*	32	3	770
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid (delayed implementation to January 1, 2009)*	31	2	394
Cladribine—*Specific rotation, Water, Related compounds, Limit of residual solvents*	32	3	774
Clarithromycin Extended-Release Tablets—*Dissolution*	32	3	775
Clonazepam Oral Suspension (new)	32	1	73
Clopidogrel Bisulfate—*Related compounds, Assay*	32	1	74
Clopidogrel Tablets—*Related compounds, Assay*	32	1	76
Clotrimazole Lozenges—*Dissolution*	32	1	78
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dantrolene Sodium (new)	32	2	327
Dantrolene Sodium Capsules (new)	32	4	1063
Dantrolene Sodium for Injection (new)	32	3	779
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Diazepam Extended-Release Capsules—*USP Reference standards, Assay*	32	2	330
Diclofenac Potassium (new)	31	5	1350
Diclofenac Potassium Tablets (new)	31	5	1352
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Didanosine (new)	32	3	781
Didanosine for Oral Solution (new)	31	5	1357
Didanosine Tablets (new)	32	3	784
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diltiazem Hydrochloride Oral Solution (new)	32	1	79
Diltiazem Hydrochloride Oral Suspension (new)	32	1	80
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1612
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1614

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Dipyridamole Oral Suspension (new)	32	1	81
Divalproex Sodium (new)	31	5	1362
Dolasetron Mesylate Oral Solution (new)	32	1	83
Dolasetron Mesylate Oral Suspension (new)	32	1	84
Doxazosin Mesylate (new)	32	4	1066
Doxazosin Tablets (new)	29	1	64
Doxepin Hydrochloride—*USP Reference standards, Identification, Melting range* (delete), *Chloride content* (delete), *Related compounds* (add)	32	2	330
Dronabinol—*USP Reference standards, Identification, Limit of* Δ^8*-tetrahydrocannabinol* (delete), *Related compounds* (add), *Assay*	32	1	86
Drospirenone (new)	32	3	787
Edetate Calcium Disodium (harmonization)	32	4	1335
Edetate Disodium—*Assay*	32	4	1070
Edetate Disodium Injection—*Assay*	32	4	1071
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Ensulizole—*Assay*	31	6	1617
Estradiol and Norethindrone Acetate Tablets (new)	31	5	1364
Estradiol Transdermal System (new)	31	4	1063
Estradiol Vaginal Inserts (new)	32	4	1071
Conjugated Estrogens—*Definition*	30	3	840
Conjugated Estrogens Tablets—*Dissolution*	32	4	1074
Synthetic Conjugated Estrogens (new)	31	6	1620
Ethotoin Tablets—*USP Reference standards, Assay*	32	2	332
Etidronate Disodium—*Limit of phosphite*	31	6	1625
Famotidine Injection (new)	32	2	333
Fenofibrate (new)	31	3	763
Fentanyl (new)	31	6	1626
Fexofenadine Hydrochloride (postponed indefinitely)	31	3	703
Fexofenadine Hydrochloride Capsules (postponed indefinitely)	31	3	705
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Fluconazole—*Related compounds*	32	2	335
Flucytozine Oral Suspension (new)	32	1	92
Flumazenil—*USP Reference standards, Related compounds, Assay*	32	1	94
Fluorometholone Acetate (new)	31	5	1371
Flurazepam Hydrochloride—*Identification*	31	3	766
Fluticasone Propionate—*Definition, Bromofluoromethane content* (delete)	32	2	337
Fluticasone Propionate Nasal Spray (new)	32	2	339
Fluvastatin Sodium—*Packaging and storage, USP Reference standards, Identification, Chromatographic purity*	32	1	103
Fluvastatin Capsules—*USP Reference standards, Identification, Chromatographic purity*	32	1	105
Fluvoxamine Maleate—*Maleic acid* (delete), *Assay*	32	2	344
Fluvoxamine Maleate Tablets (new)	30	5	1622
Formoterol Fumarate (new)	32	1	106
Fosinopril Sodium (new)	32	3	789
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Ganciclovir Oral Suspension (new)	32	1	113
Gemcitabine for Injection—*USP Reference standards, Chromatographic purity*	31	6	1630
Gemcitabine Hydrochloride—*USP Reference standards*	32	1	114
Glipizide and Metformin Hydrochloride Tablets (new)	32	4	1076
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Labeling* (add), *Dissolution* (add)	32	4	1080
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	32	3	792
Helium—*Definition, Packaging and storage*	31	4	1077
Hepatitis B Virus Vaccine Inactivated (delete)	31	6	1641

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Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hydrocortisone Tablets—*USP Reference standards, Uniformity of dosage units, Assay*	32	4	1083
Hydroxyzine Hydrochloride—*USP Reference standards, Chromatographic purity*	32	1	114
Hypromellose Ophthalmic Solution—*Assay*	32	4	1084
Ibuprofen—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	796
Ibuprofen Oral Suspension—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	796
Ibuprofen Tablets—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	798
Indinavir Sulfate—*Heavy metals, Method I,* (delete), *Heavy metals* (add), *Chromatographic purity, Assay*	32	2	345
Sodium Iodide I 123 Capsules—*Definition*	31	6	1642
Sodium Iodide I 123 Solution—*Definition, Radionuclidic purity, Bacterial endotoxins, pH*	31	6	1642
Sodium Iodide I 131 Solution—*pH*	31	6	1643
Iodoform—*Molecular weight*	32	1	115
Irbesartan—*Limit of azide, Related compounds, Assay*	32	4	1084
Irbesartan Tablets (new)	32	3	799
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082
Ivermectin—*Specific rotation, Limit of alcohol and formamide*	31	6	1645
Ketoprofen—*Assay*	31	3	772
Ketoprofen Extended-Release Capsules (new)	31	5	1378
Labetalol Hydrochloride Oral Solution (new)	32	1	116
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Lamivudine—*Assay*	32	2	346
Leflunomide (new)	31	5	1380
Leflunomide Tablets (new)	31	5	1383
Leuprolide Acetate (new)	30	3	882
Levocabastine Hydrochloride (new)	31	6	1647
Levodopa—*Related compounds*	32	4	1085
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Lindane—*Definition, Assay*	31	6	1648
Lipid Injectable Emulsion (new)	32	2	350
Lisinopril Tablets—*Assay*	32	4	1086
Loperamide Hydrochloride Oral Solution—*Assay*	32	2	353
Lovastatin—*Assay*	32	1	118
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Milk of Magnesia—*Limit of calcium* (delete)	32	2	353
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	419
Magnesium Chloride—*Identification*	31	2	420
Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	421
Magnesium Hydroxide—*Lead* (delete), *Limit of lead* (add)	32	4	1087
Magnesium Hydroxide Paste—*Definition, Soluble alkalies, Limit of lead* (add)	32	4	1088
Mangafodipir Trisodium—*Limit of residual solvents*	31	6	1650
Mannitol Injection—*Labeling*	32	2	263
Meloxicam (new)	31	1	57
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
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Methyldopa Oral Suspension—*USP Reference standards, Limit of methyldopa-glucose reaction product* (delete)	32	2	354
Methylprednisolone—*Chromatographic purity*	32	2	354
Metolazone Oral Suspension (new)	32	1	119
Metoprolol Tartrate—*Chromatographic purity*	32	4	1089
Metoprolol Tartrate Oral Solution (new)	32	1	121
Metoprolol Tartrate Oral Suspension (new)	32	1	122
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Miconazole Nitrate Cream—*Identification*	32	1	123
Mirtazapine—*Heavy metals*	31	6	1650
Mitoxantrone Injection—*Packaging and storage*	32	2	355
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Morantel Tartrate—*pH*	32	2	355
Morphine Sulfate Extended-Release Capsules—*Packaging and storage* (add)	32	1	124
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage*	32	1	124
Narasin Granular—*Molecular weight, Assay*	32	1	124
Narasin Premix—*Assay*	32	1	126
Nefazodone Hydrochloride (new)	32	3	802
Nefazodone Hydrochloride Tablets (new)	32	3	804
Netilmicin Sulfate—*Definition, Assay*	32	4	1089
Nevirapine Oral Suspension (new)	32	4	1090
Nevirapine Tablets (new)	32	3	807
Nimodipine—*Identification, Related compounds*	32	2	360
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate—*USP Reference standards, Chromatographic purity*	32	4	1094
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Ondansetron Hydrochloride—*Limit of ondansetron related compound D, Assay*	32	1	126
Ondansetron Hydrochloride Oral Suspension (new)	32	1	127
Ondansetron Injection—*Chromatographic purity*	32	4	1096
Ondansetron Oral Solution—*Packaging and storage* (add), *Limit of ondansetron related compound D, Related compounds*	32	1	128
Orphenadrine Citrate Injection—*Assay*	31	6	1651
Oxandrolone—*Ordinary impurities* (delete), *Related compounds* (add)	31	1	64
Oxaprozin—*Packaging and storage* (add)	32	1	130
Oxaprozin Tablets—*Packaging and storage* (add)	32	1	130
Oxybutynin Chloride—*Related compounds*	32	3	810
Oxybutynin Chloride Extended-Release Tablets (new)	31	6	1652
Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxygen—*Definition, Packaging and storage*	31	4	1107
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Paclitaxel—*USP Reference standards, Related compounds*	32	2	361
Pancuronium Bromide Injection (new)	32	4	1097
Paricalcitol—*Identification, Chromatographic purity, Assay*	32	1	132
Paroxetine Hydrochloride—*Assay*	32	3	811
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital Sodium—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Pentobarbital Sodium Injection—*Identification, Assay*	32	2	364
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Permethrin Cream (new)	32	4	1102
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PEG 3350 and Electrolytes for Oral Solution—*Title, Definition, Assay for potassium and sodium*	32	4	1104
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Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay (delayed implementation to January 1, 2009)*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Perchlorate—*USP Reference standards* (delete), *Assay*	32	2	364
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Pravastatin Sodium (new)	32	3	813
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Prednicarbate Cream (new)	32	3	819
Prednicarbate Ointment (new)	32	3	822
Prednisolone Sodium Phosphate—*USP Reference standards, Identification*	32	2	365
Promethazine Hydrochloride—*USP Reference standards, Related compounds*	32	4	1105
Promethazine Hydrochloride Tablets—*USP Reference standards, Related compounds, Assay*	32	4	1107
Pseudoephedrine Sulfate—*Ordinary impurities*	32	1	135
Pyridoxine Hydrochloride Injection—*Assay*	32	2	369
Quazepam Tablets—*USP Reference standards, Assay*	32	2	370
Quinapril Tablets—*Packaging and storage*	29	4	1071
Quinidine Sulfate Oral Suspension (new)	32	1	136
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Risperidone (new)	31	6	1659
Risperidone Tablets (new)	32	4	1109
Ritonavir—*Identification, X-ray diffraction* (add), *Related compounds*	32	4	1113
Ropivacaine Hydrochloride Injection (new)	32	2	374
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Saccharin Calcium—*Identification*	32	4	1114
Saccharin Sodium—*Identification*	32	4	1114
Saquinavir Capsules—*Dissolution*	32	3	824
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Senna—*Title, Definition, Packaging and storage, Labeling* (add), *USP Reference standards* (add), *Botanic characteristics, Identification, Microbial enumeration* (add) *Loss on drying* (add), *Total ash* (add), *Assay* (add)	32	1	137
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Sodium Chloride—*Identification, Loss on drying, Limit of potassium (postponed indefinitely)*	32	2	264
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Thiabendazole Chewable Tablets (new)	29	6	1991
Thimerosal—*Identification*	32	1	147
Thioridazine Hydrochloride—*Identification*	31	3	798
Tiamulin Fumarate—*Chemical name, Definition, Melting temperature, Chromatographic purity*	32	4	1115
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Tizanidine Tablets (new)	32	1	147
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Travoprost (new)	32	4	1115
Travoprost Ophthalmic Solution (new)	32	4	1118
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800
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N,N-Diethylaniline	32	2	651
Diethylene Glycol	32	2	651
Diethylene Glycol Succinate Polyester	32	2	652
Diethylenetriamine	32	2	652
Di(2-ethylhexyl)phthalate	32	2	652
Digitonin	32	2	652
10,11-Dihydrocarbamazepine (delete)	32	2	652
Dihydroquinidine Hydrochloride	32	2	653
Dihydroquinine	32	2	653
2,5-Dihydroxybenzoic Acid	32	2	653
Diiodofluorescein	32	2	653
Diisodecyl Phthalate	32	2	654
Diisopropyl Ether	32	3	901
Diisopropylamine	32	2	654
Diisopropylethylamine	32	2	654
2,5-Dimethoxybenzaldehyde	32	2	654
1,2-Dimethoxyethane	32	2	655
(3,4-Dimethoxyphenyl)acetonitrile	32	2	655
Dimethyl Phthalate	32	2	655
Dimethyl Sulfone	32	2	655
Dimethyl Sulfoxide, Spectrophotometric Grade	32	2	655
N,N-Dimethylacetamide	32	2	656
p-Dimethylaminoazobenzene	32	2	656
p-Dimethylaminobenzaldehyde,	32	2	656
2-Dimethylaminoethyl Methacrylate (new)	31	4	1190
2,6-Dimethylaniline	32	2	656
N,N-Dimethylaniline	32	2	656
3,4-Dimethylbenzophenone	32	2	657
5,5-Dimethyl-1,3-cyclohexanedione	32	2	657
N,N-Dimethyldodecylamine-*N*-oxide (new)	27	4	2837
Dimethylformamide	32	2	657
N,N-Dimethylformamide Diethyl Acetal (delete)	32	2	657
N,N-Dimethyl-1-naphthylamine	32	2	657
N,N-Dimethyloctylamine	32	2	658
2,6-Dimethylphenol	32	2	658
N,N-Dimethyl-*p*-phenylenediamine Dihydrochloride	32	2	658
m-Dinitrobenzene	32	2	658
3,5-Dinitrobenzoyl Chloride	32	2	659
2,4-Dinitrochlorobenzene	32	2	659
2,4-Dinitrofluorobenzene	32	2	659
2,4-Dinitrophenylhydrazine	32	3	901
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Diphenylamine	32	3	902
Diphenylcarbazide	32	3	902
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2,2-Diphenylglycine	32	3	902
Dipropyl Phthalate	32	3	903
4,4′-Dipyridyl Dihydrochloride	32	3	903
5,5′-Dithiobis(2-nitrobenzoic Acid)	32	3	903
Dithiothreitol	32	3	903
Dithizone	32	3	903
Docusate Sodium (new)	31	4	1190
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n-Eicosane	32	3	904
Eicosanol	32	3	904
Eosin Y (Eosin Yellowish Y)	32	3	904
Epiandrosterone	32	3	904
Equilenin	32	3	904
Eriochrome Cyanine R	32	3	904
Eriochrome Black T–Sodium Chloride Indicator (new)	32	4	1239
Ethanesulfonic Acid	32	3	905
2-Ethoxyethanol	32	3	905
Ethyl Acetate	32	3	905
Ethyl Acrylate	32	3	905
Ethyl Benzoate	32	3	905
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4-Ethylbenzaldehyde	32	3	906
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Ethylene Dichloride	32	3	907
Ethylene Glycol	32	3	907
Ethylene Oxide in Methylene Chloride (50 mg/mL) (new)	31	3	859
1-Ethylquinaldinium Iodide	32	3	907
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Fast Blue BB Salt	32	3	908
Ferric Chloride	32	3	908
Ferric Nitrate	32	3	908
Ferric Sulfate	32	3	908
Ferrous Sulfate	32	3	909
Fluorene	32	3	909
9-Fluorenylmethyl Chloroformate	32	3	909
Fluorescamine	32	3	909
4′-Fluoroacetophenone	32	3	909
Formamide	32	3	909
Formic Acid	32	3	910
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Fuchsin, Basic	32	3	910
Gadolinium (Gd III) Acetate Hydrate	32	3	910
Geneticin (new)	31	6	1700
Gitoxin	32	3	910
D-Gluconic Acid, 50 Percent in Water	32	3	911
Glucose	32	3	911
D-Glucuronolactone	32	3	911
Glycerin	32	3	911
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Gold Chloride	32	3	911
Guaiacol	32	3	912
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Guanine Hydrochloride	32	3	912
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Hexadecyl Hexadecanoate	32	3	913
Hexamethyldisilazane	32	3	913
Hexamethyleneimine	32	3	913
n-Hexane	32	3	913
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4′-Hydroxyacetophenone	32	3	916
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4-Hydroxybenzoic Acid Isopropyl Ester	32	3	916
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2-Hydroxybenzyl Alcohol	32	3	916
4-Hydroxyisophthalic Acid	32	3	917
Hydroxylamine Hydrochloride	32	3	917
Hydroxy Naphthol Blue	32	3	917
D-α-Hydroxyphenylglycine	32	3	917
4-(4-Hydroxyphenyl)-2-butanone	32	3	917
Hydroxypropyl-β-cyclodextrin (new)	31	6	1701
8-Hydroxyquinoline	32	3	918
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Lead Nitrate	32	3	922
Lithium Chloride	32	3	922
Lithium Hydroxide	32	3	922
Lithium Metaborate	32	3	922
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Magnesium Acetate	32	3	923
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Magnesium Perchlorate, Anhydrous	32	3	924
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Mercuric Bromide	32	3	925
Mercuric Chloride	32	3	925
Mercuric Iodide, Red	32	3	925
Mercuric Nitrate	32	3	925
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Mercuric Sulfate	32	3	926
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Methacrylic Acid	32	3	927
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Methyl Caprylate	32	3	928
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Methyl Ethyl Ketone	32	3	929
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2,7-Naphthalenediol	32	3	934
2-Naphthalenesulfonic Acid	32	3	934
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2-Naphthol	32	3	934
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Naphthoresorcinol	32	3	935
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2-Napthyl Chloroformate	32	3	935
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Potassium Ferricyanide	32	4	1250
Potassium Ferrocyanide	32	4	1250
Potassium Hydroxide	32	4	1250
Potassium Iodate	32	4	1250
Potassium Iodide	32	4	1250
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Potassium Sulfate	32	4	1252
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Sodium Metabisulfite	32	4	1265
Sodium Metaperiodate	32	4	1265
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Triphenylmethane	32	4	1286
Triphenylmethanol	32	4	1286
Triphenyltetrazolium Chloride	32	4	1286
Tris(2-aminoethyl)amine	32	4	1287
Tris(hydroxymethyl)aminomethane	32	4	1287
Tropaeolin OO	32	4	1287
L-Tryptophane	32	4	1287
Tubocurarine Chloride (new)	32	4	1287
Uracil	32	4	1288
Uranyl Acetate	32	4	1288
Urea	32	4	1288
Urethane	32	4	1288
Uridine	32	4	1288
Valeric Acid	32	4	1288
Valerophenone	32	4	1289
Vanadium Pentoxide	32	4	1289
Vanadyl Sulfate	32	4	1289
Vinyl Acetate	32	4	1289
1-Vinyl-2-pyrrolidone	32	4	1290
Wright's Stain	32	4	1290
Xanthine	32	4	1290
Xanthydrol	32	4	1290
Xylene	32	4	1290
o-Xylene	32	4	1291
p-Xylene	32	4	1291
Xylene Cyanole FF	32	4	1291
Xylose	32	4	1291
Zinc	32	4	1291
Zinc Acetate	32	4	1291
Zirconyl Nitrate	32	4	1292
Volumetric Solutions			
Bismuth Nitrate (new)	32	4	1292
Magnesium Chloride, 0.01 M (new)	32	4	1292
Potassium Hydroxide, Normal (1 N)	32	4	1292
Sodium Hydroxide, Normal (1 N)	32	3	940
Sodium Thiosulfate, Tenth-Normal (0.1 N)	32	3	940
Chromatographic Reagents			
Chromatographic Reagents (new)	32	4	1293
Reference Tables			
Container Specifications for Capsules and Tablets	32	4	1299
Excipients, USP and NF Excipients, Listed by Category	32	4	1144
Description and Solubility	25	4	8589
	26	4	1135
	27	1	1908
	28	2	554
	28	6	1953
	29	1	266
	29	3	812

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
	29	5	1684
	30	4	1405
	30	5	1822
	30	6	2183
	31	1	122
	31	2	591
	31	3	861
	31	4	1193
	31	5	1491
	31	6	1703
	32	1	188
	32	2	662
	32	3	942
	32	4	1301
NF Monographs			
Acetyltributyl Citrate—*Assay*	32	1	177
Acetyltriethyl Citrate—*Assay*	32	1	178
Alfadex—*Definition, Packaging and storage* (add), *Loss on drying* (delete), *Water, Method I* (add), *Reducing sugars, Light-absorbing impurities, Organic volatile impurities, Method IV* (delete), *Residual solvents* (delete), *Assay*	32	2	395
Almond Oil—*Definition, Packaging and storage, Labeling* (add), *Identification* (add), *Foreign kernel oils* (delete), *Cottonseed oil* (delete), *Sesame oil* (delete), *Mineral oil and foreign fatty oils* (delete), *Foreign oils* (delete), *Free fatty acids* (delete), *Iodine value* (delete), *Saponification value* (delete), *Acid value* (add), *Peroxide value* (add), *Unsaponifiable matter* (add), *Fatty acid composition* (add), *Sterol composition* (add), *Residual solvents* (delete)	32	4	1147
Amino Methacrylate Copolymer (new)	31	4	1137
Canola Oil (new)	31	6	1667
Carboxymethylcellulose Calcium—*Heavy metals*	31	5	1420
Carboxymethylcellulose Sodium 12—*Labeling, Viscosity, Heavy metals*	31	5	1420
Cellacefate—*USP Reference standards*	32	1	179
Coconut Oil (new)	32	2	397
Corn Syrup Solids (new)	28	6	1894
Crospovidone—*Monograph*	28	4	1257
Erythritol (new)	31	5	1422
Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion (new)	31	4	1141
Ethylcellulose Aqueous Dispersion—*Labeling, Identification*	31	6	1668
High Fructose Corn Syrup (new)	32	4	1151
Gamma Cyclodextrin (new)	31	3	812
Glyceryl Monostearate—*Labeling, USP Reference standards* (delete), *Assay for monoglycerides*	31	6	1669
Hydroxyethyl Cellulose (new)—*Harmonization*	30	2	709
Low-Substituted Hydroxypropyl Cellulose—*Harmonization*	30	1	338
Isomalt—*Identification, Related compounds*	32	4	1154
Magnesium Stearate—*Harmonization*	30	1	340
Nitrogen—*Definition, Packaging and storage, Assay*	31	4	1145
Nitrogen 97 Percent—*Definition, Packaging and storage, Assay*	31	4	1146
Oleyl Oleate (new)	31	6	1670
Polacrilin Potassium—*CAS number, Chemical name*	31	6	1671
Polydextrose (new)	32	4	1155
Polyethylene Glycol—*Harmonization*	31	3	897
Polyethylene Oxide—*Packaging and storage, USP Reference standards, Identification, Heavy metals, Method II* (delete), *Heavy metals* (add), *Limit of free ethylene oxide, Organic volatile impurities, Method I* (delete), *Residual solvents* (delete)	32	2	398
Polyisobutylene—*Loss on drying*	32	3	828
Polyoxyl 35 Castor Oil—*Viscosity*	31	6	1671
Polyvinyl Acetate (new)	32	2	400
Silicon Dioxide (new)—*Harmonization*	31	4	1229
Colloidal Silicon Dioxide (new)—*Harmonization*	31	4	1233
Tribasic Sodium Phosphate—*Loss on ignition*	32	2	402

Title and Proposal	***PF Volume, Issue, and Page Numbers of Pending Proposals***		
	Vol.	***No.***	***Page(s)***
Rice Starch (new)—*Harmonization*	30	2	721
Sucrose—*Harmonization*	31	3	902
Strawberry Syrup (new)	32	1	179
Tagatose (new)	30	5	1672
Tetrafluoroethane (new)	31	6	1672
Tributyl Citrate—*Assay*	32	1	179
Triethyl Citrate—*Assay*	32	1	180

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
General Notices and Requirements			
Tests and Assays (Foreign Substances and Impurities)	31	3	718
Preservation, Packaging, Storage, and Labeling (Repackaging Instructions)	31	3	718
USP Monographs			
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
†Albendazole Oral Suspension—*Labeling*	32	1	46
Albumin Human (entire submission)	29	4	992
Albuterol Tablets—			
Dissolution	30	1	50
Dissolution	31	1	40
Allopurinol—*USP Reference standards, Chromatographic purity, Related compounds, Assay*	28	5	1386
Alprazolam Tablets—*Dissolution*	30	5	1582
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Baclofen Tablets—*Dissolution*	30	1	61
Betamethasone Tablets—*Dissolution*	30	1	62
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Carboxymethylcellulose Sodium Suspension (entire submission)	30	3	812
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Citalopram Hydrobromide—*Related compounds*	31	3	742
Citalopram Tablets (new)—*Dissolution, Related compounds*	31	3	745
Colchicine Tablets—*Dissolution*	30	1	91
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add)	29	6	1870
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Estradiol Transdermal System (new)—*Drug release*	30	4	1201

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Ethinyl Estradiol Tablets—*Related compounds*	31	2	402
Ethosuximide Capsules—*Dissolution*	30	1	102
Fluvastatin Sodium—*Loss on drying* (add), *Water* (delete)	32	1	103
Fluticasone Propionate—*Content of acetone (Procedure)*	31	4	1070
Gabapentin Capsules (new) (entire submission)	28	2	298
Glyburide Tablets—*Dissolution*	29	2	418
Glycopyrrolate Tablets—			
Dissolution	30	1	105
Dissolution (Procedure, Tolerances)	31	4	1077
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Indocyanine Green—*Definition, Assay*	29	6	1905
Irbesartan Tablets (new)—*Dissolution*	29	4	1035
Isosorbide Dinitrate Sublingual Tablets—			
Dissolution	30	1	113
Dissolution (Procedure, Tolerances)	31	5	1377
Diluted Isosorbide Mononitrate (entire submission)	31	4	1060
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Levothyroxine Sodium Oral Solution (new)—*Preview*	31	3	938
Lisinopril Tablets—*Dissolution*	30	1	121
Loperamide Hydrochloride Tablets—*Dissolution*	30	5	1633
Magnesium Oxide—*Bulk density* (add)	29	4	1047
Mebendazole Oral Suspension—*Labeling*	32	1	119
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Meprobamate Tablets—*Dissolution*	30	1	129
Methenamine Tablets—*Dissolution*	30	1	130
Methocarbamol Tablets—*Dissolution*	30	1	130
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Morphine Sulfate Extended-Release Capsules—*Packaging and storage*	28	6	1822
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Nefazodone Hydrochloride (new)—*Related compounds*	31	4	1094
Nefazodone Hydrochloride Tablets (new) (entire submission)	31	4	1096
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Ondansetron Orally Disintegrating Tablets (new)—*Disintegration, Dissolution*	30	6	2024
Oxaprozin—*Packaging and storage*	29	4	1059
Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new) (entire submission)	30	4	1276
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
PEG 3350 and Electrolytes for Oral Solution (entire submission)	31	5	1393
Penicillamine Capsules—*Dissolution*	30	1	153
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036
Simvastatin—*Identification B, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	31	3	792
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate*	31	3	797
†Sodium Salicylate Tablets—*Dissolution*	32	3	825
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Spironolactone Oral Suspension (new) (entire submission)	30	3	929
Spironolactone and Hydrochlorothiazide Oral Suspension (new) (entire submission)	30	3	930
Sumatriptan Succinate (new)—*Preview*	27	5	3157
Terbutaline Sulfate Tablets—*Dissolution*	31	1	76
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Timolol Maleate Tablets—*Dissolution*	30	1	191
Titanium Dioxide (new) (entire submission)	30	4	1301
Titanium Dioxide (new) (entire submission)	30	4	1304
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Valproic Acid Injection (new) (entire submission)	31	3	801
	31	5	1412
Vecuronium Bromide for Injection (new)—*Preview*	25	4	8449
Dietary Supplements Monographs			
Ginkgo Capsules (new) (entire submission)	27	2	2238
Ginkgo Tablets (new) (entire submission)	27	2	2240
Powdered Ginkgo Extract (new) (entire submission)	27	2	2233
Asian Ginseng Capsules (new)—*Dissolution*	30	2	571
American Ginseng Capsules (new)—*Dissolution*	30	2	565
American Ginseng Tablets—*Dissolution*	30	2	567
Lutein—*Identification A, Zeaxanthin and other related compounds, Content of lutein*	31	4	1133
Lutein Preparation—*Identification A, Zeaxanthin and other related compounds, Content of lutein*	31	4	1134
Valerian Capsules (new)—*Disintegration and dissolution*	27	1	1825
USP General Test Chapters			
⟨1⟩ Injections—*Packaging*	31	1	192
⟨11⟩ USP Reference Standards			
USP 23-epi-26-Deoxyacetin RS	28	5	1468
USP Fluvastatin for System Suitability RS (add)	31	1	99
USP Human Albumin RS	29	6	2022
USP Polyoxyl 35 Castor Oil RS	30	5	1674
⟨41⟩ Weights and Balances (entire submission)	31	2	508
⟨267⟩ Porosimetry by Mercury Intrusion (new) (entire submission)	28	3	893
⟨386⟩ Environmentally Sensitive Preparations (new) (entire submission)	30	5	1680
⟨429⟩ Light Diffraction Measure of Particle Size (new) (entire submission)	28	3	895
⟨616⟩ Bulk Density and Tapped Density (entire submission)	28	3	901
⟨621⟩ Chromatography—*System Suitability (All revisions after the first two paragraphs, through the end up to Glossary)*	30	6	2094
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨699⟩ Density of Solids—*Preview*	28	2	603
⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets* (delete), *Interpretation*	30	1	234
USP General Information Chapters			
⟨1058⟩ Analytical Instrument Qualification (new) (entire submission)	31	1	233

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(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients (entire submission)	28	5	1504
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)—*Preview*	28	5	1650
⟨1089⟩ In Vitro, Absorption-Indicating Cell Culture System (new)—*Preview*	25	5	8733
⟨1092⟩ The Dissolution Procedure: Development and Validation (new)—*Preview*	30	1	351
⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)—*Preview*	28	5	1662
Dietary Supplements Chapters			
⟨2040⟩ Disintegration and Dissolution of Nutritional Supplements—*Preview*	28	5	1673
Reagents, Indicators, and Solutions			
1,4-Butanediol (add)—*Preview*	25	5	8747
Isoferulic Acid (add)	27	4	2837
1-Vinyl-2-pyrrolidone	31	1	108
Reference Tables			
Container Specifications			
Black Cohosh Tablets	27	4	2874
Citalopram Hydrobromide Tablets (add)	31	3	859
Description and Relative Solubility			
Magnesium Oxide	29	4	1262
Titanium Dioxide (add)	30	4	1405
NF Monographs			
Alfadex—*Packaging and storage*	30	1	202
Black Cohosh (entire submission)	28	5	1455
Powdered Black Cohosh (entire submission)	28	5	1460
Powdered Black Cohosh Extract (entire submission)	28	5	1461
Black Cohosh Tablets (entire submission)	28	5	1462
Corn Syrup (new) (entire submission)	28	2	403
High Fructose Corn Syrup (new) (entire submission)	28	2	408
Magnesium Stearate—*Microbial limits*	29	6	2018
Sodium Caprylate—*Packaging and storage*	30	3	990
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706

†New cancellations in *PF* 32(5).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

MONOGRAPHS (USP)

BRIEFING

Hypromellose. The Japanese Pharmacopoeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Hypromellose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, is based on the corresponding monograph for Hypromellose that was prepared by the Japanese Pharmacopoeia. The Japanese Pharmacopoeia draft was based in part on comments from the European Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the Japanese Pharmacopoeia.

Differences between the Japanese Pharmacopoeia Adoption Stage 6 document and the current USP monograph for Hypromellose include the following:

1. *Definition*—Provided formula weight information for methoxyl and hydroxypropoxyl groups for consistency with harmonization draft.
2. *Packaging and storage*—Retained as a nonharmonized attribute
3. *Labeling*—Added a statement to specifiy viscosity in mPa · s.
4. *Identification*—**Test A:** Modified to be an aggregation test only. Eliminated reaction with sodium hydroxide or hydrochloric acid. **Test B:** Modified cooling temperature to 10° and adjusted wording of acceptance criteria to be consistent with harmonized draft. **Test C:** Added new test in accordance with harmonized draft. **Test D:** Adjusted wording of acceptance criteria (former Test C) to be consistent with harmonized draft. **Test E:** Added new test to reflect harmonized draft.
5. *Viscosity*—Two separate methods are added with different measurement procedures. The choice of which is to be performed is dependent on the reported viscosity result.
6. *pH*—New method added to reflect harmonized draft.
7. *Heavy metals*—Changed from *Method II* to *Method III* to reflect harmonized draft.
8. *Loss on drying*—Reduced sample size to 1 g to reflect harmonized draft.
9. *Residue on ignition*—Specification changed to a maximum of 1.5% on all grades of Hypromellose.
10. *Organic volatile impurities*—No change.
11. *Assay*—Replaced existing method with new GC assay to be consistent with JP standards.

(EM1: K. Moore) RTS—C46742

No change:

Hypromellose

Add the following:

■

Attribute	JP	EP	USP
Definition	+	+	+
Labeling	+	+	+
Identification (A)	+	+	+
Identification (B)	+	+	+
Identification (C)	+	+	+
Identification (D)	+	+	+
Identification (E)	+	+	+
Viscosity, Method 1	+	+	+
Viscosity, Method 2	+	+	+
pH	+	+	+
Heavy metals	+	+	+
Loss on drying	+	+	+
Residue on ignition	+	+	+
Assay	+	+	+

Legend: + will adopt and implement; - will not stipulate.
Nonharmonized attributes: Packaging and storage
Specific local attributes: Appearance of solution (EP), OVI (USP), Description (JP), Limit of glyoxal (EP)■2S (*USP30*)

Change to read:

» Hypromellose ~~is a propylene glycol ether of methylcellulose. When dried at 105° for 2 hours, it contains methoxy (–OCH_3–) and hydroxypropoxy (–$OCH_2CHOHCH_3$–)~~

■is a methyl and hydroxypropyl mixed ether of cellulose. It contains, calculated on the dried basis, methoxy (–OCH_3: 31.03) and hydroxypropoxy (–OC_3H_6OH: 75.09)■2S (*USP30*) groups conforming to the limits for the types of Hypromellose (hydroxypropyl methylcellulose) set forth in the accompanying table.

	Methoxy (percent)		Hydroxypropoxy (percent)	
Substitution Type	Min.	Max.	Min.	Max.
1828	16.5	20.0	23.0	32.0
2208	19.0	24.0	4.0	12.0
2906	27.0	30.0	4.0	7.5
2910	28.0	30.0	7.0	12.0

No change:

Packaging and storage—Preserve in well-closed containers. No storage requirements specified.

Change to read:

Labeling—Label it to indicate its substitution type and its ~~viscosity type [viscosity of a solution (1 in 50)].~~

■nominal viscosity value in milli-Pascal per second (mPa · s).■2S (*USP30*)

Change to read:

Identification—

A: Gently add 1 g of Hypromellose to the top of 100 mL of water in a beaker, and allow to disperse over the surface, tapping the top of the container to ensure an even dispersion of the substance. Allow the beaker to stand ~~until the substance becomes transparent and mucilaginous (about 5 hours), and then swirl the beaker to wet the remaining substance. Add a stirring bar, and stir until solution is complete: the mixture remains stable when an equal volume of 1 N sodium hydroxide or 1 N hydrochloric acid is added.~~

■for 1 to 2 minutes; the powdered material aggregates on the surface.■2S (*USP30*)

B: Add 1 g of Hypromellose to 100 mL of boiling water, and stir the mixture ~~a slurry is formed, but the powdered material does not dissolve. Cool the slurry to 20°, and stir: the resulting liquid is a clear or opalescent mucilaginous colloidal mixture.~~

■using a magnetic stirrer with a bar that is 25 mm long: a slurry is formed, but the powdered material does not dissolve. Cool the slurry to 10°, and stir using a magnetic stirrer: the resulting liquid is a clear or slightly turbid solution with thickness dependent on the viscosity grade.■2S (*USP30*)

~~**C:** Pour a few mL of the mixture prepared for *Identification* test *B* onto a glass plate, and allow the water to evaporate: a thin, self-sustaining film results.~~

■**C:**

Sulfuric acid, 90%—Carefully add 9 mL of sulfuric acid to 1 mL of water. To 0.1 mL of the solution prepared for *Identification* test *B,* add 9 mL of *Sulfuric acid, 90%,* and shake. Heat in a water bath for exactly 3 minutes, immediately cool in an ice bath, and add carefully 0.6 mL of ninhydrin TS. Shake, and allow to stand at 25°: a red color develops at first that changes to purple within 100 minutes.

D: Pour 2 to 3 mL of the solution prepared for *Identification* test *B* onto a glass slide as a thin film, and allow the water to evaporate: a coherent, clear film forms on the glass slide.

E: Add exactly 50 mL of the solution prepared in *Identification* test *B* to exactly 50 mL of water in a beaker. Insert a thermometer into the solution. Stir the solution on a magnetic stirrer/hot plate, and begin heating at a rate of 2 to 5° per minute. Determine the temperature at which a turbidity increase begins to occur and designate this temperature as the flocculation temperature: the flocculation temperature is higher than 50°.■2S (*USP30*)

Change to read:

Viscosity ⟨911⟩—~~Place a quantity, accurately weighed and equivalent to 2 g of solids on the dried basis, in a tared, wide-mouth, 250-mL centrifuge bottle, and add 98 g of water previously heated to 80° to 90°. Stir with a propeller-type stirrer for 10 minutes, place the bottle in an ice bath, continue the stirring, and allow to remain in the ice bath for 40 minutes to ensure that hydration and solution are complete. Adjust the weight of the solution to 100 g, if necessary, and centrifuge the solution to expel any entrapped air. Adjust the temperature of the solution to 20 ± 0.1°, and determine the viscosity in a suitable viscosimeter of the Ubbelohde type as directed for *Procedure for Cellulose Derivatives* under *Viscosity* ⟨911⟩. Its apparent viscosity is not less than 80.0% and not more than 120.0% of that stated on the label for viscosity types of 100 centipoises or less, and not less than 75.0% and not more than 140.0% of that stated on the label for viscosity types higher than 100 centipoises.~~

■FOR HYPROMELLOSE SAMPLES HAVING A VISCOSITY TYPE OF LESS THAN 600MPA · S—Transfer an accurately weighed quantity of Hypromellose, equivalent to 4 g of solids, calculated on the dried basis, to a tared, wide-mouth centrifuge bottle. Add hot water to obtain a total weight of the sample and water of 200.0 g. Capping the bottle, stir by mechanical means at 400 ± 50 rpm for 10 to 20 minutes until the particles are thoroughly dispersed and wetted out. Scrape down the walls of the bottle with a spatula, if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water bath equilibrated at a temperature below 10° for another 20 to 40 minutes. Adjust the solution weight, if necessary, to 200.0 g using cold water. Centrifuge the solution to expel any entrapped air. If any foam is present, remove with a spatula. Determine the viscosity in a suitable viscosimeter of the Ubbelohde type as directed for *Procedure for Cellulose Derivatives* under *Viscosity* ⟨911⟩: the viscosity is not less than 80% and not more than 120% of that stated on the label.

FOR HYPROMELLOSE SAMPLES HAVING A VISCOSITY TYPE OF 600MPA · S OR HIGHER—Transfer an accurately weighed quantity of Hypromellose, equivalent to 10 g of solids, calculated on the dried basis, to a tared, wide-mouth centrifuge bottle, and add hot water to obtain a total weight of the sample and

water of 500.0 g. Capping the bottle, stir by mechanical means at 400 ± 50 rpm for 10 to 20 minutes until the particles are thoroughly dispersed and wetted out. Scrape down the walls of the bottle with a spatula, if necessary, to ensure that there is no undissolved material on the sides of the bottle, and continue the stirring in a cooling water bath equilibrated at a temperature below 10° for another 20 to 40 minutes. Adjust the solution weight if necessary to 200.0 g using cold water. Centrifuge the solution, if necessary, to expel any entrapped air. If any foam is present, remove with a spatula. Equip a suitable single cylinder type rotational viscosimeter (Brookfield type LV Model, or equivalent), and determine the viscosity of this solution at 20 ± 0.1° under the following operating conditions specified in the table below.

Labeled Viscosity* (mPa · s)	Rotor No.	Revolution (rpm)	Calculation Multiplier
600 or more and less than 1400	3	60	20
1400 or more and less than 3500	3	12	100
3500 or more and less than 9500	4	60	100
9500 or more and less than 99,500	4	6	1000
99,500 or more	4	3	2000

* NOTE: The Labeled Viscosity is based on the manufacture's specifications.

Allow the spindle to rotate for 2 minutes before taking the measurement. Allow a rest period of 2 minutes between subsequent measurements. Repeat the operation twice to rotate the spindle as specified above, and average the three readings: the viscosity is not less than 75% and not more than 140% of that stated on the label.■2S (*USP30*)

Add the following:

■**pH** ⟨791⟩**:** between 5.0 and 8.0 measured on the solution prepared in the test for *Viscosity* at a temperature of 20 ± 2°. Read the indicated pH value after the probe has been immersed for 5 ± 0.5 minutes.■2S (*USP30*)

Change to read:

Heavy metals, ~~*Method II* ⟨231⟩.~~

■*Method III* ⟨231⟩:■2S (*USP30*)

~~0.001%, 1 mL of hydroxylamine hydrochloride solution (1 in 5) being added to the solution of the residue.~~

■not more than 20 ppm.■2S (*USP30*)

Change to read:

Loss on drying ⟨731⟩~~— Dry it at 105° for 2 hours:~~

■Dry 1.0 g at 105° for 1 hour:■2S (*USP30*)
it loses not more than 5.0% of its weight.

Change to read:

Residue on ignition ⟨281⟩: ~~not more than 1.5% for Hypromellose having a labeled viscosity of greater than 50 centipoises, not more than 3% for Hypromellose having a labeled viscosity of 50 centipoises or less, and not more than 5% for Hypromellose 1828 of all labeled viscosities.~~

■not more than 1.5% on a 1.0-g sample.■2S (*USP30*)

No change:

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Change to read:

Assay—[*Caution—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps of the Assay preparation and the Standard preparation in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.]*

■*Apparatus*—For the reaction vial, use a 5-mL pressure-tight serum vial, 50 mm in height, 20 mm in outside diameter, and 13 mm in inside diameter at the mouth. The vial is equipped with a pressure-tight septum having a polytetrafluoroethylene-faced butyl rubber and an air-tight seal using an aluminum crimp or any sealing system that provides a sufficient air-tightness. Use a heater having a heating module that has a square-shape aluminum block with holes 20 mm in diameter and 32 mm in depth, into which the reaction vial fits. The heating module is also

equipped with a magnetic stirrer capable of mixing the contents of the vial, or use a reciprocal shaker that performs a reciprocating motion of approximately 100 times per minute.■2S (*USP30*)

Hydriodic acid—Use a reagent having ~~a specific gravity of at least 1.69, equivalent to 55% HI.~~

■a typical concentration of HI about 57%.■2S (*USP30*)

Internal standard solution—Transfer about ~~2.5 g of toluene,~~

■3 g of *n*-octane,■2S (*USP30*) accurately weighed, to a 100-mL volumetric flask containing 10 mL of *o*-xylene, dilute with *o*-xylene to volume, and mix.

Standard preparation—Into a suitable serum vial weigh ~~about 135 mg of adipic acid and 4.0 mL of *Hydriodic acid*~~, pipet 4 mL of *Internal standard solution* into the vial, and close the vial securely with a suitable septum stopper. ~~Weigh the vial and contents accurately, add 30 µL of isopropyl iodide through the septum with a syringe, again weigh, and calculate the weight of isopropyl iodide added, by difference. Add 90 µL of methyl iodide similarly, again weigh, and calculate the weight of methyl iodide added, by difference. Shake, and allow the layers to separate.~~

■between 60 and 100 mg of adipic acid and add 2.0 mL of *Hydriodic acid* and 2.0 mL of *Internal standard solution* into the vial. Close the vial securely with a suitable septum stopper. Weigh the vial and contents accurately, add between 15 µL to 22 µL of isopropyl iodide through the septum with a syringe, weigh again, and calculate the weight of isopropyl iodide added, by difference. Add 45 µL of methyl iodide similarly, weigh again, and calculate the weight of methyl iodide added, by difference. Shake the reaction vial well, and allow the layers to separate. Use the upper layer as the *Standard preparation*.■2S (*USP30*)

Assay preparation—Transfer about 0.065 g of dried Hypromellose, accurately weighed, to a 5-mL thick-walled reaction vial equipped with a pressure-tight septum-type closure, add ~~an amount of adipic acid equal to the weight of the test specimen,~~

■between 60 and 100 mg of adipic acid,■2S (*USP30*) and pipet 2.0 mL of *Internal standard solution* into the vial. Cautiously pipet 2.0 mL of *Hydriodic acid* into the mixture, immediately cap the vial tightly, and weigh accurately. ~~Mix the contents of the vial continuously, while heating at 150° for 60 minutes. Allow the vial to cool for about 45 minutes, and again weigh. If the weight loss is greater than 10 mg, discard the mixture, and prepare another *Assay preparation*.~~

■Using the magnetic stirrer equipped in the heating module, or using a reciprocal shaker, mix the contents of the vial continuously, heating and maintaining the temperature of the contents at 130 ± 2° for 60 minutes. If a reciprocal shaker or magnetic stirrer cannot be used, shake the vial well by hand at 5-minute intervals during the initial 30 minutes of the heating time. Allow the vial to cool, and weigh accurately. If the weight loss is greater than or equal to 0.50% of the contents or there is evidence of a leak, discard the mixture, and prepare another *Assay preparation*.■2S (*USP30*)

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a thermal conductivity detector ~~and a 4-mm × 1.8-m glass column packed with 20% liquid phase G28 on 100- to 120-mesh support S1C that is not silanized. Helium is used as the carrier gas and the temperature of the column is maintained at 130°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative retention times are about 1.0, 2.2, 3.6, and 8.0 for methyl iodide, isopropyl iodide, toluene, and *o*-xylene, respectively; and the resolution, *R*, between toluene and isopropyl iodide is not less than 2.0.~~

■or hydrogen flame-ionization detector and a 3- to 4-mm × 1.8- to 3-m glass column packed with 20% liquid phase G28 on 100- to 120-mesh support S1C that is not silanized. Helium is used as the carrier gas for use with the thermal conductivity detector; helium or nitrogen can be used for the hydrogen flame-ionization detector. The temperature of the column is maintained at 100°. Chromatograph the *Standard preparation,* and adjust the flow rate so that the retention time of the internal standard is about 10 minutes. Use a column giving well resolved peaks of methyl iodide, isopropyl iodide, and the internal standard in this order.■2S (*USP30*)

~~*Calibration*—Inject about 2 µL of the upper layer of the *Standard preparation* into the gas chromatograph, and record the chromatogram. Calculate the relative response factor, F_M, of equal weights of toluene and methyl iodide taken by the formula:~~

$$Q_M / R_{SM}$$

~~in which Q_M is the quantity ratio of methyl iodide to toluene in the *Standard preparation*, and R_{SM} is the peak area ratio of methyl iodide to toluene obtained from the *Standard preparation*. Similarly, calculate the relative response factor, F_I, of equal weights of toluene and isopropyl iodide taken by the formula:~~

$$Q_I / R_{SI}$$

~~in which Q_I is the quantity ratio of isopropyl iodide to toluene in the *Standard preparation*, and R_{SI} is the peak area ratio of isopropyl iodide to toluene obtained from the *Standard preparation*.~~

■■2S (*USP30*)

~~*Procedure*—Inject about 2 µL of the upper layer of the *Assay preparation* into the gas chromatograph, and record the chromatogram. Calculate the percentage of methoxy ($-OCH_3$) in the Hypromellose taken by the formula:~~

$$2(31/142)F_M R_{UM}(W_S/W_U)$$

~~in which 31/142 is the ratio of the formula weights of methoxy and methyl iodide; F_M is defined under *Calibration*; R_{UM} is the ratio of the area of the methyl iodide peak to that of the toluene peak obtained from the *Assay preparation*; W_S is the weight, in g, of toluene in the *Internal standard solution*; and W_U is the weight, in g, of Hypromellose taken for the *Assay*. Similarly, calculate the percentage of hydroxypropoxy ($-OCH_2CHOHCH_3$) in the Hypromellose taken by the formula:~~

$$2(75/170)F_I R_{UI}(W_S/W_U)$$

~~in which 75/170 is the ratio of the formula weights of hydroxypropoxy and isopropyl iodide; F_I is defined under *Calibration*; R_{UI} is the ratio of the area of the isopropyl iodide peak to that of the toluene~~

Harmonization

~~peak obtained from the *Assay preparation;* W_T is the weight, in g, of toluene in the *Internal standard solution;* and W_L is the weight, in g, of Hypromellose taken for the *Assay.*~~

■Separately inject about 1 to 2 µL of the upper layer of the *Standard preparation* and the *Assay preparation* into the gas chromatograph, and record the chromatograms. Calculate the following.

$$Q_{Ta}$$

which is the ratio of the peak areas of methyl iodide to *n*-octane in the *Assay preparation;*

$$Q_{Tb}$$

which is the ratio of the peak areas of isopropyl iodide to *n*-octane in the *Assay preparation;*

$$Q_{Sa}$$

which is the ratio of the peak areas of methyl iodide to *n*-octane in the *Standard preparation;* and

$$Q_{Sb}$$

which is the ratio of the peak areas of isopropyl iodide to *n*-octane in the *Standard preparation.* Calculate the percentage of methoxy ($-OCH_3$) in the Hypromellose taken by the formula:

$$21.864(Q_{Ta} / Q_{Sa})(W_{Sa} / W_U)$$

in which W_{Sa} is the weight, in mg, of methyl iodide in the *Standard preparation;* and W_U is the weight, in mg, of Hypromellose, calculated on the dried basis, taken for the *Assay preparation*. Similarly, calculate the percentage of hydroxypropoxy ($-OC_3H_6OH$) in the Hypromellose taken by the formula:

$$44.17(Q_{Tb} / Q_{Sb})(W_{Sb} / W_U)$$

in which W_{Sb} is the weight, in mg, of isopropyl iodide in the *Standard preparation;* and W_U is the weight, in mg, of Hypromellose, calculated on the dried basis, taken for the *Assay preparation*.■2S (*USP30*)

Harmonization

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

Briefings Each Preview is preceded by a Briefing in the following format:

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Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How To Use PF*), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:

(DSN: L. Evans) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in the *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

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Abstract—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

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USP Advisory Panel on the *USP* Performance Test for Topical and Transdermal Dosage Forms

Vinod P. Shah,* Co-chair and Clarence T. Ueda, Co-chair, *USP Advisory Panel on Topical and Transdermal Dosage Forms Testing*

ABSTRACT The mission of the US Pharmacopeia (USP) is to promote public health and benefit practitioners and patients by disseminating authoritative standards and information developed by its volunteers for medicines, other health care technologies, and related practices used to maintain and improve health and promote optimal health care delivery. USP publishes the *United States Pharmacopeia (USP)* and *National Formulary (NF),* which contain monographs and associated information for more than 4000 medicines, dietary supplements, and other health care products. Standards in a pharmacopeial monograph include introductory statements (definition, description, and packaging and storage statements), followed by a specification (tests, procedures, and acceptance criteria). A key test in the drug product monograph is the USP performance test, a specific (not universal) test (*1*).

INTRODUCTION

This and a following *Stimuli* article provide information about an ongoing set of activities intended to expand on the USP performance test. The activities are proceeding in Advisory Panels originally formed in connection with the Council of Experts Biopharmaceutics Expert Committee during the 2000–2005 cycle. With adjustments in membership, these Advisory Panels will continue during the 2005–2010 cycle.

BACKGROUND

Following regulatory documentation of bioavailability (BA) and/or bioequivalence (BE) and market access, the performance test becomes the sole means of directly monitoring the ongoing performance of a dosage form or drug product that may be marketed for many years. The test may be either a private (application) performance test, usually based on USP General Chapters or the USP performance test in a dosage form monograph in *USP–NF*. For this reason, the work of the Advisory Panels and that of the Biopharmaceutics Expert Committee are especially important to the public health.

USP publishes monographs for both ingredients and products, including pharmaceutical dosage forms (drug products). A key test in the product monograph for nonsolution dosage forms is the USP performance test, which assesses release of the drug in vitro. Under appropriate circumstances, the USP performance test links to BA and BE studies that are subject to regulatory review. Without this linkage, the USP performance test should be viewed solely as a quality control test. For orally administered drug products, procedures and acceptance criteria for the USP performance test appear in General Chapters*Disintegration* ⟨701⟩, *Dissolution* ⟨711⟩, and *Drug Release* ⟨724⟩. Individual product monographs may then refer to these General Chapters with suitable Drug Release adjustments in the procedure to account for a specified dosage form.

In November 2002 USP formed an Ad Hoc Committee composed of members with expertise in pharmaceutical dosage forms, biopharmaceutics, and nomenclature, who worked with the Pharmaceutical Dosage Forms Expert Committee to develop a pharmaceutical dosage forms taxonomy scheme and related glossary. The taxonomy scheme and glossary were published as a *Stimuli* article in *Pharmacopeial Forum (2)*. The taxonomy scheme is tiered: The first grouping arranges dosage forms according to five routes of administration; the second grouping aligns them by dosage form type and physical properties (e.g., solid, semi-solid, liquid, gas, or aerosol; and the third groups them according to the release pattern of the active pharmaceutic ingredient and performance characteristics of the dosage form. According to this scheme, any dosage form for any drug substance can be unambiguously identified by a combination of taxonomic terms from each tier, taking the form:
[drug substance] [route of administration] [physical state] [release pattern]

The USP Biopharmaceutics Expert Committee is responsible for reviewing the performance test requirement for all oral dosage forms. Following publication of the taxonomy *Stimuli* article, it became possible for USP to better consider dosage form specifications and to focus on improving and/or expanding the USP Performance test for dosage forms grouped by route of administration and other factors. This consideration began in the 2000–2005 cycle with creation of four additional Advisory Panels in connection with the USP Council of Experts Biopharmaceutics Expert Committee. In total, this has resulted in five routes of dosage forms, with associated Advisory Panels:

- Oral
- Parenteral
- Inhalation/Aerosol
- Topical/Dermal
- Mucosal.

The current membership of the Topical/Dermal Advisory Panel appears in the Appendix to this *Stimuli* article. According to USP's rules and procedures, the chair of the panel must be a member of the Biopharmaceutics Expert Committee.

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DISCUSSSION

USP recognizes that the task of the Advisory Panels and of the Biopharmaceutics Expert Committee in improving and expanding on the USP performance test for drug products by route of administration is not simple. Although the performance test, in both its public and private presentations, has been of considerable value in ensuring the quality and performance of dosage forms/products in the US and other markets, the general approach requires continued careful scientific study, deliberation, and adjustment as needed (*3*). Further, it must be viewed in the context of national and international advances in regulatory control, not only in terms of development of information in support of a regulatory filing (e.g., the product development report and quality by design approaches), but also in terms of postapproval change and ongoing adherence to current Good Manufacturing Practices (e.g., process analytical technology) even in the absence of change.

Because the number and types of dosage forms are rapidly evolving, the task of developing a valid specification, including a USP performance test, in applicable private or public approaches becomes even more daunting. Although the outcome of the deliberations of the Advisory Panels and Biopharmaceutics Expert Committee remain to be fully defined, USP envisions perhaps one or more General Chapters for each route of administration, for which there are now two [*Injections* ⟨1⟩ and *Aerosols, Nasal Sprays, Metered-dose Inhalers, and Dry-powder Inhalers* ⟨601⟩], coupled with corresponding General Chapters providing information about the applicable performance test(s). A manufacturer could then use these General Chapters in the development and postapproval process, if present, to establish the private or public test, procedure, and acceptance criteria—as is done now for nonsolution orally administered dosage forms using ⟨701⟩, ⟨711⟩, and ⟨724⟩.

USP ADVISORY PANEL ON TOPICAL–TRANSDERMAL DOSAGE FORM PERFORMANCE

An accompanying *Stimuli* article has been prepared by the USP Advisory Panel on Topical–Transdermal Dosage Form Performance, which held its first meeting on December 17, 2004. This meeting included discussions about regulatory and compendial goals in setting specifications for the performance of topical and transdermal drug products. The discussions included the scientific principles undergirding the performance test. Also discussed were the following relevant workshop reports:

- Assessment of value and applications of in vitro testing of topical dermatological drug products (*4*).
- Scale-up of adhesive transdermal drug delivery systems (*5*).
- FIP/AAPS Guidelines to dissolution/in vitro release testing of novel/special dosage forms (*6*).

Key Advisory Panel suggestions included:

- Identify and define essential product characteristics critical to product performance.
- Review and evaluate tests used by manufacturers of topical and transdermal dosage forms.
- Identify and assess apparatus utilized for in vitro drug release testing.
- Investigate linking in vitro drug release results to in vivo drug performance (e.g., activity) when applicable or as appropriate.

The Advisory Panel has prepared this and the following *Stimuli* articles as a means of soliciting public input and ensuring transparency about its deliberations.

SUMMARY

The USP performance test is an important tool among the tests, procedures, and acceptance criteria that form the dosage form/product specification. USP's Biopharmaceutics Expert Committee considers and evaluates USP performance tests for oral dosage forms. USP has created additional Advisory Panels to investigate application of the USP performance test to dosage forms grouped by four specified routes of administration. All Advisory Panels will work at the direction of the Biopharmaceutics Expert Committee. The following *Stimuli* article is one of several planned to ensure that USP maintains the highest scientific and public health approaches to compendial tests to ensure the safety, quality, and efficacy of compendial articles.

APPENDIX

The Advisory Panel members for the USP Performance Test on Topical and Transdermal Dosage Forms are: Clarence T. Ueda (Co-Chair), Vinod P. Shah (Co-Chair and USP Scientific Liaison), Kris Derdzinski, Gary Ewing, Gordon Flynn, Howard Maibach, Margareth Marques, Steve Shaw, Kailas Thakker, and Avi Yacobi.

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Performance Test for Topical and Transdermal Dosage Forms

The Advisory Panel for the USP Performance Test on Topical and Transdermal Dosage Forms: Clarence T. Ueda (Co-Chair), Vinod P. Shah (Co-Chair and USP Scientific Liaison),* Kris Derdzinski, Gary Ewing, Gordon Flynn, Howard Maibach, Margareth Marques (USP Scientific Liaison), Steve Shaw, Kailas Thakker, and Avi Yacobi

ABSTRACT The physical characteristics of dosage forms administered via the skin vary widely, and therefore, the in vitro release test for these products also will be significantly different and may require different types of apparatus. Currently, reasonably well described product performance tests for topically applied dosage forms exist for semisolids and transdermal systems (patches) alone. This *Stimuli* article outlines the scientific rationale for the in vitro release test for semisolid and transdermal patch topical dosage forms. It also presents a list of commonly employed product quality tests conducted during manufacturing, together with a discussion about additional performance tests that will help ensure product quality.

INTRODUCTION

Two classes of drug products are administered via the skin.

- Topical drug products are applied to the skin for local action, for dermatological diseases, or to alleviate dermatological symptoms. In general, these products are not intended to produce systemic effects. Common drug products in this category include creams, gels, solutions, suspensions, lotions, foams, sprays, and ointments. Creams, ointments, and gels generally are referred to as semisolid dosage forms.
- Transdermal drug products are applied to the skin for systemic effects. In this case, the drug penetrates the skin, is absorbed by the blood vasculature, and is taken up by the general circulation. These products generally are referred to as self-adhering transdermal drug delivery systems (TDS) or transdermal patches.

Two categories of tests are performed with drug products:

1. Product quality tests are intended to assess attributes such as assay, content uniformity, pH, minimum fill, and microbial limits and are part of the compendial monograph.
2. Product performance tests are designed to assess product performance and in many cases relate to drug release from the dosage form.

Although the former attributes *may* affect drug product performance, the product performance test is conducted to assess the release characteristics of the finished product.

For the pharmacological activity of a drug product to occur after application to the skin, the first step is the release of drug from the formulation onto the skin surface. For this reason, a performance test must be able to determine drug release from the formulation to ensure product performance.

TOPICAL DOSAGE FORMS

Topical dosage forms include solutions (for which release testing is not indicated), suspensions, emulsions (e.g., lotions), semisolids (e.g., collodions, foams, ointments, pastes, creams, and gels), solids (e.g., powders, aerosols, and patches [see TDS below]), and sprays. The 2005 *USP–NF* includes 5 emulsions, 22 lotions, 3 collodions, 1 foam, 116 ointments, 7 pastes, 75 creams, and 29 gels.

Table 1 shows typical product quality tests associated with *USP* topical dosage form monographs. In addition to these product quality tests, manufacturers may perform additional testing before product is released to the market: e.g., for creams they also may test for product description, impurities and degradation products, dose uniformity, preservative content, extractables, alcohol content, rheological properties, specific gravity, water content, and solid-state form. Many of these tests may not appear in the public monograph but are part of the private (application) standard. Some manufacturers also carry out product performance (in vitro drug release) tests.

Table 1. Topical Dosage Forms and Associated Product Quality Tests

Topical Dosage Form	Product Quality Tests
Aerosol (solid)	Assay, identification, content of ..., limits of ..., particle size
Collodion	Assay, identification, contents of ..., pH, limits of ..., + specific gravity
Cream	Assay, identification, content of ..., microbial limits, pH, minimum fill, related compounds, viscosity, homogeneity, concentration/content uniformity, phase separation.
Emulsion	Assay, identification, content of ..., microbial limits, pH, limits of ..., defoaming activity, heavy metals, phase volume (?)
Foam	Assay, identification, pH + additional tests from industry, if any
Gel	Assay, identification, content of ..., microbial limits, pH, limit of ..., minimum fill, acid-neutralizing capacity, arsenic, chloride, sulfate
Lotion	Assay, identification, content of ..., microbial limits, pH, limits of ..., minimum fill, related compounds

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Table 1. Topical Dosage Forms and Associated Product Quality Tests *(Continued)*

Topical Dosage Form	Product Quality Tests
Ointment	Assay, identification, content of ..., microbial limits, pH, limit of ..., minimum fill, concentration/content uniformity, water content
Ophthalmic ointment	Assay, identification, content of ..., pH, limit of ..., minimum fill, particle size, metal particles, osmolality, sterility, water content
Paste	Assay, identification, content of ..., microbial limits, pH, limits of ..., minimum fill, carbonate and acid-insoluble matter, consistency, heavy metals, loss on drying, soluble alkalies, soluble salts
Powder	Assay, identification, content of ..., limits of ..., particle size (?)
Solution	Assay, identification, content of ..., microbial limits, pH, limits of ..., +
Sprays	See solutions
Suspension	Assay, identification, content of ..., microbial limits, pH, limits of ..., particle size, +

Scientific Rationale for Release Rate Determination from Semisolid Dosage Forms

Current *USP* monographs for semisolid dosage forms do not contain a release test. However, the FDA/AAPS workshop, "Assessment of Value and Applications of In Vitro Testing of Topical Dermatological Drug Products" (*1*), concluded that:

- In vitro release testing is based on sound scientific principles. The procedure is rugged and reproducible, and the release rate is a distinguishing property of the formulation (i.e., semisolid drug release during in vitro testing is proportional to the square root of time, $\sqrt{t}$).
- In vitro release testing can serve as a research tool in the course of developing formulations.
- The use of in vitro release tests to demonstrate product sameness for the purposes of SUPAC-SS is acceptable.
- A release test is neither a surrogate test for bioavailability nor for bioequivalence and should be used only as supporting evidence in such evaluations.
- In vitro release testing should not be used for comparing fundamentally different formulations (e.g., ointments vs. creams).
- In vitro release generally is formulation dependent and therefore should not be used to compare similar formulations from different manufacturers (which would be analogous to comparing different manufacturers' solid oral extended-release preparations that display different release profiles but are bioequivalent).
- A change in the in vitro release rate may be indicative of a change in the clinical performance of the dosage form in question.

Release testing can, in principle, provide useful information about the physical attributes (solubility, microscopic viscosity, emulsion state, particle size, etc.) of semisolid dosage forms. A simple, reproducible drug release test that employs a vertical diffusion cell system has been developed for these dosage forms (*2*). In the test, a thick layer of the test semisolid is placed in contact with a reservoir. Diffusion of the drug out of the semisolid into the receptor medium ensues. In most instances, diffusive communication between the delivery system and the reservoir takes place through an inert support membrane. The membrane keeps the product and the receptor medium physically separate and distinct. Membranes are chosen to offer the least possible diffusional resistance and must not be rate controlling.

The system's configuration is such that after a short lag period, release of drug from the dosage form is kinetically describable by diffusion of a chemical out of a "semi-infinite medium" into a "sink." Regardless of whether the releasing system is a solution or a suspension, the momentary release rate tracks the depth of penetration of the forming gradient within the semisolid. Beginning at the moment when the receding boundary layer's diffusional resistance assumes dominance of the kinetics of release, the amount of the drug released, *M,* becomes proportional to $\sqrt{t}$ with the momentary rate of release, *dM/dt,* becoming proportional to $1/\sqrt{t}$. These quantitative dependencies of release are well characterized and established for solution and suspension systems.

The first 30% of release rate from a solution is describable by the following mathematical relationship.

$$M = 2 \cdot C_o \sqrt{\frac{D \cdot t}{\pi}} \qquad [1]$$

where A plot of M vs. $\sqrt{t}$ will be linear with a slope of

$$2 \cdot C_o \sqrt{\frac{D}{\pi}} \cdot$$

M = amount of drug released into the sink per cm^2
C_o = drug concentration in releasing matrix
D = drug diffusion coefficient through the matrix
t = time.

For suspensions, the release rate can be described by the following equation:

$$M = \sqrt{2 \cdot D_m \cdot C_s \left(Q - \frac{C_s}{2} \right) t} \quad [2]$$

where

C_s = drug solubility in the releasing matrix
D_m = drug diffusion coefficient in the semisolid matrix
Q = total amount of the drug in solution and suspended in the matrix.

When $Q >> C_s$, Eq. 2 simplifies to Eq. 3:

$$M = \sqrt{2 \cdot Q \cdot D_m \cdot C_s \cdot t} \quad [3]$$

A plot of M vs. $\sqrt{t}$ will be linear with a slope of $\sqrt{2QD_mC_S}$. During the release rate experiments, every attempt should be made to keep the composition of the formulation intact during the releasing period.

A. Vertical Diffusion Cell System Methodology

Typically, 200–400 mg of an ointment, cream, or gel is spread evenly over a suitable synthetic, inert support membrane, and the thickness of the applied layer per cm^2 is measured. The membrane, with its application side up, is placed in a vertical diffusion cell (typically of 15-mm diameter orifice), e.g., a Franz cell. The release rate experiment is carried out at 32 °C, except in the case of vaginal creams when the temperature should be 37 °C. Sampling usually is performed over 4–5 hours, and sample volume is replaced with fresh receptor medium. To achieve sink condition, the receptor medium must have a high capacity to dissolve or carry away the drug, and the receptor medium should not exceed 10% of C_s at the end of the test.

Several collaborative studies have been carried out with different types of semisolid dosage forms (creams, ointments, and gels) to evaluate within-laboratory and between-laboratory reproducibility using the vertical diffusion cell system. The results of the study are published as a *Stimuli* article immediately following the present *Stimuli* article in this issue of *PF*.

B. Alternative Methodology Using a Modified Semisolid Holding Cell System

In vitro release test procedures using modified semisolid holding cell systems, e.g., the Enhancer Cell, also have been reported (*3, 4*). With these systems the semisolid dosage form is placed in an inert holding cell, and the entire assembly is placed in a dissolution vessel and stirred by paddles. Only limited information about these systems is available, and more data, e.g., validation and reproducibility studies, are needed.

General comments about Methods A and B

Studies comparing drug release between the vertical diffusion cell system and the semisolid holding cell system have been reported in the literature (*4*). The principle of drug release with the two types of systems is the same. However, because the setups of the two diffusion cell systems are significantly different, results obtained with one system will not necessarily match those from the other system. This is to be expected because the mass of sample and the diffusion surface in the two systems are different.

Product Performance Test for Topical Semisolids

The release rate is a property of the dosage form. The in vitro release test method using the vertical diffusion cell has been found to be rugged and reproducible (*1*). This test has been utilized in FDA's Scale-Up and Post-Approval Guidance for Nonsterile Semisolid Dosage Forms (*5*) to lower regulatory burdens. In vitro release is based on sound scientific principles and can be used to ensure product sameness between prechange and postchange dosage forms. A statistical 90% confidence interval (CI) criterion has been developed to compare the release rate between approved and postapproval changes in dosage forms. The release rate of postchange dosage forms must be within a 90% CI of the original approved prechange dosage form.

TDS (TRANSDERMAL PATCHES)

TDS have different release mechanisms due to differences in their composition and fabrication. TDS systems can be categorized as 1) liquid form–fill–seal systems, 2) peripheral adhesive systems, or 3) solid matrix systems. The latter two categories include the subcategories of monolithic, matrix, multilaminate, and drug-in-adhesive systems (6). Recent advances in the design of novel TDS employ novel physicochemical principles for control or enhancement of drug delivery such as iontophoresis, heat-assisted drug delivery, and others.

In all of the three principal TDS categories, the drug substance is in solution or suspension. A number of factors can influence drug release and the performance of TDS dosage forms. These include changes in formulation composition involving adhesives, solvents, viscosity-modifying agents, enhancers, and changes in the semipermeable film or laminate.

The 2005 *USP–NF* includes only two TDS monographs even though many more have been approved by FDA and are marketed in the US. *USP* monographs include the following product quality test requirements for TDS dosage forms: assay, identification, drug release, related compounds, uniformity of dosage units, residual solvents, and microbial limits.

Manufacturers may also perform additional testing for transdermal patches, including appearance, assay for potency of critical excipient(s), related compounds (degradants), residual monomers, adhesion to release liner and standard substrates, peel, shear, tack, liner functionality, pouch (container) integrity, patch integrity (vacuum, pressure, and seal), dimensions, and system functionality tests.

The performance test for TDS should include in vitro drug release, especially testing for dose dumping, adhesion tests (for release liner and/or standard substrates), and, if appropriate, system functionality testing to ensure product performance.

Product Performance Test for TDS

In vitro drug release testing is commonly used to characterize TDS and is a basic quality control tool. USP has established three different in vitro drug release test procedures for these products: 1) the paddle over disk method (Apparatus 5), 2) the cylinder method (Apparatus 6), and 3) the reciprocating holder method (Apparatus 7).

The paddle over disk method (Apparatus 5) is the simplest procedure and is highly reproducible. However, it is not applicable to all marketed transdermal systems due to variations in sizes and shapes of the systems. Experimental evidence indicates that the same release profile is obtained when the results are compared using Apparatus 5 and 6 or Apparatus 5 and 7 (*7, 8*). The reciprocating holder method (Apparatus 7) permits different designs of sample holders to be used for TDS. The disk holder, the angled disk holder, and the reciprocating cylinder holder are used most commonly. Typically, the in vitro release test should be conducted for a period sufficient to exceed 100% of the total amount of drug delivered in vivo, and a minimum of three to four test points should be used to characterize the drug release profile.

Adhesion to the target site is another critical performance characteristic of TDS. Therefore, minimum adhesion force to release the liner should be tested, and an adhesion test using a standard substrate is recommended. For some novel TDS products, appropriate system functionality tests assessing crucial physicochemical attributes also may be required.

SUMMARY

USP encourages further investigations of performance tests that will yield increasing quality for the types of dosage forms discussed in this *Stimuli* article. USP believes that product performance tests will enhance assurance of the continuing strength, quality, and purity of both topical and TDS dosage forms that may be marketed many years without a requirement for redocumentation of bioavailability and bioequivalence. Depending on deliberations of the Topical–Transdermal Advisory Panel and its discussions with the Biopharmaceutics Expert Committee, USP believes that at least two new General Chapters may result: 1) a General Chapter analogous to ⟨1⟩ and ⟨601⟩ discussing topical–transdermal dosage forms, as well as a new General Chapter that describes general approaches for product performance tests for these types of dosage forms.

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In Vitro Release: Collaborative Study Using the Vertical Diffusion Cell

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ABSTRACT Since the inception of in vitro release testing for semisolid dosage forms using diffusion cell testing, a variety of diffusion cell styles and designs have been used. The Vertical Diffusion Cell (VDC) or "Franz Cell" has emerged as the most optimum for testing the in vitro release of topical dosage forms (*1, 2*). The VDC design incorporates a donor compartment at the top of the assembly and a receptor compartment below. These two compartments are separated by a membrane. This membrane is not intended to be a barrier but an avenue through which drug diffusion takes place. The membrane is also intended to be a support for the test product, ensuring that the product remains in place with constant and consistent contact with the receptor media. This purpose of this *Stimuli* article is to summarize the status of collaborative studies to date and to indicate next steps for a USP Performance test for semisolid dosage forms.

INTRODUCTION

In 1997 FDA released the SUPAC-SS Guideline (*3*). This guideline recommends in vitro diffusion cell testing for semisolid dosage forms when manufacturing or material changes were made to an approved topical dosage form. If any of a variety of changes occurs, the SUPAC-SS Guideline requires an in vitro release test comparing the product prior and subsequent to the change to assess similarity in performance.

As with all test methods it is important to demonstrate robustness. To understand the robustness and reproducibility of the in vitro test using the VDC, the USP Biopharmaceutics Expert Committee requested additional information in the form of a collaborative study. This study was conducted using four laboratory sites and four topical products: Hydrocortisone Cream, Betamethasone Dipropionate Cream, Betamethasone Dipropionate Gel, and Betamethasone Dipropionate Ointment.

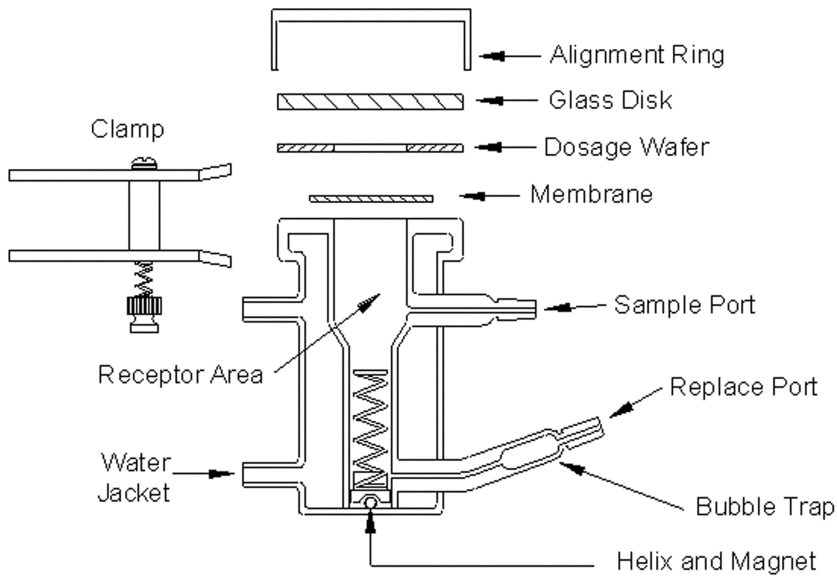

Figure 1. Vertical diffusion cell

The VDC used for this collaborative study is illustrated in *Figure 1*. This type of cell is commonly used for testing the in vitro release rate of topical drug products such as creams, gels, and ointments. The cell is made from clear glass and uses a clamp to secure the donor side of the cell to the receptor side. The clamp also ensures that all of the components and the membrane remain in place during the test. A glass disk is used to support the dosage wafer and to facilitate viewing of the donor material during the test. The cell is temperature controlled via the water jacket ports using a bath circulator. The alignment ring ensures that the positions between the donor and receptor orifices are accurately aligned. The sampling and replace ports have Luer connections that facilitate the collection of sample and media replacement. In addition, a bubble trap is incorporated into the replace port to seize any bubbles

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that may be inadvertently introduced by the sampling process. A magnetic stirrer is used to turn the helix and magnet, mixing the receptor media to maintain a homogeneous mixture.

IN VITRO RELEASE COLLABORATIVE STUDY PHASE I

Collaborators

- C1: Hanson Research
- C2: FDA
- C3: USP
- C4: Taro Pharmaceuticals

Products Studied

- Hydrocortisone Cream 1%, Pharmacia, Lot 03JDM, expiration date (exp.) 10-2004
- Betamethasone Dipropionate Cream 0.05%, Taro, Lot 26057, exp. 07-2005
- Betamethasone Dipropionate Gel 0.05%, Schering, Lot 2RFH104, exp. 10-2005
- Betamethasone Dipropionate Ointment 0.05%, Warrick, Lot 1HYA301, exp. 10-2005.

Each of these products was tested by C1 prior to beginning Collaborative Phase 1 of the study.

Criteria for Product Selection

Semisolid dosage forms (creams, ointments, and gels) containing the same active ingredient were selected for ease of operating the analytical procedure and HPLC system and at the same time providing the information that the procedure is workable for all types of topical dosage forms.

Objectives

The objective for this phase of the study was for each collaborator to conduct the specified test one time for each product. Testing was accomplished manually, and all test data were calculated following the SUPAC-SS Guideline. The results were calculated using in vitro release data of C1 as the ''Reference'' data and using the in vitro release data of other collaborators as the ''Test'' data. The results from this study were presented to the USP Biopharmaceutics Expert Committee on 25 May 2004.

Test Method

During the test of the Betamethasone Cream and Gel, the synthetic membrane was saturated in a 15% solution of Ethomeen in isopropyl myristate (IPM) for 30 minutes and placed on the dosage wafer (*2*). During the test of the Betamethasone Ointment, the synthetic membrane was saturated in IPM for 30 minutes and placed on the dosage wafer. In either case, the dosage wafer was inverted and then filled with the test product. This (approximately) 300-mg dose is defined as an infinite dose for these tests. The dosage wafer was then placed on a cell filled with receptor media which had come to temperature (32 °C). The glass disk, alignment ring, and clamp were applied to the cell and the stirring initiated, constituting time zero for the test.

Sample time points were at 1, 2, 3, 4, and 6 hours. The VDC was equipped with a check valve attached to the replace port and a sampling port canula (both not shown in figure) to aid in the manual sampling process (*4*). The purpose of the check valve is to allow replacement solution to be introduced into the VDC without allowing media to flow back out once the syringe is removed. The sampling process introduces approximately 1 mL of replacement media through the check valve and into the replace port, concurrently pushing sample out of the sampling port for collection. Half of this 1-mL sample was used for rinsing the sample port and canula, and the other half was collected for HPLC analysis. The sampling process was accomplished with the stirring device off.

Role of In Vitro Release Rate of Hydrocortisone Cream

The results from Hydrocortisone Cream were used to check the performance of the operating system. This included set-up of the equipment, preparation of the samples by the analyst, sample collection, and analysis. The in vitro release rate data from collaborators C2, C3, and C4 were compared with the release rate data from C1, the reference laboratory. The release rate data from C2, C3, and C4 collaborators were within a 90% confidence interval (CI) of C1 data, verifying the performance of the other systems.

Sample Analysis

Table 1. Chromatographic Conditions for Analysis Using Reversed-phase HPLC

	Hydrocortisone Cream	Betamethasone Dipropionate Creams, Gels, and Ointments
Wavelength	242 nm	239 nm
Flow Rate	1.0 mL/min	1.5 mL/min
Injection Volume	10 µL	50 µL
Runtime	10 min	10 min
Column	50 mm × 3.9 mm Symmetry C-18, 5 µm	300 mm × 3.9 mm µBondapak C-18
Mobile Phase	20:80::ACN*:H_2O	60:40::ACN:H_2O

* ACN=acetonitrile

Data Calculations

The peak area data from each sampling time point was used to calculate the amount released (µg/cm^2) into each VDC and then plotted against the square root of time. The slope of the line (release rate) was calculated using linear regression. These slopes (one for each VDC) were then compared to another set of test slopes to obtain a pass or fail as described by the SUPACC-SS Guideline using a 90% CI (*3*).

Results from Collaborative Study Phase I

Table 2. Pass–fail results from C2, C3, and C4

Collaborator	Hydrocortisone Cream	Betamethasone Dipropionate Cream	Betamethasone Dipropionate Gel	Betamethasone Dipropionate Ointment
C2	Pass	Fail	Pass	Fail
C3	Pass	Fail	Pass	Pass
C4	Pass	Pass	Pass	Fail

- Within-lab reproducibility: 11 of 13 runs pass 90% CI limits (SUPAC-SS)
- Between-lab reproducibility: 8 of 12 runs pass 90% CI limits (SUPAC-SS).

Conclusions from Collaborative Study Phase I

After reviewing and discussing the results from the first phase, the Biopharmaceutics Expert Committee agreed that the failures and inconsistent results possibly were associated with variations among the laboratories in performing the methods and protocols. The Expert Committee also concluded that the best way to better understand the variability would be to repeat the study. Beforehand, however, the Expert Committee recommended that training should be conducted to ensure that all collaborators had a complete understanding of the methods and protocols. This training was carried out in April 2005, when each participating laboratory sent two analysts for one day of training.

IN VITRO RELEASE COLLABORATIVE STUDY PHASE II

For this phase of the collaborative study, testing levels were increased from one test per product to three tests per product for a total of 18 cells tested per product per laboratory. Procedures like those described in Collaborative Study Phase 1 were used.

Collaborators

Collaborators were the same laboratories as in the Collaborative Study Phase I, although only analyst "C" conducted tests in both Phase I and Phase II.

Products Studied

- Hydrocortisone Cream 1%, Pharmacia, Lot 20KJM, exp. 10-2005
- Betamethasone Dipropionate Cream 0.05%, Taro, Lot 31119, exp. 09-2006
- Betamethasone Dipropionate Gel 0.05%, Taro, Lot 4B055, exp. 09-2005
- Betamethasone Dipropionate Ointment 0.05%, Alpharma, Lot 310046, exp. 10-2005.

Although the same types of products were used for Collaborative Study Phase II, new lots/manufacturers were needed. These new products were all tested by C1 prior to training and beginning the second phase of the study as also was the case during the first phase of the study. This initial testing by C1 ensured that consistent SUPAC-SS results were attainable for these products and that the methods and protocols were still valid. As in the first phase, sampling was performed manually.

For this part of the collaborative study, C1 ran at least three tests for each product using 12 VDCs with Groups A and B consisting of six cells each. Each of the other collaborators tested each product three times with a single set of six cells. As in the previous testing phase, C1's first test was used as the "Reference," and the other collaborators' data were used as the "Test" set. In addition, each collaborator's first test was also used as the "Reference" against which subsequent tests were then evaluated (see results in the following tables). For convenience, the tables use the following abbreviations:

- Hydrocortisone Cream=HCC
- Bethamethasone Dipropionate Cream=BDC
- Bethamethasone Dipropionate Gel=BDG
- Bethamethasone Dipropionate Ointment=BDO

Not all tests were completed by C2; tests not completed are shown as blank.

The following tables are an overview of the results from Collaborative Study Phase II. Each table represents one of the products tested, the results from all four collaborators, and pass–fail notations. In addition, test slope averages and % RSD also are listed for each of the tests, along with an identification of the analyst who conducted that specific test.

All collaborators' tests were evaluated two different ways—against the preparatory tests performed by C1, and within their own laboratories all subsequent tests were compared to the first test. The results from C4's HCC test reveal a point of interest: Tests one and three failed, but test two passed the SUPAC-SS requirements when compared with C1. Although two of these tests failed against C1, all of C4's tests passed when the results were evaluated against all tests within their laboratory.

Table 3: Collaborative Study Phase II Testing of Hydrocortisone Cream

Betamethasone Dipropionate Gel					
Test	Reference Test	SUPAC-SS Pass/Fail	Test Slope Average	Test Slope % RSD	Analyst
C1-BDG-001A	C1-BDG-001B	*Pass*	1.569	3.709	A
C1-BDG-001B	C1-BDG-001A	*Pass*	1.553	3.438	A
C1-BDG-002A	"	*Pass*	1.629	2.241	A
C1-BDG-002B	"	*Pass*	1.620	5.834	A
C1-BDG-003A	"	*Pass*	1.553	4.346	A
C1-BDG-003B		*Pass*	1.553	3.081	A
C2-BDG-001	C1-BDG-001A	*Pass*	1.432	6.994	C
C2-BDG-002	"				
C2-BDG-003	"				
C2-BDG-002	C2-BDG-001				
C2-BDG-003	"				
C3-BDG-001	C1-BDG-001A	*Pass*	1.469	11.817	*F
C3-BDG-002	"	*Fail*	1.245	7.433	E
C3-BDG-003	"	*Pass*	1.343	10.278	E
C3-BDG-002	C3-BDG-001	*Pass*	1.245	7.433	E
C3-BDG-003	"	*Pass*	1.343	10.278	E
C4-BDG-001	C1-BDG-001A	*Pass*	1.585	5.065	G
C4-BDG-002	"	*Pass*	1.508	6.389	G
C4-BDG-003	"	*Pass*	1.591	3.875	H
C4-BDG-002	C4-BDG-001	*Pass*	1.508	6.389	G

* = Did not attend training

Table 4: Collaborative Study Phase II Testing of Betamethasone Dipropionate Cream

Betamethasone Dipropionate Cream					
Test	Reference Test	SUPAC-SS Pass/Fail	Test Slope Average	Test Slope % RSD	Analyst
C1-BDC-001A	C1-BDC-001B	*Pass*	0.798	10.824	A
C1-BDC-001B	C1-BDC-001A	*Pass*	0.769	11.222	A
C1-BDC-002A	"	*Pass*	0.774	9.542	A
C1-BDC-002B	"	*Pass*	0.792	7.561	A
C1-BDC-003A	"	*Pass*	0.937	8.941	A
C1-BDC-003B	"	*Pass*	0.900	8.127	A
C1-BDC-004A	"	*Pass*	0.955	8.925	A
C1-BDC-004B	"	*Fail*	0.968	11.044	A
C2-BDC-001	C1-BDC-001A	*Pass*	0.649	4.766	C
C3-BDC-001	C1-BDC-001A	*Pass*	0.804	8.421	*F
C3-BDC-002	"	*Pass*	0.879	10.472	E
C3-BDC-003	"	*Pass*	0.880	8.834	*F
C3-BDC-002	C3-BDC-001	*Pass*	0.879	10.472	E
C3-BDC-003	"	*Pass*	0.880	8.834	*F
C4-BDC-001	C1-BDC-001A	*Pass*	0.884	7.610	H
C4-BDC-002	"	*Pass*	0.827	8.614	H
C4-BDC-003	"	*Pass*	0.800	9.872	G
C4-BDC-002	C4-BDC-001	*Pass*	0.827	8.614	H
C4-BDC-003	"	*Pass*	0.800	9.872	G

* = Did not attend training

Table 5. Collaborative Study Phase II Testing of Betamethasone Dipropionate Gel

Betamethasone Dipropionate Gel					
Test	Reference Test	SUPAC-SS Pass/Fail	Test Slope Average	Test Slope % RSD	Analyst
C1-BDG-001A	C1-BDG-001B	*Pass*	1.569	3.709	A
C1-BDG-001B	C1-BDG-001A	*Pass*	1.553	3.438	A
C1-BDG-002A	C1-BDG-001A	*Pass*	1.629	2.241	A
C1-BDG-002B	C1-BDG-001A	*Pass*	1.620	5.834	A
C1-BDG-003A	C1-BDG-001A	*Pass*	1.553	4.346	A
C1-BDG-003B	C1-BDG-001A	*Pass*	1.553	3.081	A
C2-BDG-001	C1-BDG-001A	*Pass*	1.432	6.994	C
C3-BDG-001	C1-BDG-001A	*Pass*	1.469	11.817	F*
C3-BDG-002	C1-BDG-001A	*Fail*	1.245	7.433	E
C3-BDG-003	C1-BDG-001A	*Pass*	1.343	10.278	E
C3-BDG-002	C3-BDG-001	*Pass*	1.245	7.433	E
C3-BDG-003	C3-BDG-001	*Pass*	1.343	10.278	E
C4-BDG-001	C1-BDG-001A	*Pass*	1.585	5.065	G
C4-BDG-002	C1-BDG-001A	*Pass*	1.508	6.389	G
C4-BDG-003	C1-BDG-001A	*Pass*	1.591	3.875	H
C4-BDG-002	C4-BDG-001	*Pass*	1.508	6.389	G
C4-BDG-003	C4-BDG-001	*Pass*	1.591	3.875	H

* Did not attend training. Note: C3 reported bubbles under the membrane(s) during all three tests.

Table 6. Collaborative Study Phase II Testing of Betamethasone Dipropionate Ointment

Betamethasone Dipropionate Ointment					
Test	Reference Test	SUPAC-SS Pass/Fail	Test Slope Average	Test Slope % RSD	Analyst
C1-BDO-001A	C1-BDO-001B	*Pass*	1.786	3.052	B
C1-BDO-001B	C1-BDO-001A	*Pass*	1.848	3.625	B
C1-BDO-002A	"	*Pass*	1.847	4.728	A
C1-BDO-002B	"	*Pass*	1.860	4.871	A
C1-BDO-003A	"	*Pass*	1.668	4.340	A
C1-BDO-003B	"	*Pass*	1.715	3.887	A
C2-BDO-001	C1-BDO-001A	*Pass*	1.950	3.582	C
C3-BDO-001	C1-BDO-001A	*Pass*	1.687	4.131	*F
C3-BDO-002	"	*Pass*	1.605	6.907	*F
C3-BDO-003	"	*Pass*	1.559	4.922	E
C3-BDO-002	C3-BDO-001	*Pass*	1.605	6.907	*F
C3-BDO-003	"	*Pass*	1.559	4.922	E
C4-BDO-001	C3-BDO-001A	*Pass*	2.083	5.862	G
C4-BDO-002	"	*Pass*	1.723	3.071	G
C4-BDO-003	"	*Pass*	1.750	2.235	H
C4-BDO-002	C4-BDO-001	*Pass*	1.723	3.071	G
C4-BDO-003	"	*Pass*	1.750	2.235	H

* = Did not attend training

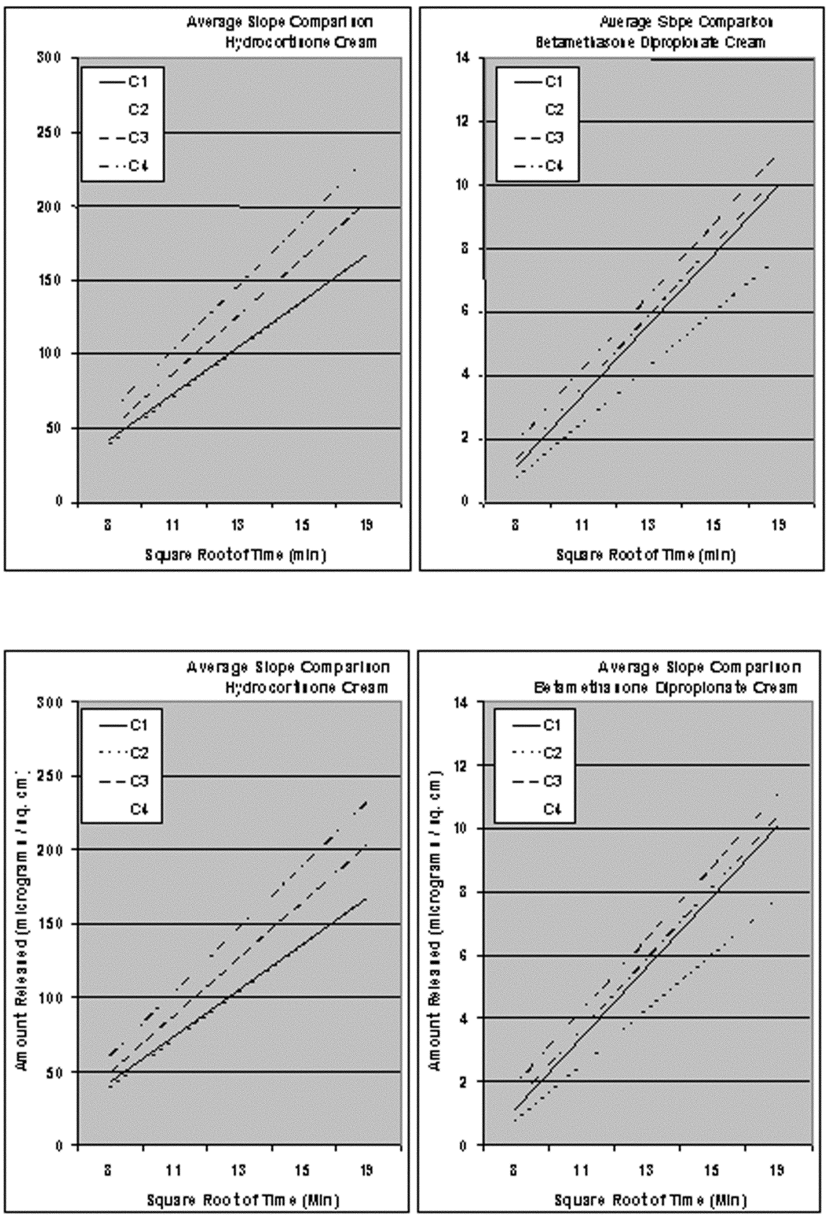

Figure 2. The graphs show the slope average for all tests reported by each laboratory

In summary:

- 17 runs pass 90% CI limits
- BDO 12 of 12 runs pass 90% CI limits.

- Between-lab reproducibility:
  - HCC 11 of 14 runs pass 90% CI limits
  - BDC 14 of 15 runs pass 90% CI limits
  - BDG 16 of 17 runs pass 90% CI limits
  - BDO 12 of 12 runs pass 90% CI limits.

Conclusions from Collaborative Study Phase II

The test results from Collaborative Study Phase II demonstrate improvement by comparison with those from Study Phase I. All tests from Study Phase II passed SUPAC-SS requirements within a single laboratory and with an analyst who attended training. Thus the improved results for Phase II suggest that training was a key component in ensuring analysts' understanding of the method steps and procedures. This study also shows that the test is robust and repeatable even when one evaluates results both from different laboratories and analysts.

The most consistent and repeatable results were obtained when one analyst ran the test. Further improvement also occurred when the test was conducted with a group of 12 VDCs simultaneously. To ensure the most accurate results, testing should be conducted with as few variables as possible, including the time between tests when using only one group of samples.

Automation

The manual method described here is an emulation of the automated process, which further enhances this type of test method. A manual sampling procedure may be easily migrated to an automated sampling system, allowing pharmaceutical

companies options for their diffusion test requirements. Manual sampling may be used as well to validate automated methods (*4*).

NEXT STEPS

- Specifications should be established to ensure control and consistency of the test apparatus.
- Method development guidelines also should be elaborated and published to aid analysts in the start-up and maintenance of this test procedure.
- Expert practitioners should work together to publish a simple method for performance verification that can be used to ensure an analyst's comprehensive understanding of the methods and procedures.
- Hydrocortisone Cream 1% (Pharmacia) can be used as a performance verification test product. Appropriate in vitro release rate parameters should be disseminated.

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1. Flynn GL, Shah VP, Tenjarla SN, et al. Assessment of value and application of in vitro testing of topical dermatological drug products [Workshop Report]. *Pharm Res.* 1999;16:1325–1330.
2. Shah VP, Elkins JS, Williams RL. Evaluation of the test system used for in vitro release of drugs for topical dermatological drug products. *Pharm Dev Technol.* 1999;4:377–385.
3. FDA. Guidance for industry: SUPAC-SS—nonsterile semisolid dosage forms. Scale-up and post approval changes: chemistry, manufacturing, and controls. 1997. Available at: www.fda.gov/cder/guidance/1447fnl.pdf. Accessed 5 April 2006.
4. Shah VP, Elkins J, Shaw S, Hanson R. In vitro release: comparative evaluation of vertical diffusion cell system and automated procedure. *Pharm Dev Technol.* 2003;8:97–102.

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

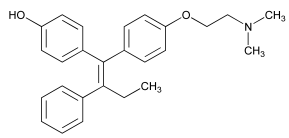
USP Dictionary of USAN and International Drug Names
2006 USP DICTIONARY SUPPLEMENT 3

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2006 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2006) edition will be included in the next complete edition of the Dictionary.

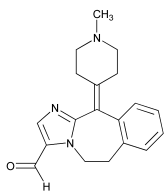
Newly Approved United States Adopted Names (USAN), Released for Publication

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

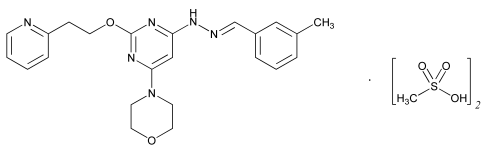
Afimoxifene [*2006*] (a fim ox′ i feen). $C_{26}H_{29}NO_2$. 387.51. (1) Phenol, 4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenyl-1-butenyl]-; (2) 4-[1-[4-[2-(Dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenol. *CAS-68392-35-8*. *Local treatment of estrogen dependent conditions of the breast.* TamoGel (Ascend Therapeutics) ✧*4-OHT*



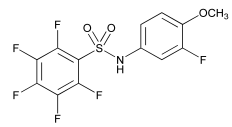
Alcaftadine [*2006*] (al kaf′ ta deen). $C_{19}H_{21}N_3O$. 307.39. (1) 5*H*-Imidazo[2,1-*b*][3]benzazepine-3-carboxaldehyde, 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-; (2) 11-(1-Methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-imidazolo[2,1-*b*][3]benzazepine-3-carbaldehyde; (3) 4-(1-Methyl-piperidin-4-ylidene)-9,10-dihydro-4*H*-3,10a-diaza-benzo[f]azulene-1-carbaldehyde. *CAS-147084-10-4*. INN. *Antiallergic, histaminic H-1 receptor antagonist, anti-inflammatory.* (Janssen Cilag) ✧*R 89674*



Apilimod Mesylate [*2006*] (a pil i mod). $C_{23}H_{26}N_6O_2 \cdot 2CH_4O_3S$. 610.70. (1) Benzaldehyde, 3-methyl-, [6-(4-morpholinyl)-2-[2-(2-pyridinyl)ethoxy]-4-pyrimidinyl]hydrazone mesylate; (2) *N*-(3-Methylbensylidene) *N*-[6-morpholin-4-yl-2(2-pyridin-2-yl-ethoxy)-pyrimidin-4-yl]-hydrazine bismesylate. *CAS-870087-36-8*. *Treatment of inflammatory diseases* (*inhibits production of IL-12*). (Synta) ✧*STA-5326 mesylate*

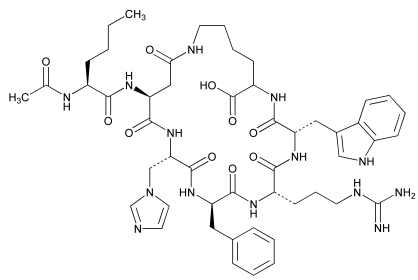


Batabulin [*2006*] (ba′′ ta bue′ lin). $C_{13}H_7F_6NO_3S$. 371.25. (1) Benzenesulfonamide, 2,3,4,5,6-pentafluoro-*N*-(3-fluoro-4-methoxyphenyl)-; (2) 2,3,4,5,6-Pentafluoro-*N*-(3-fluoro-4-methoxyphenyl)benzenesulfonamide. *CAS-195533-53-0*. *Treatment of various advanced refractory cancers* (*binds to* β-*tubulin*). (Tularik) ✧*T138067; T67; TL 057*

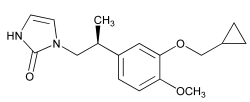


Bavituximab [[*2006*] (bav i tux′ i mab). $C_{6446}H_{9946}N_{1702}O_{2042}S_{32}$. Immunoglobulin G1, anti-(phosphatidylserine)(human-mouse monoclonal ch3G4 heavy chain), disulfide with human-mouse monoclonal ch3G4 κ-chain, dimer. Molecular weight is approximately 145,300 daltons. *CAS-648904-28-3*. *Anti-cancer and anti-viral.* (Peregrine)

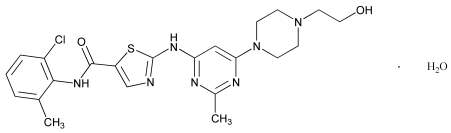
Bremelanotide [*2006*] (bre′′ mel an′ oh tide). $C_{50}H_{68}N_{14}O_{10}$. 1025.16. (1) L-Lysine, *N*-acetyl-L-norleucyl-L-α-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-, (2→7)-lactam; (2) *N*-Acetyl-L-2-aminohexanoyl-L-α-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-L-lysine-(2→7)-lactam. *CAS-189691-06-3*. *Treatment of sexual dysfunction* (*melanocortin receptor agonist*). (Palatin) ✧*PT-141*



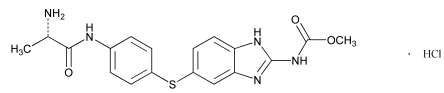
Catramilast [*2006*] (ka tra′ mi last). $C_{17}H_{22}N_2O_3$. 302.37. (1) 2*H*-Imidazol-2-one, 1-[2-[3-(cyclopropylmethoxy)-4-methoxyphenyl]propyl]-1,3-dihydro-, (*S*)-; (2) 1-[(2*S*)-2-[3-(Cyclopropylmethoxy)-4-methoxyphenyl]propyl]-1,3-dihydro-2*H*-imidazol-2-one. *CAS-183659-72-5*. *Treatment of atopic dermatitis.* (Barrier) ✧*R115500*



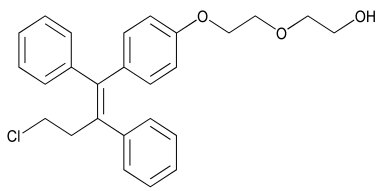
Dasatinib [*2005*] (da sa′ ti nib). $C_{22}H_{26}ClN_7O_2S \cdot H_2O$. 506.02. (1) 5-Thiazolecarboxamide-*N*-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-, monohydrate; (2) *N*-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl]amino]thiazole-5-carboxamide hydrate. *CAS-863127-77-9*. INN. *Anticancer.* (Bristol-Myers Squibb) ✧*BMS-354825-03*



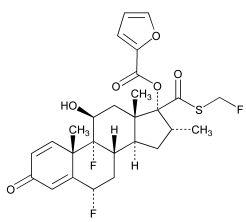
Denibulin Hydrochloride [*2006*] (den i bue′ lin). $C_{18}H_{19}N_5O_3S \cdot HCl$. 421.90. (1) Carbamic acid, [5-[[4-[[(2*S*)-2-amino-1-oxopropyl]amino]phenyl]thio]-1*H*-benzimidazol-2-yl]-, methyl ester, monohydrochloride; (2) Methyl [5-[[4-[[(2*S*)-2-aminopropanoyl]amino]phenyl]sulfanyl]-1*H*-benzimidazol-2-yl]carbamate monohydrochloride. *CAS-779356-64-8*. *Treatment of solid tumors.* (Medical Arts) ✧*MN-029*



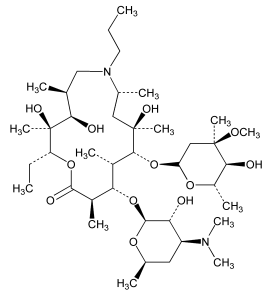
Fispemifene [*2006*] (fis pem′ i feen). $C_{26}H_{27}ClO_3$. 422.94. (1) Ethanol, 2-[2-[4-[(1*Z*)-4-chloro-1,2-diphenyl-1-butenyl]phenoxy]ethoxy]-; (2) 2-[2-[4-[(1*Z*)-4-Chloro-1,2-diphenylbut-1-enyl]phenoxy]ethoxy]ethanol.*CAS-341524-89-8*. INN. *Male hypogonadism, male urinary tract symptoms.* (Quatrx) ✧*HM-101; HM-101a*



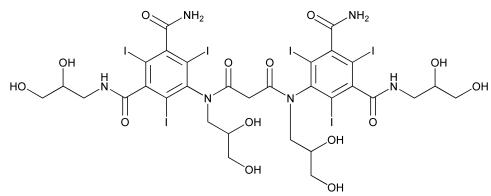
Fluticasone Furoate [*2006*] (floo tik′ a sone fur′ oh ate). $C_{27}H_{29}F_3O_6S$. 538.60. (1) Androsta-1,4-diene-17-carbothioic acid, 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-, *S*-(fluoromethyl) ester, (6α,11β,16α,17α)-; (2) 6α,9-Difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate; (3) (6α,11β,16α,17α)-6,9-Difluoro-17-(((fluoromethyl)thio)carbonyl)-11-hydroxy-16-methyl-3-oxoandrosta-1,4-dien-17-yl-2-furancarboxylate.*CAS-397864-44-7*. *Asthma, allergy, and chronic obstructive pulmonary disease.* (GlaxoSmithKline) ✧*GW685698X*



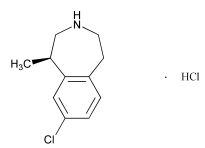
Gamithromycin [*2006*] (gam ith″ roe mye′ sin). $C_{40}H_{76}N_2O_{12}$. 777.04. (1) 1-Oxa-7-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-7-propyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-, (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-; (2) (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-7-propyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-7-azacyclopentadecan-15-one.*CAS-145435-72-9*. *Veterinary antibacterial.* (Merial) ✧*ML-1,709,460*



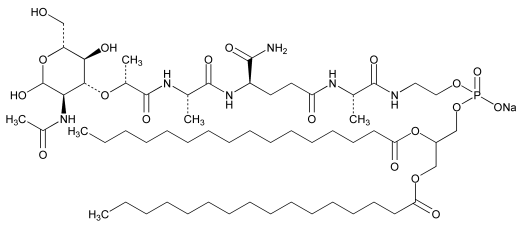
Iosimenol [*2006*] (eye′ oh sim′ e nol). $C_{31}H_{36}I_6N_6O_{14}$. 1478.08. (1) 1,3-Benzenedicarboxamide, 5,5′-(1,3-dioxo-1,3-propanediyl)-bis[(2,3-dihydroxypropyl)imino]]bis[*N*-(2,3-dihydroxypropyl)-2,4,6-triiodo-; (2) 5,5′-[Propanedioylbis[(2,3-dihydroxypropyl)imino]]bis[*N*-(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide]. *CAS-181872-90-2*. INN. *Iodinated x-ray contrast agent.* (Mallinckrodt Tyco Healthcare) ✧*MP-3047-04; BP-13; ICJ 3393*



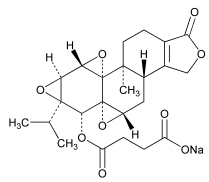
Lorcaserin Hydrochloride [*2006*] (lor ca ser′ in). $C_{11}H_{14}ClN \cdot HCl$. 232.15. (1) 1*H*-3-Benzazepine, 8-chloro-2,3,4,5-tetrahydro-1-methyl-, hydrochloride, (1*R*)-; (2) (1*R*)-8-Chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride. *CAS-846589-98-8*. *Anti-obesity* (*activate 5-HT$_{2c}$ receptor*). (Arena) ✧*APD356*



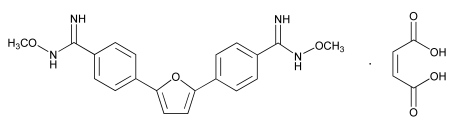
Mifamurtide [*2006*] (mif am′ ure tide). $C_{59}H_{108}N_6NaO_{19}P \cdot xH_2O$. 1259.48 (anhydrous). (1) L-Alaninamide, *N*-(*N*-acetylmuramoyl)-L-alanyl-D-α-glutaminyl-*N*-[(7*R*)-4-hydroxy-4-oxido-10-oxo-7-[(1-oxohexadecyl)oxy]-3,5,9-trioxa-4-phosphapentacos-1-yl]-, monosodium salt, hydrate; (2) 2-[[*N*-[(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(Acetylamino)-2,5-dihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-4-yloxy]propanoyl]-L-alanyl-D-isoglutaminyl-L-alanyl]amino]ethyl (2*R*)-2,3-bis(hexanoyloxy)-propyl sodium phosphate hydrate. *CAS-838853-48-8*. *Osteosarcoma.* (Immuno-Designed Molecules) ✧*L-MTP-PE*



Omtriptolide Sodium [*2006*] (ohm trip′ toe lide). $C_{24}H_{27}NaO_9$. 482.46. (1) Butanedioic acid, mono[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahydro-8b-methyl-6a-(1-methylethyl)-1-oxotrisoxireno[4b,5:6,7:8a,9]phenanthro[1,2-*c*]furan-6-yl] ester, sodium salt; (2) Sodium 4-[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-8b-methyl-6a-(1-methylethyl)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahydrotrisoxireno[4b,5:6,7:8a,9]phenanthro[1,2-*c*]furan-6-yl]-4-oxobutanoate. *CAS-195883-09-1*. *Anti-neoplastic.* (Pharma Mar) ✧*PG490-88Na*

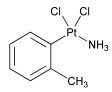


Pafuramidine Maleate [*2006*] (pa″ fur am′ i deen). $C_{20}H_{20}N_4O_3 \cdot C_4H_4O_4$. 480.47. (1) Benzenecarboximidamide, 4,4′-(2,5-furandiyl)bis[*N*-methoxy-, (2*Z*)]-2-butenedioate (1:1); (2) 4,4′-(Furan-2,5-diyl)bis(*N*-methoxybenzenecarboximidamide) (2*Z*)-2-butenedioate (1:1); (3) 2,5-Bis[4-(*N*-methoxyamidino)phenyl] furan monomaleate salt. *CAS-837369-26-3*. *Treatment of malaria, African sleeping sickness, and pneumocystis pneumonia.* (Cambrex Charles City) ✧*DB289*

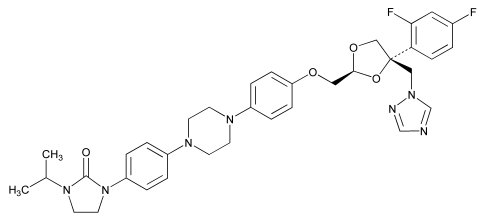


Pagibaximab [*2004*] (paj″ ee bax′ i mab). $C_{6462}H_{9996}N_{1728}O_{2028}S_{54}$. (10 Immunoglobulin G1, anti-(*Staphylococcus epidermidis* lipoteichoic acid) (human-mouse monoclonal heavy chain), disulfide with human-mouse monoclonal κ-chain, dimer; (2) Immunoglobulin G1, anti-(*Staphylococcus epidermidis* lipoteichoic acid) (human-mouse monoclonal HU96-110 heavy chain), disulfide with human-mouse monoclonal HU96-110 κ-chain, dimer. *CAS-595566-61-3*. INN. *Prevention of staphylococcal sepsis in premature neonates.* (GlaxoSmithKline) ✧*A110*

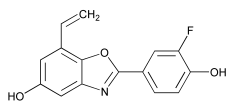
Picoplatin [*2006*] (pi″ koe pla′ tin). $C_6H_{10}Cl_2N_2Pt$. 376.14. (1) Platinum, amminedichloro(2-methylpyridine)-, (*SP*-4-3)-; (2) (*SP*-4-3)-Amminedichloro(2-methylpyridine)platinium. *CAS-181630-15-9*. INN; BAN. *Treatment of cancer.* (NeoRx) ✧*NX 473; ZD0473; AMD473*



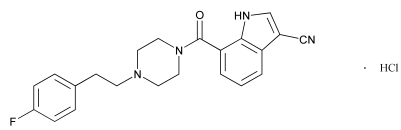
Pramiconazole [*2006*] (pram″ i kon′ a zole). $C_{35}H_{39}F_2N_7O_4$. 659.73. (1) 2-Imidazolidinone, 1-[4-[4-[4-[[(2*S*,4*R*)-4-(2,4-difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-3-(1-methylethyl)-; (2) 1-[4-[4-[4-[[(2*S*,4*R*)-4-(2,4-Difluorophenyl)-4-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-2-yl]methoxy]phenyl]piperazin-1-yl]-phenyl]-3-(1-methylethyl)imidazolidin-2-one.*CAS-219923-85-0*. *Antifungal agent.* (Barrier) ✧*R126638*



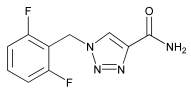
Prinaberel [*2006*] (prin a ber′ el). $C_{15}H_{10}FNO_3$. 271.29. (1) 5-Benzoxazolol, 7-ethenyl-2-(3-fluoro-4-hydroxyphenyl)-; (2) 7-Ethenyl-2-(3-fluoro-4-hydroxyphenyl)benzoxazol-5-ol. *CAS-524684-52-4*. *Treatment of arthritis.* (Wyeth) ✧*ERB-041*



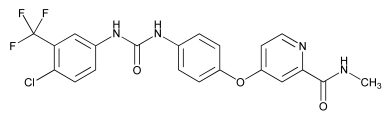
Pruvanserin Hydrochloride [*2006*] (prue van′ ser in). $C_{22}H_{21}FN_4O \cdot HCl$. 412.89. [Pruvanserin is INN.] (1) Piperazine, 1-[(3-cyano-1*H*-indol-7-yl)carbonyl]-4-[2-(4-fluorophenyl)ethyl]-, monohydrochloride; (2) 7-{4-[2-(4-fluorophenyl)ethyl]piperazine-1-carbonyl}-1*H*-indole-3-carbonitrile, monohydrochloride; (3) 7-{4-[2-(4-fluorophenyl)ethyl]piperazine-1-ylcarbonyl}-1*H*-indole-3-carbonitrile hydrochloride. *CAS-443144-27-2; CAS-443144-26-1* [pruvanserin]. *Insomnia, major depression, and schizophrenia.* (Lilly) ✧*LY2422347 HCl; LSN2420586*



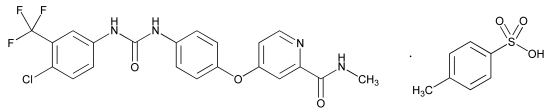
Rufinamide [*2000*] (roo fin′ a mide). $C_{10}H_8F_2N_4O$. 238.19. (1) 1*H*-1,2,3-Triazole-4-carboxamide, 1-[(2,6-difluorophenyl)methyl]-; (2) 1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide. *CAS-106308-44-5*. INN; BAN. *Treatment of partial-onset seizures and seizures in Lennox-Gastaut syndrome.* (Eisai Medical Research) ✧*CGP 33101; RUF 331; E2080; 60231/4*



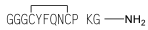
Sorafenib [*2006*] (soe raf′ e nib). $C_{21}H_{16}ClF_3N_4O_3$. 464.82. (1) 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-*N*-methyl-; (2) 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N^2-methylpyridine-2-carboxamide. *CAS-284461-73-0*. INN. *Treatment of cancer.* Nexavar (Bayer HealthCare); Xarelto (Bayer HealthCare) ✧*BAY 43-9006*



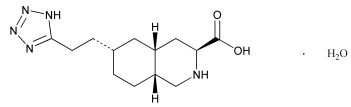
Sorafenib Tosylate [*2006*]. $C_{21}H_{16}ClF_3N_4O_3 \cdot C_7H_8O_3S$. 637.00. (1) 2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)-phenyl]amino]carbonyl]amino]phenoxy]-*N*-methyl-, mono(4-methylbenzenesulfonate); (2) 1-[4-Chloro-3-(trifluoromethyl)-phenyl]-3-[4-[[2-(methylcarbamoyl)pyridin-4-yl]oxy]phenyl]urea mono(4-methylbenzenesulfonate); (3) 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N^2-methylpyridine-2-carboxamide mono (4-methylbenzenesulfonate). *CAS-475207-59-1*. *Treatment of cancer.* Nexavar (Bayer HealthCare); Xarelto (Bayer HealthCare) ✧*BAY 54-9085*



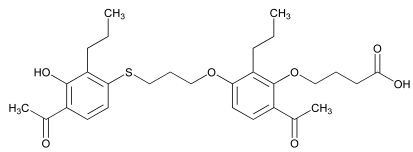
Terlipressin [*2006*] (ter″ li pres′ in). $C_{52}H_{74}N_{16}O_{15}S_2$. 1227.37. (1) *N*-[*N*-(*N*-Glycylglycyl)glycyl]-8-L-lysinevasopressin; (2) Glycylglycylglycyl[8-L-lysine]vasopressin. *CAS-14636-12-5*. INN; BAN; MI. *Vasoconstrictor* (*vasopressin derivative*). (Orphan Therapeutics)



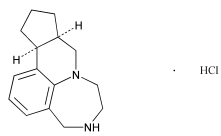
Tezampanel [*2006*] (tez am′ pan el). $C_{13}H_{21}N_5O_2 \cdot H_2O$. 297.35. (1) 3-Isoquinolinecarboxylic acid, decahydro-6-[2-(1*H*-tetrazol-5-yl)ethyl]-, monohydrate, (3*S*,4a*R*,6*R*,8a*R*)-; (2) (3*S*,4a*R*,6-*R*,8a*R*)-6-[2-(1*H*-Tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid monohydrate. *CAS-317819-68-4*. *Treatment of migraine, neuropathic pain.* (Torreypines Therapeutics) ✧*LY293558; NGX424*



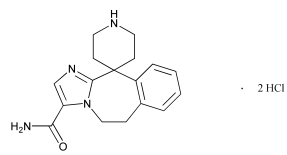
Tipelukast [*2006*] (tye″ pe loo′ kast). $C_{29}H_{38}O_7S$. 530.67. (1) Butanoic acid, 4-[6-acetyl-3-[3-[(4-acetyl-3-hydroxy-2-propylphenyl)thio]propoxy]-2-propylphenoxy]-; (2) 4-[6-Acetyl-3-[3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]propoxy]-2-propylphenoxy]butanoic acid. *CAS-125961-82-2*. *Treatment of asthma and interstitial cystitis.* (Medical Arts) ✧*KCA-757; MN-001*



Vabicaserin Hydrochloride [*2006*] (va bik″ a ser′ in). $C_{15}H_{20}N_2 \cdot HCl$. 264.79. (1) Cyclopenta[4,5]pyrido[3,2,1-*jk*][1,4]benzodiazepine, 4,5,6,7,9,9a,10,11,12,12a-decahydro-, monohydrochloride, (9a*R*,12a*S*)-rel-(−)-; (2) (−)-(9a*R**,12a*S**)-4,5,6,7,9,9a,10,11,12,12a-Decahydrocyclopenta[4,5]pyrido[3,2,1-*jk*][1,4]benzodiazepine monohydrochloride. *CAS-620948-34-7*. *Treatment of schizophrenia.* (Wyeth) ✧*SCA-136*



Vapitadine Dihydrochloride [*2006*] (va pi′ ta deen). $C_{17}H_{20}N_4O \cdot 2HCl$. 369.29. (1) Spiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-3-carboxamide, 5,6-dihydro-, dihydrochloride; (2) 5,6-Dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazepine-11,4′-piperidine]-3-carboxamide dihydrochloride. *CAS-279253-83-7*. *Treatment of atopic dermatitis.* (Barrier) ✧*R129160*



Veliflapon [*2006*] (vel″ i flap′ on). $C_{23}H_{23}NO_3$. 361.43. (1) Benzeneacetic acid, α-cyclopentyl-4-(2-quinolinylmethoxy)-, (α*R*)-; (2) (+)-(*R*)-Cyclopentyl-2-[4-(quinolin-2-ylmethoxy)phenyl]acetic acid. *CAS-128253-31-6*. *Prevention of acute cardiovascular events.* (Debio Recherche Pharmaceutique, Switzerland) ✧*DG-031; Bay x 1005*

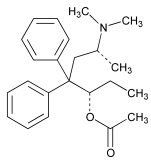
Nomenclature

Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

Alphacetylmethadol

Change the chemical structure to read:



Alphameprodine

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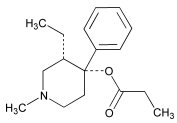

Bumecaine

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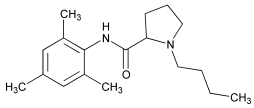

Cefuracetime

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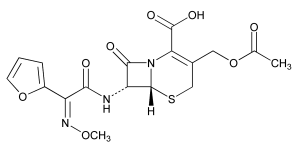

Darunavir

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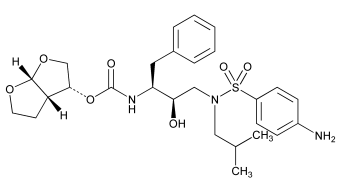

Gemcitabine

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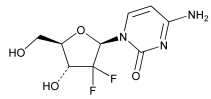

Gemcitabine Hydrochloride

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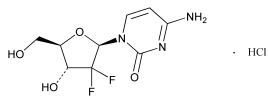
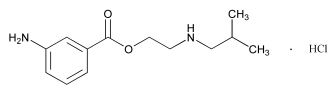


Metabutethamine Hydrochloride

Add the chemical information and structure to read:

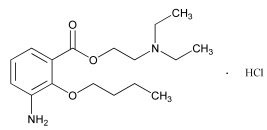
$C_{13}H_{20}N_2O_2 \cdot HCl$. 272.77. 2-(Isobutylamino)ethanol *m*-aminobenzoate, hydrochloride.



Metabutoxycaine Hydrochloride

Add the chemical information and structure to read:

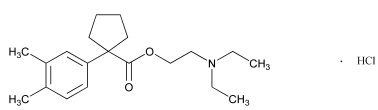
$C_{17}H_{28}N_2O_2 \cdot HCl$. 344.88. 2-(Diethylamino)ethyl 3-amino-2-butoxybenzoate hydrochloride.



Metcaraphen Hydrochloride

Add the chemical information and structure to read:

$C_{20}H_{31}NO_2 \cdot HCl$. 353.93. (1) Cyclopentanecarboxylic acid, 1-(3,4-xylyl)-, 2-(diethylamino)ethyl ester, hydrochloride; (2) 2-(Diethylamino)ethyl 1-(3,4-dimethylphenyl)cyclopentanecarboxylate hydrochloride.



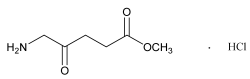
Methacholine Bromide

Add the chemical information to read:

$C_8H_{18}BrNO_2$. 240.14.

Methyl Aminolevulinate Hydrochloride

Add the chemical structure to read:



Meticrane

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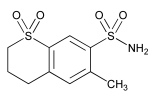

Midazolam Maleate

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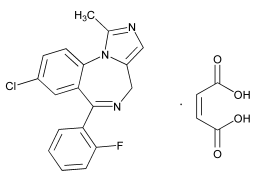

Mideplanin

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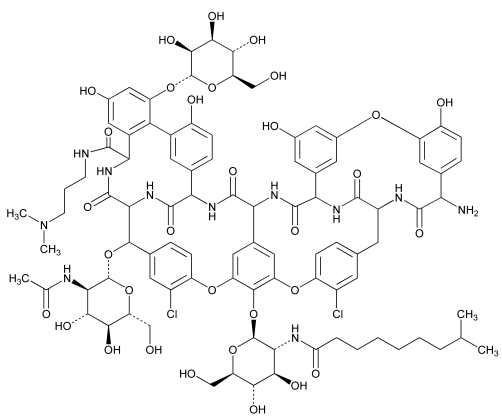
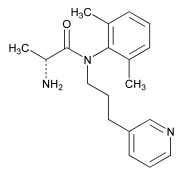


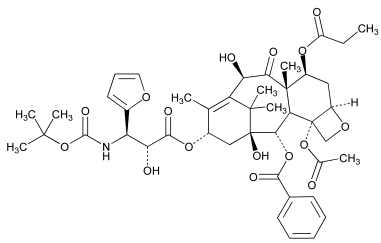
Milacainide

Add the chemical structure to read:



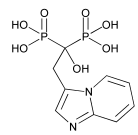
Milataxel

Add the chemical structure to read:



Minodronic Acid

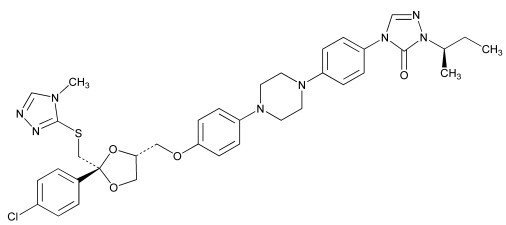
Add the chemical structure to read:



Mitratapide

Add the molecular weight and change the chemical structure to read:

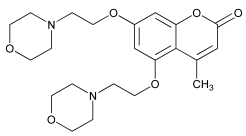
717.28.



Moxicoumone

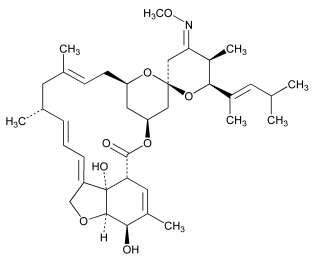
Change the chemical name and structure to read:

4-Methyl-5,7-bis(2-morpholinoethoxy)coumarin.



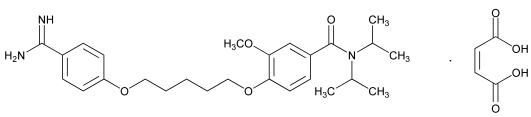
Moxidectin

Change the chemical structure to read:



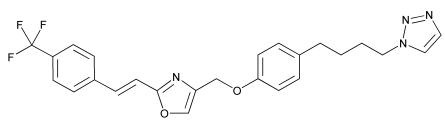
Moxilubant Maleate

Add the chemical structure to read:



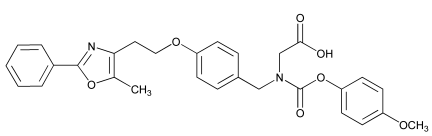
Mubritinib

Add the chemical structure to read:



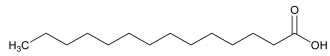
Muraglitazar

Add the chemical structure to read:



Myristic Acid

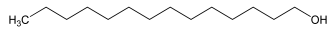
Add the chemical structure to read:



Myristyl Alcohol

Add the chemical information and structure to read:

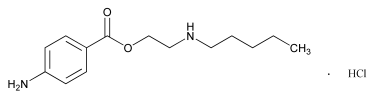
$C_{14}H_{30}O$. 214.39. Tetradecanol. *CAS-112-72-1.*



Naepaine Hydrochloride

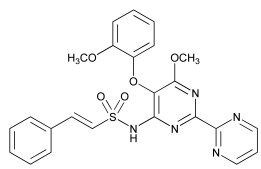
Add the chemical information and structure to read:

$C_{14}H_{22}N_2O_2 \cdot HCl$. 286.80. (1) Benzoic acid, *p*-amino-, 2-(pentylamino)ethyl ester, hydrochloride; (2) 2-(pentylamino)ethyl 4-aminobenzoate.



Nebentan

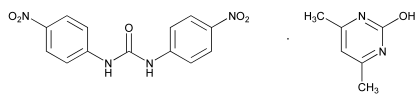
Add the chemical structure to read:



Nicarbazin

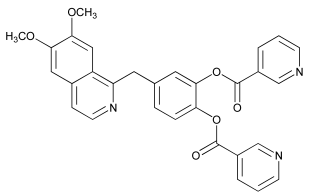
Change the chemical information and add the structure to read:

$C_{13}H_{10}N_4O_5 \cdot C_6H_8N_2O$. 1,3-Bis(4-nitrophenyl)urea complex with 4,6-dimethylpyrimidin-2-ol.



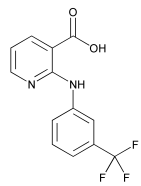
Niceverine

Change the chemical structure to read:



Niflumic Acid

Add the chemical structure to read:



Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO).

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

Recommended International Nonproprietary Names

The following 52 nonproprietary names have been selected by the World Health Organization (WHO) as Recommended International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information,* Vol. 20, No. 1, 2006.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Apixaban	Ispronicline	Peforelin	Tasidotin
Apratastat	Istaroxime	Plerixafor	Tasquinimod
Arasertaconazole	Lecozotan	Plitidepsin	Terutroban
Bapineuzumab	Levolansoprazole	Pradefovir	Tesetaxel
Brivaracetam	Manitimus	Radequinil	Tretazicar
Caricotamide	Mapatumumab	Rimacalib	Udenafil
Catumaxomab	Nebicapone	Rivanicline	Valategrast
Dapiclermin	Nerispirdine	Rivenprost	Valopicitabine
Dexlansoprazole	Ofatumumab	Satavaptan	Volociximab
Dianicline	Olmesartan	Seletracetam	Yttrium (^{90}Y) Tacatuzumab Tetraxetan
Ecallantide	Padoporfin	Sipoglitazar	Zabofloxacin
Ertumaxomab	Pagibaximab	Sunitinib	Zalutumumab
Esmirtazapine	Paliroden	Surinabant	
Fosfluridine Tidoxil			

Nomenclature

INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

[*Note—This index covers Vol. 32 No. 1, pp. 1–224; Vol. 32 No. 2, pp. 225–704; Vol. 32 No. 3, pp. 705–987; Vol. 32 No. 4, pp. 989–1388; Vol. 32 No. 5, pp. 1389–1617*]

GENERAL NOTICES AND REQUIREMENTS

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PHARMACOPEIAL FORUM VOL. 32 NO. 6 NOV.–DEC. 2006

* The *USP–NF* (*USP 31–NF 26*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

Please address comments on *PF* content to Executive Secretariat
USP–NF, 12601 Twinbrook Pkwy.,
Rockville, MD 20852

Telephone: 1-301-816-8345
Fax: 1-301-816-8373
http://www.usp.org

Pharmacopeial Forum is covered in *Current Contents/Life Sciences* and in the *Science Citation Index (SCI),* in *International Pharmaceutical Abstracts*, and in *Current Awareness in Biological Sciences.*

The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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Our subscribers' records and publication labels are computer-generated. Please send your new address, and your latest label, or an exact copy of it, to: USPC, *PF* Customer Service Dept., 12601 Twinbrook Parkway, Rockville, MD 20852.
Fax: (301) 816-8148.

STANDARDS DEVELOPMENT

This section presents an overview of the public review and comment process, conducted through *Pharmacopeial Forum* (*PF*), for the development of official pharmaceutical standards.

USP publishes *Pharmacopeial Forum* (*PF*) bimonthly as the working vehicle of the USP Council of Experts. *PF* provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the *United States Pharmacopeia* and the *National Formulary* (*USP–NF*).

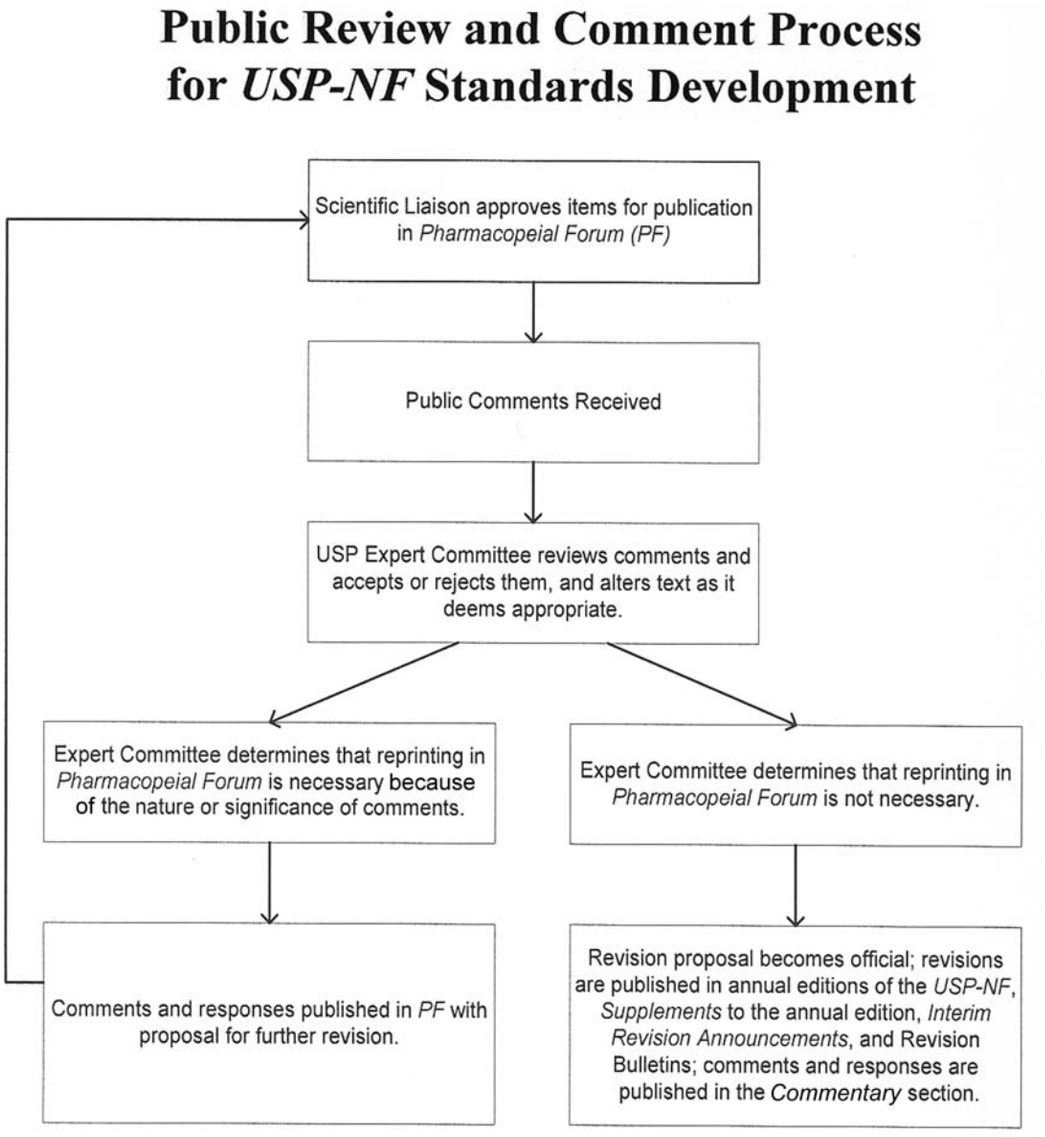
PF includes the following:

1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official and binding before the publication of the next *USP–NF* or *Supplement* (*Interim Revision Announcement*)

USP welcomes comments and data on potential, proposed, or official standards.* Comments, along with USP's responses, will be published either in *PF Briefings*, the *Commentary* section of *PF*, the *Commentary* section of *Supplements* to *USP–NF*, or the *Commentary* section of *USP–NF*.

* If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before the section *Chromatographic Reagents Used in USP–NF and PF*.

The chart below shows the public review and comment process and its relationship to standards development.



Questions on the process should be addressed to Director, Executive Secretariat, U.S. Pharmacopeia, 12601 Twinbrook Parkway, Rockville, MD 20852 (e-mail: execsec@usp.org).

HOW TO USE *PF*

This section provides descriptions of the various parts of *PF*. It also includes *Committee Designations* and the *Staff Directory.*

The content of the different sections of *PF* is briefly described below. A more detailed description of each section is provided at the beginning of that section. A general description of the types and amount of information expected in a *Request for Revision* is available in the *Guideline for Submitting Requests for Revision to the USP–NF* on the USP website (www.usp.org/USPNF/submitMonograph/subGuide.html).

Proposed and Adopted Revisions to the *USP–NF*

Section	Content	How Readers Can Respond
Pharmacopeial Previews Early ideas for revisions	•BRIEFING: Scientific rationale for potential inclusion or change. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. •Potential revisions not yet targeted for official adoption that require a longer public review and comment process because of issues such as: — the controversial nature of an item; — the application of new technologies that require further study; and — articles produced by multiple sources.	Review drafts and provide comments to the appropriate staff liaison cited in the *Briefing* preceding each *Preview.*
In-Process Revision Revisions targeted for adoption	•BRIEFING: Scientific rationale for proposed changes. May include other information useful to the analyst such as the brand name of the column used in developing the proposed procedure and the USP scientific staff liaison who handled the issue. •New and revised standards that have been approved for publication by the appropriate USP Committee when it is considering whether to advance standards to official status (see *Standards Development*). New or revised text is marked with symbols (■ or ● or ▲) to specify the tentative earliest date on which the revision would be officially adopted.	Review material and send comments promptly to USP staff liaison (see the *Staff Directory*). Guidelines on how to comment are found at the end of the *Policies and Announcements* section.
Harmonization Items the Pharmacopeial Discussion Group (PDG) is working to harmonize internationally	•BRIEFING: Scientific rationale for the potential inclusion or change or for the proposed change. The designated stage of harmonization. The stage determines whether an item appears under *Pharmacopeial Previews* or under *In-Process Revision,* both separate sections of *Harmonization.* •For *In-Process Revision,* new or revised text is marked with symbols (■) to specify the tentative, earliest date on which the revision would be officially adopted.	Review material and provide comments to the appropriate staff liaison cited in the *Briefing* preceding each *Preview* or *In-Process Revision.*
Interim Revision Announcement Adopted standards	Standards that have been adopted and will become officially binding on the specified date. Effective date is specified in the section's introductory page or within parentheses following a particular item. New or revised text is set off by the symbols ●.	Review to see if affected by any of the changes. Note effective date when standards become official and ensure compliance.
Pending Proposals	In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *PF* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in either the *USP–NF*, its supplements, or an *IRA*. Those items that have not yet been adopted are still pending.	Review items to track pending proposals.
Canceled Proposals	Canceled proposals are items that were published in *PF* and were pending, but have since been canceled. Note that canceled proposals may be republished to be considered in the future for adoption into the *USP–NF.*	Review items to track canceled proposals.

Other Sections

Committee Designations
Names of the committees (composed of volunteer scientific experts) that USP staff work with on the development of standards.

Staff Directory
Names of all USP scientific staff liaisons with contact information.

Policies and Announcements
- General scientific and policy issues affecting *USP–NF* standards and processes
- Update on standards-related issues being considered by USP
- Where to find summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules

Stimuli to the Revision Process
- Articles on standards development issues authored by the USP Council of Experts, USP staff, or other interested parties
- Discussions of issues on which USP desires public input prior to further development

Nomenclature
- Latest adopted United States Adopted Names (USAN) and International Nonproprietary Names (INN) for drugs
- Revisions to existing names as a supplement to the *USP Dictionary of USAN and International Drug Names*
- Suggested, proposed, and recommended USAN and INN
- Information on how nonproprietary drug names are devised
- Articles relevant to compendial nomenclature issues

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Cumulative directory for the content of all issues of *PF* beginning with *PF* 32(1).

Reference Standards Catalog
List of official USP Reference Standards specified in *USP–NF*, along with availability and ordering information.

Chromatographic Reagents Used in USP–NF and Pharmacopeial Forum
Update of chromatographic reagents based on the proposals published in this issue of *PF*.

EXPERT COMMITTEE DESIGNATIONS*

2005–2010

AER	Aerosols
BB BBP	B&B Blood and Blood Products
BB CGT	B&B Cell, Gene, and Tissue Therapies
BB PP	B&B Proteins and Polysaccharides
BB VV	B&B Vaccines and Virology
BPC	Biopharmaceutics
CRX	Compounding Pharmacy
DS-BA	Dietary Supplements—Bioavailability
DSB	Dietary Supplements—Botanicals
DS-GC	Dietary Supplements—General Chapters
DSI	Dietary Supplements—Information
DSN	Dietary Supplements—Non-Botanicals
EM1	Excipient Monographs 1
EM2	Excipient Monographs 2
EGC	Excipient General Chapters
GC	General Chapters
GTMDB	General Toxicity and Medical Device Biocompatibility
IH	International Health
MSA	Microbiology and Sterility Assurance
MD-ANT	Monograph Development—Antibiotics
MD-AA	Monograph Development—Antivirals and Antimicrobials
MD-CV	Monograph Development—Cardiovascular
MD-CCA	Monograph Development—Cough, Cold, and Analgesics
MD-GRE	Monograph Development—Gastrointestinal, Renal, and Endocrine
MD-OOD	Monograph Development—Ophthalmology, Oncology, and Dermatology
MD-PP	Monograph Development—Psychiatrics and Psychoactives
MD-PS	Monograph Development—Pulmonary and Steroids
NOM	Nomenclature
P&S	Packaging and Storage
PPI	Parenteral Products—Industrial
PDF	Pharmaceutical Dosage Forms
PW	Pharmaceutical Waters
SMU	Safe Medication Use
SCC	Sterile Compounding
RMI	Radiopharmaceuticals and Medical Imaging Agents
RI	Radiopharmaceutical Information
RS	Reference Standards
STAT	Statistics

VET	Veterinary Drugs
VMI	Veterinary Medicine Information

* **HDQ** Indicates USP Headquarters items.

STAFF DIRECTORY

This updated directory reflects assignment changes based on 2005–2010 Expert Committees. The general USP telephone number, (301) 881-0666, may still be used for general inquiries or when a particular Expert Committee is not identified. The fax number is (301) 816-8373.

STAFF	E-MAIL	PHONE	ASSIGNMENT
Clydewyn M. Anthony, Ph.D., Scientist	cma@usp.org	(301) 816-8139	Monograph Development—Cough, Cold, and Analgesics (MD-CCA)
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Claudia C. Okeke, Ph.D., Scientific Fellow, Patient Safety	cco@usp.org	(301) 816-8243	Sterile Compounding (SCC)
Horacio Pappa, Ph.D., Senior Scientist and Latin American Liaison	hp@usp.org	(301) 816-8319	General Chapters (GC); Statistics (STAT)
W. Larry Paul, Ph.D., Scientific Fellow	wlp@usp.org	(301) 816-8331	Nomenclature (NOM)
Denise Penn, R.Ph., Drug Information Specialist	dsp@usp.org	(301) 816-8392	Drug Information
Deborah G. Perfetto, Pharm.D., Director, Information Programs	dgp@usp.org	(301) 816-8317	
Sujatha Ramakrishna, Ph.D., Scientist	syk@usp.org	(301) 816-8349	Monograph Development—Cardiovascular (MD-CV)
Ravi Ravichandran, Ph.D., Senior Scientist	rr@usp.org	(301) 816-8330	Monograph Development—Psychiatrics and Psychoactives (MD-PP)
Gary E. Ritchie, M.S., Scientific Fellow for PAT	ger@usp.org	(301) 816-8353	General Chapters (GC); Pharmaceutical Waters (PW); Statistics (STAT)
Karen A. Russo, Ph.D., Director, Small Molecules and Monograph Acquisition	kar@usp.org	(301) 816-8379	Monograph Acquisition and Infrastructure

STAFF	E-MAIL	PHONE	ASSIGNMENT
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Dandapantula Sarma, Senior Scientist	dns@usp.org	(301) 816-8354	Dietary Supplements Information (DSI)
Stefan P. Schuber, Ph.D., Director, Scientific Reports	sps@usp.org	(301) 816-8551	
Maged H. M. Sharaf, Ph.D., Senior Scientist	mhs@usp.org	(301) 816-8318	Dietary Supplements—Botanicals (DSB); Dietary Supplements—General Chapters (DS-GC)
Catherine M. Sheehan, Director, Excipients	cxs@usp.org	(301) 816-8262	Excipient Monographs 1 (EM1); Excipient General Chapters (EGC)
Anita Y. Szajek, Ph.D., Senior Scientist	aey@usp.org	(301) 816-8325	B&B Blood and Blood Products (BB BBP)
Radhakrishna S. Tirumalai, Ph.D., Senior Scientist	rst@usp.org	(301) 816-8339	General Toxicity and Medical Device Biocompatibility (GTMDB); Microbiology and Sterility Assurance (MSA)
Beryl Voigt, Director, Executive Secretariat	bev@usp.org	(301) 816-8155	
Hong Wang, Ph.D., Senior Scientific Associate	hw@usp.org	(301) 816-8351	Excipient Monographs 2 (EM2); Excipient General Chapters (EGC)
Andrzej Wilk, Ph.D., Scientist	aw@usp.org	(301) 816-8305	Radiopharmaceuticals and Medical Imaging Agents (RMI); Radiopharmaceutical Information (RI)
Kahkashan Zaidi, Ph.D., Senior Scientist	kxz@usp.org	(301) 816-8269	Aerosols (AER); General Chapters (GC)

POLICIES AND ANNOUNCEMENTS

This section includes information about general scientific and policy issues that may have an impact on *USP–NF* standards and processes and announcements about issues being considered by USP. This section also includes publication and comment schedules.

USP TO PUBLISH FOOD CHEMICALS CODEX. The U.S. Pharmacopeia (USP) will assume responsibility for publishing and distributing future editions of the *Food Chemicals Codex,* a compendium of standards that promotes the quality and safety of food additives such as preservatives, flavoring, coloring, and nutrients.

First published in 1966, the *Food Chemicals Codex* is cited in U.S. law and widely used for industry self-regulation and regulatory oversight by the Food and Drug Administration. The *Food Chemicals Codex,* currently in its fifth edition, has been an activity of the Food and Nutrition Board of the Institute of Medicine, with monographs developed by the voluntary experts of the Committee on Food Chemicals Codex.

USP anticipates publishing the sixth edition in the summer of 2007. Until publication of the sixth edition, the *Food Chemicals Codex: Fifth Edition* and its first supplement will continue to be the authoritative source, available through the National Academies Press at www.nap.edu or via electronic subscription at http://www.knovel.com.

The process for establishing standards for the *Food Chemicals Codex* will mirror that used for the *United States Pharmacopeia* and *National Formulary (USP–NF).* This process includes publication of proposed standards for public review and comment, and decision-making by the Expert Committees of the USP Council of Experts, a distinguished body of voluntary experts who are responsible for USP's scientific determinations and standards-setting.

For more information, contact Catherine Sheehan, Director, Excipients (301-816-8262 or cxs@usp.org).

USP PARTNERS WITH THE INDIAN PHARMACOPOEIA. On August 1, 2006, the Indian Pharmacopoeia Commission (IPC) and USP signed a Memorandum of Understanding (MoU) to promote greater cooperation through the exchange of information and to increase awareness of the importance of the quality and safety of medicines. The signing ceremony took place at the Nirman Bhavan, Ministry of Health and Family Welfare in New Delhi. The MoU provides for IPC and USP collaboration on regional scientific conferences, seminars, training, and workshops. It will also facilitate communication and activity to obtain the necessary information and chemicals to develop monographs and reference standards of mutual interest, and promote collaboration on testing for reference standards. The MoU is another example of USP's commitment to working with partners in India. The IPC is a member organization of the USP Convention.

IN MEMORIAM.

William W. Wright, Ph.D.

It is with great sorrow that USP reports the passing of a pharmacopeial legend, Dr. William Wynn Wright, on July 15, 2006.

For those of us who were privileged to know and work closely with Dr. Wright, his death also represents the passing of an era. He was an internationally recognized expert in antibiotics and was instrumental in the transfer of antibiotic standards from FDA to USP. Following a career of 33 years at the Food and Drug Administration, during which he advanced to become deputy director of the Office of Pharmaceutical Research and Testing overseeing certification of antibiotics and insulin, Dr. Wright served for over 25 years at USP as the Scientific Liaison for the Antibiotics and Chemistry Subcommittee/ Pharmaceutical Analysis 7 Expert Committee. He also served as a U.S. representative and an expert on pharmaceutical sciences for the World Health Organization for 30 years. In 2004, he was recognized by two associations in India for his contributions and services to the field of pharmaceutical analytical chemistry.

Many were impressed by his vast knowledge of antibiotic drugs and compendial standards, but they were even more impressed by his refined and courteous manner of personal conduct. He always made time to help others, and many within USP remember him as a mentor and friend. He talked with pride about his children, grandchildren and great-grandchildren and spoke fondly of his wife, Tess, and their life together.

Dr. Wright's charm and graciousness to all will be a legacy forever. Knowing him enriched all of our lives.

USP RULES AND PROCEDURES OF THE COUNCIL OF EXPERTS REVISED, REFLECTING CHANGES TO THE STANDARDS-SETTING PROCESS. The 2005–2010 USP Council of Experts has voted to approve changes to the *Rules and Procedures of the 2005–2010 Council of Experts,* which were originally adopted on a provisional basis in April 2005. Pursuant to USP's Bylaws, the revised Rules and Procedures were made available to USP's Convention membership for comment, reviewed and approved by USP's Board of Trustees and formally adopted by the Council of Experts. The effective date for these changes was September 1, 2006.

While the revised *Rules and Procedures* and details about the changes are posted on USP's website (http://www.usp.org/USPNF/notices/), the following summarizes those changes:

- A strengthened ability for Expert Committees to make final decisions on standards without multiple resubmissions to *PF*.
- An increased responsibility by USP to respond to public comments, both to the commenter and in the *USP–NF* or *Supplement*.
- The ability for increased use of the USP website for the standards-setting process.
- Provisions for Information Expert Committees, which were previously omitted due to the delay in electing Information Expert Committee chairs and members.
- Provisions for several new USP initiatives, including Standards for Articles Legally Marketed Outside the U.S. (SALMOUS), Standards for Articles Pending FDA Approval (SAPFA), and *USP–NF* translations.
- Provisions to enable a third classification of observers, FDA Observers, to participate in USP Expert Committee meetings.
- Miscellaneous clarifications/corrections.

Please direct any comments or questions on this topic to Susan de Mars, Chief Legal Officer (301-816-8296 or sdm@usp.org).

USP DISCONTINUES USE OF INTENT TO COMMENT FORM. Beginning with the next issue of *Pharmacopeial Forum,* the Intent to Comment form will no longer exist. Previously, the comment period for each issue of *PF* was 60 days. In 2005, the comment period was increased to 90 days. With this expansion in the comment period, it was no longer viewed as necessary or appropriate to allow further extensions of time to comment through the Intent to Comment form. In order for a comment on a proposed revision to be considered by the Expert Committee in determining whether and how a proposed revision should proceed, it must be received within the 90-day comment period.

Please direct any comments or questions on this topic to Beryl Voigt, Director, Executive Secretariat (301-816-8155 or execsec@usp.org).

IMPLEMENTATION PERIOD FOR UPCOMING OFFICIAL REVISIONS TO THE *USP–NF* EXTENDED. To provide additional time to adopt revisions made to the compendia, USP is pleased to announce that effective beginning with the publication of *USP 30–NF 25,* implementation periods for revisions to official text in *United States Pharmacopeia–National Formulary (USP–NF)* and its *Supplements* are being extended. This change responds to stakeholder requests (see the *Pharmacopeial Forum (PF)* 31(2) *Stimuli* article, "The USP Revision Process: Recommendations for Enhancements"). As a result of this change, users will have six months from the publication date to implement new official texts as opposed to the previous 60-day period. *USP 29–NF 24* remains official until May 1, 2007. The complete revised Publication Schedule for *USP 30–NF 25* reflecting this new six-month implementation period is outlined below.

Publication Schedule for *USP 30–NF 25*

***USP–NF* Publication**	**Publication Date**	**Official Date**
USP–NF (Book)	November 2006	May 1, 2007
Supplement One	February 2007	August 1, 2007
Supplement Two	June 2007	December 1, 2007

Users may implement the newly official texts prior to the official date and the use becomes mandatory on the official date.

Please direct any comments or questions on this topic to Beryl Voigt, Director, Executive Secretariat (301-816-8155 or execsec@usp.org).

ERRATA FOR SPANISH EDITION OF *USP–NF* TO APPEAR ON WEBSITE. A Spanish version of the list of errata and corrections to the *Spanish Edition* of the *USP–NF* is available on the USP Spanish website. The errata are presented as a cumulative table and, if necessary, will be updated concurrently with every issue of *PF*. This information will also be published in each *Supplement* of the *Spanish Edition* of *USP–NF* and will appear in its corrected form in a future annual edition of these compendia. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

CATALOG TO BE REMOVED FROM *PHARMACOPEIAL FORUM* PRINT PUBLICATION. Starting with *Pharmacopeial Forum (PF)* 33(1), the *USP Catalog* will no longer be included in the back of the publication. This change was made to reduce the bulk of the publication and, therefore, increase ease of handling and use.

The *USP Catalog* is still available in online and stand-alone print versions. Online bi-monthly and daily catalogs can be accessed at www.usp.org/referenceStandards/catalog.html. To receive the *USP Catalog* in print (via postal mail) along with monthly e-mail alerts that will keep you informed about new Reference Standards, availability, and current lots, send an e-mail to marketing@usp.org or call 301-816-8237.

STIMULI ARTICLES TO BE POSTED ON USP'S WEBSITE. Starting in January 2007, the *Stimuli* articles that are published in *Pharmacopeial Forum* will be simultaneously published on USP's website. Look for them at www.usp.org. For more information, please contact Stefan Schuber, Ph.D., Director, Scientific Reports (301-816-8551 or sps@usp.org).

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education courses offer specialized instruction for chemists, other scientists, and professionals in the pharmaceutical and allied industries. USP scientists, who play a key role in establishing official USP standards, teach these courses and provide expert insights on the practical applications of official test procedures and best practices in using the *USP–NF* and other USP resources. The courses also give participants an opportunity to learn how to get involved in USP's standards-setting processes and the benefits of participating in standards development. Courses offered in 2006 are listed below. For more information and to register, visit www.usp.org/goto/pe. To discuss how USP can bring courses to a location of your choice, call 301-816-8589, or e-mail PharmacopeialEducation@usp.org.

Calendar of Forthcoming Pharmacopeial Education Courses as of September 1, 2006

Date	Name of Course	Location	Price
The Americas			
16-Nov-06	Introduction to HPCL	Raleigh, NC	$450
30-Nov-06	Effectively Using the USP–NF—Sessions I & II	San Francisco, CA	$595
6-Dec-06	Effectively Using the USP–NF—Sessions I & II	Cambridge, MA	$595
7-Dec-06	Analytical Method Validation	Dallas, TX	$595
Europe/ Middle East/ Africa/ India			
7-Nov-06	Analytical Method Validation	Milan, Italy (with Nova Chimica)	[2]
8-9 Nov-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for Italian)	Milan, Italy (with Sotax)	[1]
14-15 Nov-06	Fundamentals of Dissolution—Lecture and Laboratory (in English with assistance for Italian)	Rome, Italy (with Sotax)	[1]

[1] Registration handled by:
Sotax AG
Binningerstrasse 106
CH-4123 Allschwil, Switzerland
Phone: +41 61 487 54 54
Fax: +41 61 482 13 31
E-mail: sales@sotax.ch

[2] Registration handled by:
Nova Chimica
Via Galileo Galilei, 47
20092 Cinisello Balsamo (MI) Italy
Phone: +39 (02) 66045392
Fax: +39 (02) 66045394
E-mail: info@novachimica.com

VISIT THE USP WEB SITE AT ⟨http://www.usp.org⟩. Various resources related to Pharmacopeial standards are presented, including highlights from *PF*.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia, with a copy to USP, for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the European
Pharmacopoeia Commission
B.P. 907
F 67029 Strasbourg Cedex 1
France

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

HOW TO SUBMIT COMMENTS. The USP welcomes and encourages interested parties to submit comments and data regarding potential, proposed, or adopted (official) standards. Submissions concerning a particular item that has appeared in an issue of *PF* should be submitted to the appropriate USP scientific staff liaison identified at the end of the *Briefing* accompanying each item. To submit comments and data to a liaison, use the e-mail address and telephone numbers listed in the *Staff Directory* included in every *PF*.

Please note that *USP–NF* is being published in an annual edition with one main book and two *Supplements* a year. In addition, the schedule provided below will repeat every year so that users will know what to expect and become familiar with the deadlines.

For general inquiries or in cases where a particular liaison is not identified, use the general USP telephone number 301-881-0666 or FAX number 301-816-8373.

***PHARMACOPEIAL FORUM* PUBLIC REVIEW AND COMMENT PERIOD DEADLINES.** The full year's listing of comment period deadlines and the targeted official publications appears below. In accordance with the Rules and Procedures of the 2005–2010 Council of Experts, USP has implemented a 90-day comment period by providing a deadline for each issue of *PF* unless otherwise stated in the individual briefing. As previously indicated, due to the comment deadlines extension, the Intent to Comment form will no longer be used and will be removed from *PF*.

The listing of comment period deadlines and the targeted official publications appears below.

Pharmacopeial Forum	Comment Deadline	Targeted Official Publication	Publication Date	Official Date
PF 32(4)	October 16, 2006	*USP 30–NF 25 2nd Supplement*	June 2007	December 2007
PF 32(5)	December 15, 2006			
PF 32(6)	February 15, 2007	*USP 31–NF 26*	November 2007	May 2008
PF 33(1)	April 16, 2007			
PF 33(2)	June 15, 2007	*USP 31–NF 26 1st Supplement*	February 2008	August 2008
PF 33(3)	August 15, 2007			
PF 33(4)	October 15, 2007	*USP 31–NF 26 2nd Supplement*	June 2008	December 2008
PF 33(5)	December 15, 2007			

All official revisions are published in the annual edition or *Supplements* to *USP–NF* (twice yearly). Between these publications, official revisions are published in *PF* in the *Interim Revision Announcement;* these revisions are also incorporated in the upcoming *Supplement.* The official publication in which an *IRA* is incorporated will depend upon publication deadlines. The 5th *IRA* and the 6th *IRA* will not appear until *Supplement 1*. See table below. The electronic version of *USP–NF* is updated as each *Supplement* becomes available and, therefore, contains all official text up to and including the contents of the latest *Supplement.* The new table below outlines the publications and their release and official dates, and the book or supplement which supersedes them.

Publication Schedules

Publication	Release Date	Official Date	Superseded by
4th *IRA* [*PF* 32(4)]	July 1, 2006	Aug. 1, 2006	*USP 30–NF 25*
5th *IRA* [*PF* 32(5)]	Sept. 1, 2006*	Oct. 1, 2006*	*1st Supplement*
6th *IRA* [*PF* 32(6)]	Nov. 1, 2006*	Dec. 1, 2006*	*1st Supplement*
USP 30–NF 25	Nov. 1, 2006*	May 1, 2007*	*1st Supplement*
IRA [*PF* 33(1)]	Jan. 1, 2007*	Feb. 1, 2007*	*2nd Supplement*
1st Supplement	Feb. 1, 2007*	Aug. 1, 2007*	*2nd Supplement*
IRA [*PF* 33(2)]	Mar. 1, 2007*	Apr. 1, 2007*	*2nd Supplement*
IRA [*PF* 33(3)]	May 1, 2007*	June 1, 2007*	*USP 31–NF 26*
2nd Supplement	June 1, 2007*	Dec. 1, 2007*	*USP 31–NF 26*
IRA [*PF* 33(4)]	July 1, 2007*	Aug. 1, 2007*	*USP 31–NF 26*
IRA [*PF* 33(5)]	Sept. 1, 2007*	Oct. 1, 2007*	*1st Supplement to USP 31– NF 26*
IRA [*PF* 33(6)]	Nov. 1, 2007*	Dec. 1, 2007*	*1st Supplement to USP 31– NF 26*
USP 31–NF 26	Nov. 1, 2007*	May 1, 2008*	*1st Supplement to USP 31– NF 26*

* Tentative

PRIORITY NEW MONOGRAPH ITEMS. USP is seeking monographs for the following drug substances and drug products that are or soon will be off patent and thus are of the highest priority. USP also is seeking monographs for the excipients listed below. Monographs are marked received upon receipt of monograph proposal. Received monographs are removed from this list upon publication in *Pharmacopeial Forum.* (This list has been updated as of September 1, 2006.) For additional information, contact Karen A. Russo, Ph.D., kar@usp.org. Monograph sponsors should consult USP's *Guideline for Submitting Requests for Revision to the USP–NF.*

Noncomplex Actives (Drug Substances)

Acarbose	Alatrofloxacin Mesylate	Alfuzosin
Allopurinol Sodium	Aminopromazine Fumarate	Aminopterin Sodium
Anagrelide Hydrochloride	Arsenic Trioxide	Azelaic Acid
Balsalazide Disodium	Bentoquatam	Bepridil Hydrochloride
Bivalirudin	Cabergoline	Calcipotriene
Calcium Trisodium Pentetate	Calfactant	Candesartan Cilexetil
Carmustine ***(Received)***	Cefdinir ***(Received)***	Cefditoren Pivoxil
Ceftibuten	Cetrorelix	Cevimeline
Chloroxine	Colfosceril	Cytarabine Liposome
Dalfopristin	Dapirazole Hydrochloride	Desirudin
Desonide ***(Received)***	Dexrazoxane	Difloxacin Hydrochloride
Docosanol	Entacapone	Epoprostenol Sodium ***(Received)***
Erythromycin Phosphate	Erythromycin Thiocyanate	Esmolol
Esomeprazole Magnesium ***(Received)***	Estazolam	Estradiol Benzoate ***(Received)***
Estramustine Phosphate Sodium	Ethanolamine Oleate	Etomidate ***(Received)***
Etoposide Phosphate	Exemestane	Felbamate
Flavoxate Hydrochloride	Fluoromethane F 18	Foscarnet Sodium ***(Received)***
Fosfomycin Tromethamine ***(Received)***	Gadobenate Dimeglumine	Gadopentetic Acid
Galantamine Hydrobromide ***(Received)***	Gallium Nitrate	Ganirelix
Glyceryl Aminobenzoate	Granisetron	Halobetasol Propionate ***(Received)***
Haloperidol Decanoate ***(Received)***	Hydrocodone Polistirex	Ibandronate Sodium
Imipramine Pamoate	Imiquimod	Irinotecan
Isosulfan Blue	Itraconazole ***(Received)***	Lamotrigine ***(Received)***
Latanoprost	Lawsone	Levetriacepam
Levobetaxolol	Levomethadyl Acetate	Lomustine
Lopinavir	Metipranolol Hydrochloride	Midazolam Hydrochloride
Mifepristone ***(Received)***	Miglitol	Misoprostol ***(Received)***
Mivacurium	Moexipril	Nalbuphine Hydrochloride
Nalmefene Hydrochloride	Nateglinide ***(Received)***	Nedocromil Sodium
Nicardipine Hydrochloride	Nilutamide	Nisoldipine
Olopatadine	Olsalazine Sodium ***(Received)***	Orbifloxacin ***(Received)***
Orlistat ***(Received)***	Oxcarbazepine ***(Received)***	Pantoprazole Sodium ***(Received)***
Pemoline	Pentamidine Isethionate ***(Received)***	Piperonyl Butoxide
Pirbuterol Acetate	Poractant Alpha	Proguanil
Quetiapine Fumarate ***(Received)***	Rose Bengal	Salmeterol Xinafoate
Sertraline Hydrochloride ***(Received)***	Sodium Phenylbutyrate	Sterile Methotrexate Sodium
Streptozocin	Sulfacytine	Tacrolimus
Terbinafine Hydrochloride ***(Received)***	Terconazole ***(Received)***	Tiludronate Disodium
Tiopronin	Tranexamic Acid ***(Received)***	Trimipramine Maleate ***(Received)***
Trovafloxacin Mesylate	Voriconazole	Zinc Tridosium Pentetate

Noncomplex Actives (Drug Products)

Abacavir Sulfate, Lamivudine, and Zidovudine Tablets	Acarbose Tablets	Acetaminophen, Butalbital, Caffeine, and Codeine Phosphate Capsules
Acetaminophen, Clemastine Fumarate, and Pseudoephedrine Hydrochloride Tablets	Acetazolamide Extended-Release Capsules	Albuterol Extended-Release Tablets
Albuterol for Inhalation	Albuterol Inhalation Aerosol	Alendronate Sodium Oral Solution
Alfuzosin Tablets	Allopurinol for Injection	Alprazolam Extended-Release Tablets
Alprostadil Urethral Suppository	Aminopromazine Fumarate and Neomycin Sulfate Tablets	Aminopromazine Fumarate Injection
Aminopromazine Fumarate Tablets	Aminopterin Sodium Tablets	Amlodipine and Benazepril Hydrochloride Capsules

Noncomplex Actives (Drug Products) *(Continued)*		
Amphotericin B Injection	Anagrelide Hydrochloride Capsules	Arsenic Trioxide Injection
Atovaquone and Proguanil Hydrochloride Tablets	Atovaquone Tablets	Auranofin Capsules
Azatadine Maleate and Pseudoephedrine Sulfate Extended-Release Tablets	Azelaic Acid Cream	Azithromycin for Injection ***(Received)***
Azithromycin Tablets	Baclofen Injection	Balsalazide Disodium Capsules
Beclomethasone Dipropionate Inhalation Aerosol	Beclomethasone Dipropionate Nasal Suspension	Bentoquatam Topical Suspension
Benzocaine and Cetylpyridinium Chloride Lozenges	Benzocaine and Menthol Lotion	Benzphetamine Hydrochloride Tablets
Bepridil Tablets	Bicalutamide Tablets	Bivalirudin Injection
Brompheniramine Maleate, Dextromethorphan Hydrobromide, and Pseudoephedrine Hydrochloride Oral Solution	Budesonide Inhalation Aerosol	Bupivacaine and Lidocaine Hydrochlorides Injection
Buprenorphine Hydrochloride Injection	Butalbital and Acetaminophen Capsules	Butalbital and Acetaminophen Tablets
Calcipotriene Cream	Calcipotriene Ointment	Calcipotriene Topical Solution
Cabergoline Tablets	Calcitriol Capsules	Calcitriol Oral Solution
Calcium Acetate Capsules	Calcium Trisodium Pentetate Injection	Calfactant Intratracheal Suspension
Carbidopa and Levodopa Extended-Release Tablets ***(Received)***	Carbidopa and Levodopa Tablets for Oral Suspension ***(Received)***	Carbidopa, Levodopa, and Entacapone Tablets
Carmustine for Injection ***(Received)***	Carmustine Implant	Carvedilol Tablets ***(Received)***
Cefdinir Tablets	Cefditoren Pivoxil Tablets	Ceftibuten Capsules
Ceftibuten for Oral Suspension	Ceftiofur Hydrochloride Oral Suspension	Cetirizine Hydrochloride Oral Solution
Cetirizine Hydrochloride Tablets ***(Received)***	Cetrorelix Injection	Cevimeline Hydrochloride Capsules
Chloroxine Cream	Chlorpromazine Hydrochloride Extended-Release Capsules	Choline and Magnesium Salicylates Oral Solution
Choline and Magnesium Salicylates Tablets	Choline Salicylate Oral Solution ***(Received)***	Ciclopirox Shampoo
Ciclopirox Topical Gel	Ciclopirox Topical Solution	Cilostazol Tablets ***(Received)***
Cimetidine Oral Solution	Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension	Ciprofloxacin Otic Solution
Citalopram Hydrobromide Oral Solution	Citric Acid, Gluconolactone, and Magnesium Carbonate Irrigation	Cladribine Injection
Clemastine Fumarate Syrup	Clobetasol Propionate Gel	Clonazepam Orally-Disintegrating Tablets
Clorazepate Dipotassium Capsules	Clorazepate Dipotassium Extended-Release Tablets	Clotrimazole and Betamethasone Dipropionate Lotion
Colestipol Hydrochloride Tablets	Colfosceril and Tyloxapol Suspension	Compound Undecylenic Acid Cream
Compound Undecylenic Acid Topical Powder	Conjugated Estrogens and Medroxyprogesterone Acetate Tablets	Cromolyn Sodium Nasal Solution
Cyclosporine Modified Capsules	Cyclosporine Modified Oral Solution	Cyclosporine Ointment
Cyclosporine Topical Solution	Cysteamine Bitartrate Capsules	Cytarabine Liposome Injection
Dalfopristin and Quinupristin Injection	Dantrolene Sodium Oral Suspension	Dapiprazole for Ophthalmic Solution
Desirudin for Injection	Desonide Cream	Dexrazoxane for Injection
Dextroamphetamine Sulfate Extended-Release Capsules	Dextromethorphan Polistirex Extended-Release Oral Suspension	Diazepam Injectable Emulsion
Diclofenac Sodium Ophthalmic Solution	Diethylpropion Hydrochloride Extended-Release Tablets	Difenoxin and Atropine Tablets
Difloxacin Hydrochloride Tablets	Dihydroergotamine Mesylate Metered Spray	Diltiazem Malate Extended-Release Tablets
Dinoprostone Vaginal Suppositories	Diphenhydramine Hydrochloride and Acetaminophen Tablets	Divalproex Sodium Delayed-Release Capsules
Dorzolamide and Timolol Ophthalmic Solution	Dorzolamide Ophthalmic Solution	Doxacurium Chloride Injection
Doxepin Hydrochloride Cream	Doxycycline Oral Gel	Econazole Nitrate Cream
Edrophonium Chloride and Atropine Sulfate Injection	Enalapril Maleate and Diltiazem Malate Extended-Release Tablets	Enalapril Maleate and Felodipine Extended-Release Tablets
Enalaprilat Injection	Entacapone Tablets	Ephedrine Sulfate and Guaifenesin Tablets
Epoprostenol for Injection	Epoprostenol Injection	Esmolol Hydrochloride Injection
Esomeprazole Magnesium Capsules	Estazolam Tablets	Estramustine Phosphate Sodium Capsules
Ethanolamine Oleate Injection	Etidronate Disodium Injection Concentrate	Etomidate Injection

Noncomplex Actives (Drug Products) *(Continued)*

Exemestane Tablets	Famotidine Orally Disintegrating Tablets	Felbamate Oral Suspension
Felbamate Tablets	Fentanyl Lozenges	Fentanyl Transdermal System ***(Received)***
Ferrous Fumarate and Docusate Sodium Extended-Release Capsules	Flavoxate Hydrochloride Tablets	Fluconazole Injection ***(Received)***
Fluconazole Tablets	Flunisolide Inhalation Aerosol	Flunisolide Nasal Spray
Fluocinolone Acetonide Shampoo	Fluorescein Sodium Ophthalmic Solution	Fluorometholone Ointment
Fluticasone Propionate Cream ***(Received)***	Fluticasone Propionate Inhalation Powder	Fluticasone Propionate Ointment ***(Received)***
Fluticasone Propionate Pressurized Inhaler	Foscarnet Sodium Injection	Fosfomycin for Oral Solution
Gabapentin Oral Solution	Gabapentin Tablets ***(Received)***	Gadobenate Dimeglumine Injection
Galantamine Tablets ***(Received)***	Gallium Nitrate Injection	Ganciclovir Capsules
Ganirelix Acetate Injection	Gatifloxacin Injection	Gatifloxacin Tablets
Gentamicin Sulfate Oral Solution	Gentamicin Sulfate Soluble Powder	Glimepiride Tablets ***(Received)***
Glipizide Extended-Release Tablets	Granisetron Injection	Granisetron Tablets
Guaifenesin and Salts of Dextromethorphan and Pseudoephedrine Oral Solution	Guaifenesin and Pseudoephedrine Hydrochloride Extended-Release Tablets	Guanidine Hydrochloride
Guanidine Hydrochloride Tablets	Halobetasol Propionate Cream	Halobetasol Propionate Ointment
Haloperidol Decanoate Injection	Haloperidol Lactate Injection	Haloperidol Lactate Oral Concentrate
Hydralazine Hydrochloride and Hydrochlorothiazide Capsules	Hydrochlorothiazide Capsules	Hydrochlorothiazide Oral Solution Concentrate
Hydrocodone Bitartrate and Acetaminophen Oral Solution	Hydrocodone Bitartrate and Aspirin Tablets	Hydrocodone Bitartrate and Guaifenesin Oral Solution
Hydrocodone Bitartrate and Homatropine Methylbromide Syrup	Hydrocodone Bitartrate and Homatropine Methylbromide Tablets	Hydrocortisone Acetate Dental Paste
Hydrocortisone Acetate Rectal Foam Aerosol	Hydrocortisone Butyrate Lotion	Hydroflumethiazide and Reserpine Tablets
Hydromorphone Hydrochloride Oral Solution ***(Received)***	Hydroquinone Lotion	Ibandronate Sodium Tablets
Ibuprofen Capsules	Idarubicin Hydrochloride Injection	Imipramine Pamoate Capsules
Imiquimod Topical Cream	Ipratropium Bromide Inhalation Aerosol	Ipratropium Bromide Inhalation Solution
Irinotecan Hydrochloride Injection	Isosulfan Blue Injection	Isradipine Extended-Release Tablets
Itraconazole Injection	Itraconazole Oral Solution	Ketoconazole Cream
Ketoconazole Shampoo	Ketoprofen Capsules ***(Received)***	Ketoprofen Extended-Release Capsules
Ketoprofen Tablets	Ketotifen Fumarate	Ketotifen Fumarate Ophthalmic Solution
Lactic Acid Lotion	Lamivudine Tablets ***(Received)***	Latanoprost Ophthalmic Solution
Leucovorin Calcium for Injection	Levetriacepam Tablets	Levobetaxolol Ophthalmic Suspension
Levocabastine Ophthalmic Suspension	Levofloxacin Solution	Levomethadyl Acetate Hydrochloride Oral Concentrate
Lincomycin Hydrochloride and Spectinomycin Sulfate Soluble Powder	Liothyronine Injection	Lisinopril and Hydrochlorothiazide Tablets ***(Received)***
Lomustine Capsules	Lopinavir and Ritonavir Solution	Lopinavir Capsules
Lopinavir Solution	Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets ***(Received)***	Loratadine Orally-Disintegrating Tablets
Losartan Potassium Tablets	Mefloquine Hydrochloride Tablets	Melphalan for Injection
Mesalamine Suppositories	Mesoridazine Besylate Concentrate	Metaraminol Bitartrate Injection
Methacholine Chloride for Inhalation Solution	Methadone Hydrochloride Oral Concentrate	Methocarbamol and Aspirin Tablets
Methoxsalen Softgels	Methyclothiazide and Deserpidine Tablets	Methylphenidate Hydochloride Chewable Tablets
Metipranolol Ophthalmic Solution	Metronidazole Capsules	Metronidazole Cream
Metronidazole Extended-Release Tablets	Metronidazole Hydrochloride for Injection	Metronidazole Lotion
Miconazole Nitrate Topical Aerosol	Midazolam Injection ***(Received)***	Mifepristone Tablets
Miglitol Tablets	Milrinone Injection	Misoprostol Tablets ***(Received)***
Mivacurium In Dextrose Injection	Mivacurium Injection	Moexipril Hydrochloride and Hydrochlorothiazide Tablets
Moexipril Hydrochloride Tablets	Molindone Hydrochloride Oral Solution	Morphine Sulfate for Injection Concentrate
Morphine Sulfate Oral Solution	Morphine Sulfate Oral Solution Concentrate	Morphine Sulfate Tablets

Noncomplex Actives (Drug Products) *(Continued)*		
Mycophenolate Mofetil Capsules	Mycophenolate Mofetil Oral Solution	Mycophenolate Mofetil Tablets
Nalbuphine Hydrochloride Injection	Nalmefene Hydrochloride Injection	Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution
Naproxen Extended-Release Tablets	Nateglinide Tablets	Nedocromil Sodium Inhalation Aerosol
Neomycin Sulfate Oral Powder	Nicardipine Hydrochloride Capsules	Nilutamide Tablets
Nimodipine Capsules	Nisoldipine Extended-Release Tablets	Nitroglycerin Solution in Acrylic Adhesive
Nizatidine Tablets	Ofloxacin in Dextrose Injection	Ofloxacin Injection
Ofloxacin Tablets ***(Received)***	Olopatadine Ophthalmic Solution	Olsalazine Sodium Capsules
Ondansetron Tablets	Orbifloxacin Tablets ***(Received)***	Orlistat Capsules ***(Received)***
Orphenadrine Citrate Extended-Release Tablets	Orphenadrine Citrate, Aspirin, and Caffeine Tablets	Oxcarbazepine Suspension
Oxcarbazepine Tablets	Oxiconazole Cream	Pantoprazole Sodium for Injection
Pantoprazole Sodium Tablets	Paroxetine Hydrochloride Extended-Release Tablets	Paroxetine Oral Suspension
Pemirolast Potassium Ophthalmic Solution	Pemoline Tablets	Penicillin G Potassium Tablets for Oral Solution
Pentaerythritol Tetranitrate Extended-Release Capsules	Pentaerythritol Tetranitrate Extended-Release Tablets	Pentamidine Isethionate for Inhalation
Pentamidine Isethionate for Injection	Pentazocine Hydrochloride and Acetaminophen Tablets	Phendimetrazine Tartrate Extended-Release Capsules
Phenobarbital Capsules	Phentermine Resin Complex	Phentermine Resin Complex Capsules
Phenylephrine Hydrochloride and Chlorpheniramine Maleate Extended-Release Capsules	Phenylephrine Hydrochloride, Chlorpheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pilocarpine Hydrochloride Ophthalmic Gel
Pilocarpine Hydrochloride Ophthalmic Ointment	Pilocarpine Hydrochloride Tablets	Piperonyl Butoxide and Pyrethrins Aerosol Foam
Pirbuterol Acetate Inhalation Aerosol	Poractant Alpha Supension	Porfimer Sodium for Injection
Povacrylate Solution	Povacrylate-Iodine Topical Solution	Povidone-Iodine Gauze
Povidone-Iodine Swabsticks	Povidone-Iodine Topical Aerosol Foam	Povidone-Iodine Vaginal Suppositories
Pramipexole Dihydrochloride Tablets	Prazosin Hydrochloride and Polythiazide Capsules	Prednisolone Sodium Phosphate Oral Solution
Prochlorperazine Maleate Extended-Release Capsules	Progesterone Capsules	Promethazine and Phenylephrine Hydrochlorides and Codeine Phosphate Syrup
Promethazine and Phenylephrine Hydrochlorides Syrup	Promethazine Hydrochloride and Codeine Phosphate Oral Solution	Promethazine Hydrochloride and Dextromethorphan Hydrobromide Syrup
Propafenone Hydrochloride Tablets	Pseudoephedrine Hydrochloride and Brompheniramine Maleate Extended-Release Tablets	Pseudoephedrine Hydrochloride and Naproxen Sodium Extended-Release Tablets
Pseudoephedrine Hydrochloride, Chlorpheniramine Maleate, and Codeine Phosphate Oral Solution	Pseudoephedrine Hydrochloride, Guaifenesin, and Codeine Phosphate Oral Solution	Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Extended-Release Tablets
Pseudoephedrine Sulfate and Dexbrompheniramine Maleate Oral Solution	Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets	Pseudoephedrine Sulfate, Dexbrompheniramine Maleate, and Acetaminophen Extended-Release Tablets
Quinidine Sulfate Injection	Ramipril Capsules	Ranitidine Capsules
Rauwolfia Serpentina and Endroflumethiazide Tablets	Reserpine and Polythiazide Tablets	Rimantadine Hydrochloride Oral Solution
Risperidone Oral Solution	Risperidone Orally Disintegrating Tablets	Rivastigmine Tartrate Capsules
Rivastigmine Tartrate Oral Solution	Rocuronium Bromide Injection	Ropinirole Hydrochloride Tablets
Rose Bengal Ophthalmic Solution	Rosiglitazone Maleate Tablets	Salicylic Acid and Sulfur Cleansing Lotion
Salicylic Acid and Sulfur Lotion	Salicylic Acid and Sulfur Shampoo	Salicylic Acid Cream
Salicylic Acid Ointment	Salmeterol Inhalation Aerosol	Salmeterol Xinafoate Inhalation Powder
Scopolamine Transdermal System	Selegiline Hydrochloride Capsules	Serpacwa Topical Cream
Sertraline Hydrochloride Oral Solution	Sibutramine Hydrochloride Capsules	Sodium Bicarbonate and Sodium Citrate for Oral Solution
Sodium Bicarbonate, Sodium Citrate, and Sodium Tartrate for Oral Suspension	Sodium Chlorophyllin Copper Complex Tablets	Sodium Iodide Injection
Sodium Phenylbutyrate Oral Powder	Sodium Phenylbutyrate Tablets	Sodium Phosphates for Oral Suspension
Sodium Phosphates Tablets	Sodium Salicylate and Sulfur Shampoo	Sterile Talc Aerosol
Streptozocin for Injection	Sucralfate Oral Suspension	Sulconazole Nitrate Cream

Noncomplex Actives (Drug Products) *(Continued)*

Sulfacetamide Sodium and Fluorometholone Ophthalmic Suspension	Sulfacetamide Sodium and Prednisolone Sodium Phosphate Ophthalmic Solution	Sulfacytine Tablets
Sulfanilamide Vaginal Cream	Sulfasalazine Oral Suspension	Sulisobenzone Lotion
Sumatriptan Injection	Sumatriptan Tablets	Tacrolimus Capsules
Tacrolimus Injection	Tacrolimus Ointment	Tamsulosin Hydrochloride Capsules ***(Received)***
Technetium Tc 99m Teboroxime Injection	Tenofovir Disoproxil Fumarate Tablets	Terbinafine Hydrochloride Cream
Terbinafine Tablets	Terbinafine Topical Solution	Terconazole Vaginal Cream
Terconazole Vaginal Suppositories	Testosterone Transdermal System	Tetracycline Hydrochloride Periodontal Fiber
Theophylline Extended-Release Tablets	Tioconazole Vaginal Ointment	Tiopronin Tablets
Tolnaftate Topical Aerosol Solution	Topiramate Capsules ***(Received)***	Topiramate Tablets
Torsemide Injection	Torsemide Tablets ***(Received)***	Trandolapril and Verapamil Hydrochloride Extended-Release Tablets
Trandolapril Tablets	Tranexamic Acid Injection	Tranylcypromine Sulfate
Tranylcypromine Sulfate Tablets	Tretinoin Capsules	Tretinoin Microsphere Gel
Triamcinolone Acetonide Nasal Suspension	Trifluridine Ophthalmic Solution	Trimetrexate for Injection
Trimipramine Maleate Capsules	Triprolidine and Pseudoephedrine Hydrochlorides and Codeine Phosphate Syrup	Trolamine Salicylate Cream
Trolamine Salicylate Gel	Trolamine Salicylate Topical Emulsion	Trovafloxacin Injection
Trovafloxacin Mesylate for Injection	Undecylenic Acid Topical Foam Aerosol	Unoprostone Isopropyl Ophthalmic Solution
Urea Cream	Vecuronium Bromide for Injection	Venlafaxine Extended-Release Capsules ***(Received)***
Venlafaxine Tablets	Verapamil Hydrochloride Capsules	Verapamil Hydrochloride Extended-Release Capsules
Voriconazole Injection	Voriconazole Oral Suspension	Voriconazole Tablets
Yttrium Y-90 Chloride Solution	Yttrium Y-90 Glass Microspheres	Yttrium Y-90 Microspheres Injection
Zidovudine and Lamivudine Tablets ***(Received)***	Zinc Acetate Capsules	Zinc Tridosium Pentetate Injection
Ziprasidone Hydrochloride Capsules	Zoledronic Acid for Injection	

Excipients

Acetone Sodium Bisulfite	Acetylated Monoglycerides	Aconitic Acid (Achilleic Acid)
Acrylic Acid-Octyl Acrylate Copolymer	Albumin Colloidal	Aliphatic Polyesters
Allantoin-Sodium Pyrrolidone Carboxylate	Aluminum Ammonium Sulfate	Aluminum Lactate
Aluminum Oxide	Aluminum Potassium Sulfate	Aluminum Silicate
Aluminum Sodium Sulfate	Aluminum Stearate	Ammonium Bicarbonate
Ammonium Calcium Alginate	Ammonium Phosphate	Batylalcohol Monostearate
Beeswax, Synthetic	Benzododecinium Bromide	Benzyl Chloride
Benzyl Nicotinate	Beta Naphthol	Brominated Vegetable Oil
Butadiene-Styrene Rubber	Butylated Hydromethylphenol	Butylene Glycol
Butylphthalyl Butylglycolate	Calcium Acid Pyrophosphate	Calcium Alginate
Calcium Alginate and Ammonium Alginate	Calcium Bromide	Calcium Chloride Solution
Calcium Glycerophosphate ***(Received)***	Calcium Phosphate Monobasic	Calcium Propionate
Calcium Pyrophosphate	Calcium Sorbate	Calcium Stearoyl Lactylate
Caldiamide Sodium	Calteridol Calcium	Canola Oil
Capric Acid	Caprylic/Capric Diglyceryl Succinate	Carbon
Carboxymethyl Starch	Carboxymethylamylopectin Sodium	Carboxymethylcellulose Potassium
Cetostearyl Isononanoate	Chlorodifluoroethane	Cholic Acid
Cinnamaldehyde	Cocamide Diethanolamine	Cocamide Oxide
Cocoyl Caprylocaprate	Crystal Gum	Cutina
Cystine	Dammar Gum	Decanoic Acid
Decyl Oleate	Dehydroacetic Acid	Desoxycholic Acid
Dextrin Palmitate	Dextrins Modified	Diacetyl Tartaric Acid Esters of Mono- and Diglycerides

Excipients *(Continued)*		
Dicetyl Phosphate	Dichlorofluoromethane	Diethyl Sebacate
Difluoroethane	Diglycol Stearate	Diisobutyl Adipate
Diisopropyl Adipate	Diisopropylbenzothiazyl-2-Sulfenamide	Dilauryl Thiodipropionate
Dimethyl Dicarbonate	Dimyristoyl Lecithin	Dimyristoyl Phosphatidylglycerol
Dipropylene Glycol	Disodium Edisylate	Disodium Guanylate
Disodium Inosinate	Disodium Monooleamide Sulfasuccinate	D-Mannose
Docusate Sodium/Sodium Benzoate	Erythorbic Acid	Erythrosine
Ethoxylated Mono- and Diglycerides	Ethoxyquin	Ethyl Hexanediol
Ethyl Linoleate	Ethyl Maltol	Ethylene Dichloride
Ethylurea	Ferric Ammonium Citrate	Ferric Citrate
Ferric Oxide, Brown	Ferric Phosphate	Ferric Pyrophosphate
Ferrous Citrate	Ferrous Glycinate	Ferrous Lactate
Fluorochlorohydrocarbons	Formic Acid	Furcelleran
Gamma-Cyclodextrin	Gentistic Acid	Geraniol
Glutamic Acid Hydrochloride	Gluten	Glycerol Ester Of Gum Rosin (Ester Gum)
Glyceryl Laurate	Glyceryl Palmitate	Glyceryl Ricinoleate
Glyceryl Tristearate	Glycine Hydrochloride	Glycofurol
Glycol Stearate	Heptafluoropropane	Heptylparaben
Hexadecyl Isostearate	Hexane	Hexanetriol(-1,2,6-)
Hydrocarbon Gel	Hydrogenated Starch Hydrolysate	Hydroxyethylmethylcellulose
Hydroxylated Lecithin	Hydroxypropyl Beta Cyclodextrin	Indigotine
Inositol	Iron Carbonyl	Iron Subcarbonate
Isobutylated-Isoprene Copolymer	Isooctylacrylate	Isopropyl Isostearate
Isopropyl Stearate	Isostearic Acid	Isostearyl Alcohol
Lactobionic Acid	Lactose Ferrin, Bovine	Lactylated Fatty Acid Esters of Glycerol and Propylene Glycol
Lactylic Esters of Fatty Acids	Lanolin (Wool Fat), Hydrogenated	Lanolin Alcohols, Acetylated
Lanolin Hydrous	L-Ascorbyl Stearate	Lauramine Oxide
Lauric Myristic Diethanolamide	Lauric Acid	Lauric Diethanolamide
Lavender Oil	L-Cysteine Monohydrochloride	Lecithin, Hydroxylated
L-Glutamic Acid	Linoleic Acid	L-Leucine
Macrogol Sorbitan Tristearate	Macrogolglycerol Cocoates	Macrogolglycerol Triisostearate
Magnesium Aluminum Silicate Hydrate	Magnesium Aspartame Dihydrate	Magnesium Aspartate
Magnesium Phosphate Tribasic	Magnesium Phosphate, Dibasic, Trihydrate	Magnesium Tartrate
Malt Syrup	Maltitol Syrup	Maltol Isobutyrate
Manganese Chloride	Manganese Citrate	Manganese Glycerophosphate
Manganese Hypophosphite	Medical Antifoam Emulsion C	Medronate Disodium
Medronic Acid	Methyl Chloride	Methylchloroisothiazolinone
Methylisothiazolinone	Microcrystalline Cellulose, Silicified ***(Received)***	Mineral Spirits
Monoisostearyl Glyceryl Ester	Monopotassium Glutamate Monohydrate	Monosodium Citrate
Mullein Leaf	Myristyl Gamma-Picolinium Chloride	Myristyl Lactate
N,N-Bis(2-Hydroxyethyl)Stearamide	*N*-Acetyl-L-Methionine	Naphtha
N-Methylpyrrolidone ***(Received)***	Non-Pareil Seeds	Nutmeg Oil
Octanoic Acid	Oxystearin	Palm Kernel Oil ***(Received)***
Palm Oil	Pentasodium Triphosphate	Pentetate Calcium Trisodium
Pentetate Pentasodium	Phenprobamate	Phenylmercuric Acetate
Phenylmercuric Nitrate	Pine Oil	Polacrilin
Polydextrose ***(Received)***	Polydextrose Solution	Polyglycerol Esters of Fatty Acids
Polyglycerol Polyricinoleic Acid	Polyoxyethylene Castor Oil (USP has 35)	Polyoxyl Stearate (USP has 40)
Polypropylene Oleate	Polypropylene Stearyl Ether	Polysorbate 65
Polyvinylacetal	Polyvinylacetal Diethylanoacetate	Polyvinylpolypyrrolidone
Polyvinylpyrrolidone Ethylcellulose	Potassium Acid Tartrate	Potassium Bromate
Potassium Carbonate Solution	Potassium Dichloroisocyanurate	Potassium Gibberellate
Potassium Glycerophospate	Potassium Iodate	Potassium Nitrite
Potassium Phosphate	Potassium Phosphate Tribasic	Potassium Polymetaphosphate
Potassium Pyrophosphate	Potassium Stearate	Potassium Sulfate

Excipients *(Continued)*

Potassium Sulfite	Potassium Tripolyphosphate	Propyl Propionate
Propylene Glycol Diacetate	Propylene Glycol Mono- and Diesters	Purified Polyoxyl 35 Castor Oil ***(Received)***
Rapeseed Oil, Hydrogenated ***(Received)***	Rapeseed Oil, Superglycerinated ***(Received)***	Rice Bran Wax
Rosin	Silicone	Sodium Acid Pyrophosphate
Sodium Aluminosilicate	Sodium Aluminum Phosphate Acidic	Sodium Aluminum Phosphate Basic
Sodium Aspartate	Sodium Bisulfate	Sodium Bisulfite
Sodium Carbonate Hydrate	Sodium Carboxymethyl Betaglucan	Sodium Caseinate
Sodium Chlorate	Sodium Citrate, Dibasic	Sodium Citrate, Monobasic
Sodium Dehydroacetate	Sodium Diacetate	Sodium Erythorbate
Sodium Ferric Pyrophosphate	Sodium Ferrocyanide	Sodium Hypophosphite
Sodium Laureth Sulfate	Sodium Lauroyl Sarcosinate	Sodium Lauryl Sulfoacetate
Sodium Magnesium Aluminosilicate	Sodium Magnesium Silicate	Sodium Malate
Sodium Metaphosphate, Insoluble	Sodium Metasilicate	Sodium Methylate
Sodium Polyphosphates Glassy	Sodium Potassium Tripolyphosphate	Sodium Pyrophosphate
Sodium Pyrrolidone Carboxylate	Sodium Sesquicarbonate	Sodium Sesquinoleate
Sodium Stearoyl Lactylate	Sodium Thiomalate	Sodium Trimetaphosphate
Sodium Trioleate	Sodium Tripolyphosphate	Soy Polysaccharides
Stannous Chloride	Stannous Tartrate	Starch, Pregelatinized Corn
Starch, Pregelatinized Tapioca	Stearalkonium Chloride	Stearyl Citrate
Stearyl Monoglyceridyl Citrate	Succinylated Monoglycerides	Sucrose Acetate Isobutyrate
Sucrose Fatty Acid Esters	Sucrose Stearate	Sugar Fruit Fine
Sulfobutyl Ether Beta Cyclodextran	Tallow	Tallow Glycerides
Tallow Oil	Tetrafluoroethane	Thioglycerol
Thyme Oil	Tribehenin	Tricetearet-4 Phosphate
Trichloroethylene	Trimyristin	Trisodium Citrate
Trolamine Lauryl Sulfate	Vegetable Oil	Wheat Flour
Wheat Germ Oil	Wheat Gluten ***(Received)***	Whey

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

- The list of new USP Reference Standards that have become available
- The list of assays or tests that are adopted but held in abeyance pending availability of required USP Reference Standards
- New adopted (official) revisions to the *USP–NF* that become effective before the effective date of the next *Supplement* or that were not ready for adoption by the closing date for the upcoming *Supplement*. (The effective date for these revisions is stated on the next page.)

Readers should review this section to determine if they are affected by any of the changes.

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ▪new text▪, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ▪▪, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement,* and ▪2S (*USP29*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 29*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in future *Supplements,* and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

SIXTH INTERIM REVISION ANNOUNCEMENT to *USP 29* and to *NF 24*

By authority of the United States Pharmacopeial Convention, Inc.
Prepared by the Council of Experts and published by the Board of Trustees

John W. Mauger, *Chair*
USP Board of Trustees

Roger L. Williams, *Executive Vice President*
and *Chairman, USP Council of Experts*

Roger L. Williams, M.D., *Chief Standards Officer, Acting*

Official December 1, 2006 **Released November 1, 2006**

All inquiries and comments regarding *USP 29* text and *NF 24* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were not available when the associated monograph was made official, have since become available. The respective official date of each *USP 29* or *NF 24* standard, test, or assay requiring the use of the following USP Reference Standards is indicated in parentheses after the name of the Reference Standard.

USP Citalopram Hydrobromide RS (May 1, 2007)
USP Escin RS (January 1, 2007)
USP Fluticasone Propionate RS (November 1, 2006)
USP Fluvastatin Related Compound B RS (November 1, 2006)
USP Fluvastatin Sodium RS (March 1, 2007)
USP Hexacosanol RS (March 1, 2007)
USP Mecamylamine Related Compound A RS (March 1, 2007)
USP Naratriptan Resolution Mixture RS (May 1, 2007)
USP Cultured Rat Pheochromocytoma Reference Photomicrographs RS (May 1, 2007)
USP Polyisobutylene RS (November 1, 2006)
USP Ramipril Related Compound B RS (May 1, 2007)
USP Ropivocaine Hydrochloride RS (November 1, 2006)
USP Saccharin Sodium RS (March 1, 2007)
USP Sulisobenzone RS (January 1, 2007)

Unavailable First-Time Official USP Reference Standards

The official dates of any *USP 29* or *NF 24* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards. This listing was updated as of September 1, 2006.

USP Albumin Human RS
USP Alteplase RS
USP Amifostine RS
USP Amifostine Thiol RS
USP Antithrombin III Human RS
USP Aprotinin RS
USP Aprotinin System Suitability RS
USP Cetrimonium Bromide RS
USP Cladribine RS
USP Cladribine Related Compound A RS
USP Copolymer Polypropylene RS
USP Decoquinate RS
USP Cryopreserved Human Fibroblast-Derived Dermal Substitute Reference Photomicrographs RS
USP Diethylstilbestrol Diphosphate RS
USP Docosyl Ferulate RS
USP Powdered *Echinacea pallida* Extract RS
USP Eucatropine Hydrochloride RS
USP Fluvastatin Related Compound A RS
USP Gabapentin Related Compound B RS
USP Ginkgo Terpene Lactones RS
USP Powdered American Ginseng Extract RS
USP Glyceryl Monolinoleate RS
USP Glyceryl Monooleate RS
USP Gonadorelin Hydrochloride RS
USP Hemoglobin RS
USP Irbesartan RS
USP Irbesartan Related Compound A RS
USP Isosorbide Mononitrate RS
USP Isosorbide Mononitrate Related Compound A RS
USP Alpha Lipoic Acid RS
USP Maritime Pine Extract RS
USP Menotropins RS
USP Methyldopa-Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Near Infrared Calibrator RS
USP Nimodipine RS
USP Nimodipine Related Compound A RS
USP Polyoxyl 10 Oleyl Ether RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Quinapril Hydrochloride RS
USP Powdered St. John's Wort Extract RS
USP Sargramostim RS
USP Sincalide RS
USP Human Fibroblast-Derived Temporary Skin Substitute Reference Photomicrographs RS
USP Δ^8-Tetrahydrocannabinol RS
USP Δ^9-Tetrahydrocannabinol RS
USP Tizanidine Hydrochloride RS
USP Tizanidine Related Compound A RS
USP Tizanidine Related Compound B RS
USP Tizanidine Related Compound C RS
USP Valrubicin RS
USP Valrubicin Related Compound A RS
USP Vasopressin RS

GENERAL CHAPTERS

General Tests and Assays

Physical Tests and Determinations

⟨905⟩ UNIFORMITY OF DOSAGE UNITS

Change to read:

[NOTE—In this chapter, *unit* and *dosage unit* are synonymous.]

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. •The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for topical administration.•6

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified in the individual monograph.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or *Weight Variation* (see *Table 1*). The test for *Content Uniformity* is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases. The test for *Content Uniformity* is required for those dosage forms described in *(C1)–(C6)* below:

(C1) coated tablets, other than film-coated tablets containing 25 mg or more of a drug substance that comprises 25% or more (by weight) of one tablet;

(C2) transdermal systems;

(C3) suspensions or emulsions or gels in •single-unit•6 containers or in soft capsules that are intended for systemic administration only (not for those drug products that are intended for •topical•6 administration);

(C4) inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units. For inhalers and premetered dosage units labeled for use with a named inhalation device, also see *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩;

(C5) solids (including sterile solids) that are packaged in single-unit containers and that contain active or inactive added substances, except that the test for *Weight Variation* may be applied in the special •cases•6 stated in ••6 *(W3)* below; and

(C6) suppositories.

The test for *Weight Variation* is applicable for the following dosage forms:

(W1) solutions for inhalation that are packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules;

(W2) solids (including sterile solids) that are packaged in single-unit containers and contain no added substances, whether active or inactive;

(W3) solids (including sterile solids) that are packaged in single-unit containers, with or without added substances, whether active or inactive, that have been prepared from true solutions and freeze-dried in the final containers and are labeled to indicate this method of preparation; and

(W4) hard capsules, uncoated tablets, or film-coated tablets, containing 25 mg or more of a drug substance comprising 25% or more, by weight, of the dosage unit or, in the case of hard capsules, the capsule contents, except that uniformity of other drug substances present in lesser proportions is demonstrated by meeting *Content Uniformity* requirements.

The test for *Content Uniformity* is required for all dosage forms not meeting the above conditions for the *Weight Variation* test. •Where compliance with the *Content Uniformity* test is required, then, by application of the provision for use of alternative methods provided in the *General Notices* section of this Pharmacopeia, it is possible for manufacturers to ensure this compliance by application of the *Weight Variation* test where the concentration relative standard deviation (RSD) of the drug substance in the final dosage units is not more than 2%. This RSD determination may be based on the manufacturer's process validation and product development data.•6 The concentration RSD is the RSD of the concentration per dosage unit (w/w or w/v), where concentration per dosage unit equals the assay result per dosage unit divided by the individual dosage unit weight. See the RSD formula in *Table 2*. •Where the *Weight Variation* test is used in this way, the product must, if tested, nevertheless comply with the official compendial test for *Content Uniformity.*•6

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg & ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms *(Continued)*

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg & ≥25%	<25 mg or <25%
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Suspension, emulsion, or gel for systemic use only, packaged in single-unit containers			CU	CU
Solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, and oral solutions packaged in unit-dose containers and into soft capsules			WV	WV
Inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers packaged in premetered dosage units			CU	CU
Transdermal systems			CU	CU
Suppositories			CU	CU
Others			CU	CU

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Change to read:

CONTENT UNIFORMITY

Select not fewer than 30 units, and proceed as follows for the dosage form designated. Where the amount of drug substance in a single dosage unit differs from that required in the *Assay,* adjust the degree of dilution of the solutions and/or the volume of aliquots so that the concentration of the drug substances in the final solution is of the same order as that obtained in the *Assay* procedure; or, in the case of a titrimetric assay, use a titrant of a different concentration, if necessary, so that an adequate volume of titrant is required (see *Titrimetry* ⟨541⟩); see also *Procedures* under *Tests and Assays* in the *General Notices and Requirements*. If any such modifications are made in the *Assay* procedure set forth in the individual monograph, make the appropriate corresponding changes in the calculation formula and titration factor.

Where a special *Procedure for content uniformity* is specified in the test for *Uniformity of dosage units* in the individual monograph, make any necessary correction of the results obtained as follows.

(1) Prepare a composite specimen of a sufficient number of dosage units to provide the amount of specimen called for in the *Assay* in the individual monograph plus the amount required for the special *Procedure for content uniformity* in the monograph by finely powdering tablets or mixing the contents of capsules or oral solutions, suspensions, emulsions, gels, or solids in single-unit containers to obtain a homogeneous mixture. If a homogeneous mixture cannot be obtained in this manner, use suitable solvents or other procedures to prepare a solution containing all of the drug substance, and use appropriate aliquot portions of this solution for the specified procedures.

(2) Assay separate, accurately measured portions of the composite specimen of capsules or tablets or suspensions or inhalations or solids in single-unit containers, both (a) as directed in the *Assay,* and (b) using the special *Procedure for content uniformity* in the monograph.

(3) Calculate the weight of drug substance equivalent to 1 average dosage unit, by (a) using the results obtained by the *Assay* procedure, and by (b) using the results obtained by the special procedure.

(4) Calculate the correction factor, *F,* by the formula:

$$F = W/P$$

in which W is the weight of drug substance equivalent to 1 average dosage unit obtained by the *Assay* procedure, and P is the weight of drug substance equivalent to 1 average dosage unit obtained by the special procedure. If

$$\frac{100|W - P|}{W}$$

is greater than 10, the use of a correction factor is not valid.

(5) The correction factor is to be applied only if F is not less than 1.030 nor greater than 1.100, or not less than 0.900 nor greater than 0.970. If F is between 0.970 and 1.030, no correction is required.

(6) If F lies between 1.030 and 1.100, or between 0.900 and 0.970, calculate the weight of drug substance in each dosage unit by multiplying each of the weights found using the special procedure by F.

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in •Unit-Dose Containers, Suspensions or Emulsions or Gels in Single-Unit Containers (that are intended for systemic administration only),•6 and Solids (including Sterile Solids) in Single-Unit Containers—Assay 10 units individually as directed in the *Assay* in the individual monograph, unless otherwise specified in the *Procedure for content uniformity* in the individual monograph. Calculate the acceptance value as directed below.

For oral solutions •in unit-dose containers, and for suspensions, emulsions, or gels in single-unit containers that are intended for systemic administration only,•6 conduct the *Assay* on the amount of well-mixed material that drains from an individual container in not more than 5 seconds, or for highly viscous products, conduct the *Assay* on the amount of well-mixed material that is obtained by quantitatively removing the contents from an individual container, and express the results as the delivered dose.

Calculation of Acceptance Value—Calculate the acceptance value by the formula:

$$\left|M - \overline{X}\right| + ks$$

in which the terms are as defined in *Table 2*.

Table 2

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents (χ_1, χ_2, … , χ_n), expressed as a percentage of the label claim		
χ_1, χ_2, … , χ_n	Individual contents of the units tested, expressed as a percentage of the label claim		
n	Sample size (number of units in a sample)		
k	Acceptability constant	If n = 10, then k =	2.4
		If n = 30, then k =	2.0
s	Sample standard deviation		$\left[\frac{\sum_{i=1}^{n}\left(\chi_i-\overline{X}\right)^2}{n-1}\right]^{\frac{1}{2}}$
RSD	Relative standard deviation (the sample standard deviation expressed as a percentage of the mean)		$\frac{100s}{\overline{X}}$
M (case 1) to be applied when $T \leq 101.5$	Reference value	If 98.5% $\leq \overline{X} \leq$ 101.5%, then	$M = \overline{X}$ $(AV = ks)$
		If $\overline{X}$ < 98.5%, then	M = 98.5% $(AV = 98.5 - \overline{X} + ks)$
		If $\overline{X}$ > 101.5%, then	M = 101.5% $(AV = \overline{X} - 101.5 + ks)$
M (case 2) to be applied when $T > 101.5$	Reference value	If 98.5 $\leq \overline{X} \leq T$, then	$M = \overline{X}$ $(AV = ks)$
		If $\overline{X}$ < 98.5%, then	M = 98.5% $(AV = 98.5 - \overline{X} + ks)$
		If $\overline{X} > T$, then	$M = T\%$ $(AV = \overline{X} - T + ks)$

Table 2 *(Continued)*

Variable	Definition	Conditions	Value
Acceptance value *(AV)*			general formula: $\left\|M - \overline{X}\right\| + ks$ (Calculations are specified above for the different cases.)
L1	Maximum allowed acceptance value		*L1* = 15.0 unless otherwise specified in the individual monograph
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of *M*	On the low side, no dosage unit result can be less than •[1 – (0.01)(*L2*)]*M*,•6 while on the high side no dosage unit result can be greater than •[1 + (0.01)(*L2*)]M•6 (This is based on an *L2* value of 25.0.)	*L2* = 25.0 unless otherwise specified in the individual monograph
T	Target •content per dosage unit at the time of manufacture, expressed as a percentage of the label claim.•6 For purposes of this Pharmacopeia, unless otherwise specified in the individual monograph, *T* is •the average of the limits specified in the potency definition in the individual monograph.•6		

Suppositories, Transdermal Systems, and Inhalations Packaged in Premetered Dosage Units—[NOTE—Acceptance value calculations are not required for these dosage forms.] Assay 10 units individually as directed in the *Assay* in the individual monograph, unless otherwise specified in the *Procedure for content uniformity.*

Change to read:

WEIGHT VARIATION

Select not fewer than 30 dosage units, and proceed as follows for the dosage form designated. The result of the *Assay,* obtained as directed in the individual monograph, is designated as result *A,* expressed as % of label claim (see *Calculation of the Acceptance Value*). Assume that the concentration (weight of drug substance per weight of dosage unit) is uniform. [NOTE—Specimens other than these test units may be drawn from the same batch for assay determinations.]

Uncoated or Film-Coated Tablets—Accurately weigh 10 tablets individually. Calculate the drug substance content, expressed as % of label claim, of each tablet from the weight of the individual tablet and the result of the *Assay.* Calculate the acceptance value.

Hard Capsules—Accurately weigh 10 capsules individually, taking care to preserve the identity of each capsule. Remove the contents of each capsule by a suitable means. Accurately weigh the emptied shells individually, and calculate for each capsule the net weight of its contents by subtracting the weight of the shell from the respective gross weight. Calculate the drug substance content, expressed as % of label claim, of each capsule from the net weight of the individual capsule content and the result of the *Assay.* Calculate the acceptance value.

Soft Capsules—Accurately weigh 10 intact capsules individually to obtain their gross weights, taking care to preserve the identity of each capsule. Then cut open the capsules by means of a suitable clean, dry cutting instrument such as scissors or a sharp open blade, and remove the contents by washing with a suitable solvent. Allow the occluded solvent to evaporate from the shells at room temperature over a period of about 30 minutes, taking precautions to avoid uptake or loss of moisture. Weigh the individual shells, and calculate the net contents. Calculate the drug substance content, expressed as % of label claim, in each capsule from the net weight of product removed from the individual capsules and the result of the *Assay.* Calculate the acceptance value.

Solids (including Sterile Solids) in Single-Unit Containers—Proceed as directed for *Hard Capsules,* treating each unit as described therein. Calculate the acceptance value.

Oral Solutions Packaged in •Unit-Dose$_{•6}$ Containers—Accurately weigh the amount of liquid that drains in not more than 5 seconds from each of 10 individual containers. If necessary, compute the equivalent volume after determining the density. Calculate the drug substance content, expressed as % of label claim, in the liquid drained from each unit from the net weight of the individual container content and the result of the *Assay.* Calculate the acceptance value.

Calculation of Acceptance Value—Calculate the acceptance value as shown in *Content Uniformity,* except that the individual contents of the units are replaced with the individual estimated contents defined below.

$\chi_1, \chi_2, \ldots, \chi_n$ = individual estimated contents of the units tested, where $\chi_i = w_i \times A / \overline{W}$,

$w_1, w_2, \ldots, w_n$ = individual weights of the units tested •for weight variation,$_{•6}$

A = content of drug substance (% of label claim) determined as described in the *Assay,* and

$\overline{W}$ = mean of individual weights $(w_1, w_2, \ldots, w_n)$ •of the units used in the *Assay.*$_{•6}$

Solutions for Inhalation Packaged in Glass or Plastic Ampuls and Intended for Use in Nebulizers—[NOTE—Acceptance value calculations are not required for these dosage forms.] Accurately weigh 10 containers individually, taking care to preserve the identity of each container. Remove the contents of each container by a suitable means. Accurately weigh the emptied containers individually, and calculate for each container the net weight of its contents by subtracting the weight of the container from the respective gross weight. From the results of the *Assay,* obtained as directed in the individual monograph, calculate the drug substance content, expressed as % of label claim, in each of the containers.

Change to read:

CRITERIA

Apply the following criteria, unless otherwise specified in the individual monograph.

Uncoated, Coated, or Molded Tablets, Capsules, Oral Solutions in •Unit-Dose Containers, Suspensions or Emulsions or Gels in Single-Unit Containers (that are intended for systemic administration only),$_{•6}$ and Solids (including Sterile Solids) in Single-Unit Containers—The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to *L1*%. If the acceptance value is greater than *L1*%, test the next 20 units, and calculate the acceptance value. The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to *L1*%, and no individual content of any dosage unit is less than •$[1 - (0.01)(L2)]\,M_{•6}$ nor more than •$[1 + (0.01)(L2)]\,M_{•6}$ as specified in the *Calculation of Acceptance Value* under *Content Uniformity* or under *Weight Variation.* Unless otherwise specified in the individual monograph, *L1* is 15.0 and *L2* is 25.0.

Suppositories—

Limit A (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)—Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in each of the 10 dosage units as determined from the *Content Uniformity* method lies within the range of 85.0% to 115.0% of the label claim, and the RSD is less than or equal to 6.0%.

If 1 unit is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim and the RSD of the 30 dosage units does not exceed 7.8%.

Limit B (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

(1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A.*

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(2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A,* except that the words ''label claim'' are replaced by the words ''label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100''.

(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A,* except that the words ''label claim'' are replaced by the words ''label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100''.

Transdermal Systems and Inhalations Packaged in Premetered Dosage Units—

Limit A (if the average of the limits specified in the potency definition in the individual monograph is 100.0 percent or less)—Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the drug substance in not fewer than 9 of the 10 dosage units as determined from the *Content Uniformity* method (or, in the case of solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers, from either the *Content Uniformity* or the *Weight Variation* method) lies within the range of 85.0% to 115.0% of label claim, and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 10 dosage units is less than or equal to 6.0%.

If 2 or 3 dosage units are outside the range of 85.0% to 115.0% of label claim, but not outside the range of 75.0% to 125.0% of label claim, or if the RSD is greater than 6.0% or if both conditions prevail, test 20 additional units. The requirements are met if not more than 3 units of the 30 are outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, and the RSD of the 30 dosage units does not exceed 7.8%.

Limit B (if the average of the limits specified in the potency definition in the individual monograph is greater than 100.0 percent)—

(1) If the average value of the dosage units tested is 100.0 percent or less, the requirements are as in *Limit A.*

(2) If the average value of the dosage units tested is greater than or equal to the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words ''label claim'' are replaced by the words ''label claim multiplied by the average of the limits specified in the potency definition in the monograph divided by 100''.

(3) If the average value of the dosage units tested is between 100 percent and the average of the limits specified in the potency definition in the individual monograph, the requirements are as specified under *Limit A*, except that the words ''label claim'' are replaced by the words ''label claim multiplied by the average value of the dosage units tested (expressed as a percent of label claim) divided by 100''.

•(Official January 1, 2007)•6

ERRATA

Following is a list of errata and corrections to *USP 29–NF 24*. The page number indicates where the item is found in *USP 29–NF 24*. If necessary, this list will be updated with every issue of *PF*. This information will also be available as a cumulative table in future *Supplements* and will appear in its corrected form in a future annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff is available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
1892	*Ranitidine Injection*	*Chromatographic purity*	Line 8 under *Procedure*: Change ''Perform the chromatography as described in *Chromatographic purity* under *Ranitidine Hydrochloride.*'' to: Allow the spots to dry, and develop the chromatograms in a solvent system consisting of a mixture of ethyl acetate, isopropyl alcohol, ammonium hydroxide, and water (25 : 15 : 5 : 1) until the solvent front has moved not less than 15 cm from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow to air-dry. Expose the plate to iodine vapors in a closed chamber until the chromatogram is fully revealed.
		Assay	Delete the single subsection beginning with ''*Mobile phase, Standard preparation, System suitability solution,* and *Chromatographic system*''. Replace with: *Mobile phase*—Prepare a filtered and degassed mixture of methanol and 0.1 M aqueous ammonium acetate (85:15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). *Standard preparation*—Dissolve an accurately weighed quantity of USP Ranitidine Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.112 mg (equivalent to 0.100 mg of ranitidine base) per mL. *System suitability solution*—Dissolve accurately weighed quantities of USP Ranitidine Hydrochloride RS and USP Ranitidine Related Compound C RS in *Mobile phase* to obtain a solution having known concentrations of about 0.112 mg per mL and 0.01 mg per mL, respectively. *Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 322-nm detector and a 4.6-mm × 20- to 30-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between ranitidine hydrochloride and *N*-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]-sulfinyl]ethyl]-*N′*-methyl-2-nitro-1,1-ethenediamine (ranitidine related compound C) is not less than 1.5. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the tailing factor for the ranitidine hydrochloride peak is not more than 2.0; the column efficiency determined from the ranitidine hydrochloride peak is not less than 700 theoretical plates; and the relative standard deviation for replicate injections is not more than 2%.
1892	*Ranitidine Oral Solution*	*Chromatographic purity*	Line 8 under *Procedure*: Change ''Perform the chromatography as described in *Chromatographic purity* under *Ranitidine Hydrochloride.*'' to: Allow the spots to dry, and develop the chromatograms in a solvent system consisting of a mixture of ethyl acetate, isopropyl alcohol, ammonium hydroxide, and water (25 : 15 : 5 : 1) until the solvent front has moved not less than 15 cm from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow to air-dry. Expose the plate to iodine vapors in a closed chamber until the chromatogram is fully revealed.
		Assay	Line 3 under *Mobile phase, Standard preparation, System suitability solution,* and *Chromatographic system:* Change the reference to ''*Ranitidine Hydrochloride*'' to: *Ranitidine Injection*

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Page	Title	Section	Description
1893	*Ranitidine Tablets*	*Assay*	Line 3 under *Mobile phase, Standard preparation, System suitability solution,* and *Chromatographic system:* Change the reference to "*Ranitidine Hydrochloride*" to: *Ranitidine Injection*
1894	*Ranitidine in Sodium Chloride Injection*	*Chromatographic purity*	Line 8 under *Procedure*: Change "Perform the chromatography as described in *Chromatographic purity* under *Ranitidine Hydrochloride.*" to: Allow the spots to dry, and develop the chromatograms in a solvent system consisting of a mixture of ethyl acetate, isopropyl alcohol, ammonium hydroxide, and water (25 : 15 : 5 : 1) until the solvent front has moved not less than 15 cm from the origin. Remove the plate from the developing chamber, mark the solvent front, and allow to air-dry. Expose the plate to iodine vapors in a closed chamber until the chromatogram is fully revealed.
		Assay	Line 3 under *Mobile phase, Standard preparation, System suitability solution,* and *Chromatographic system:* Change the reference to "*Ranitidine Hydrochloride*" to: *Ranitidine Injection*
2013	*Succinylcholine Chloride for Injection*	*Other requirements*	Line 3 under *Mobile phase, Standard preparation, System suitability solution,* and *Chromatographic system:* Delete reference to "*Limit of ammonium salt*"
First Supplement			
3592	⟨121⟩ *Insulin Assays*	*Rabbit Blood Sugar Method—Quantitative*	Under *Calculations,* lines 7 and 8 of the third paragraph: Change "Standard dilution" and "Assay dilution" to: Standard solution and Assay solution
			Line 6 under *Appendix:* Change the formula $$(L,U)=\frac{M'\pm\frac{t}{T_b}\sqrt{(1-g)S_N^2+(M')S_D^2}}{1-g}$$ to: $$(L,U)=\frac{M'\pm\frac{t}{T_b}\sqrt{(1-g)S_N^2+(M')^2S_D}}{1-g}$$

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IN-PROCESS REVISION

This section contains proposals for adoption as official *USP* or *NF* standards (either proposed *new* standards or proposed *revisions* of current *USP* or *NF* standards). These may be any of the following: (1) items that previously appeared under *Pharmacopeial Previews* and are now formally proposed as revisions, (2) proposed revisions placed directly under *In-Process Revision,* or (3) modifications of revisions previously proposed under *In-Process Revision*. Readers should review material in this section and provide comments to the staff liaison (use the *Staff Directory* to find the contact information). Information on how to comment is found in the *Policies and Announcements* section. It is important to send comments promptly so that the Committee members can consider readers' input as they are deciding whether to advance standards to official status.

Briefings Each Proposal is preceded by a Briefing in the following format:

BRIEFING

> **Name of Item**, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being proposed, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How to Use PF*), the name of the scientific staff liaison who handled the particular issue, and the USP tracking correspondence number, as shown in the example below:
>
> (DSN: L. Evans) RTS—C-55678-1

Symbols Proposed revisions are shown with language proposed for deletion or replacement crossed off. New text (if any) follows, and is enclosed in symbols and set off from the current official text by a paragraph break and by larger type (print edition only), as shown in the examples below:

•new text•

if slated for an *Interim Revision Announcement to USP 29–NF 24* (*IRA*);

▲new text▲*USP30*

if slated for *USP 30–NF 25*; and

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, ■2S (*USP 29*) indicates that the proposed revision is slated for the *Second Supplement to USP 29*, and ▲*USP30* and ▲*NF25* indicate that the revisions are proposed for *USP 30* and *NF 25*, respectively.

Official Title Changes Where the specification ***"Monograph title change"*** is found, it indicates that the official title stated after that specification will be substituted for the former title in the appropriate places throughout that monograph once this revision becomes official.

MONOGRAPHS (USP)

BRIEFING

Acetaminophen Extended-Release Tablets, *USP 29* page 22 and page 1161 of *PF* 30(4) [July–Aug. 2004]. It is proposed to add a *Dissolution Test 2* to this monograph because FDA recently approved a new generic version of this product. Also, in *Dissolution Test 1* it is proposed to change the wavelength in the quantitation step from 243 nm to 280 nm because a more linear relationship is obtained at this wavelength. In the absence of any significant adverse comment, it is proposed to implement the inclusion of *Dissolution Test 2* via the *Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of April 1, 2007.

(BPC: M. Marques) RTS—C43633

Add the following:

▲**Packaging and storage—**Preserve in tight containers.▲*USP30*

Change to read:

Labeling—Where the Tablets are gelatin-coated, the label so states.

•When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.•2

Change to read:

Dissolution ⟨711⟩—

TEST 1—
Medium: simulated gastric fluid TS (without enzyme); 900 mL.
Apparatus 2: 50 rpm.
Times: 15 minutes, 1 hour, and 3 hours.
Procedure—Determine the amount of $C_8H_9NO_2$ dissolved from UV absorbances at ~~243 nm,~~

•280 nm,•2
using a filtered portion of the solution under test in comparison with a Standard solution having a known concentration of USP Acetaminophen RS in the same *Medium.*
Tolerances—The percentages of the labeled amount of $C_8H_9NO_2$ dissolved at the times specified conform to *Acceptance Table 2*.

Time	Amount dissolved
15 minutes	between 45% and 65%
1 hour	between 60% and 85%
3 hours	not less than 85%

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1*.

Tolerances—The percentages of the labeled amount of $C_8H_9NO_2$ dissolved at the times specified conform to *Acceptance Table 2*.

Time	Amount dissolved
15 minutes	between 40% and 60%
1 hour	between 55% and 75%
3 hours	not less than 80%

•2

BRIEFING

Bisoprolol Fumarate Tablets, *USP 29* page 293. It is proposed to add a *Dissolution Test 2* because FDA recently approved a new generic version of this product. In the absence of negative comments, it is proposed to implement this inclusion via the *Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of February 1, 2007. Also, it is proposed to correct the dimensions of the column used in the chromatographic procedure in the *Dissolution* test to be in accordance with the validation documentation.

(BPC: M. Marques) RTS—C48402

Add the following:

•**Labeling—**When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.•1

Change to read:

Dissolution ⟨711⟩—

•TEST 1—•1
Medium: water; 900 mL.
Apparatus 2: 75 rpm.
Time: 20 minutes.
Determine the amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ dissolved by employing the following method.
Diluent—Prepare a mixture of methanol, water, triethylamine, and phosphoric acid (160 : 35 : 5 : 2.5).
Mobile phase—Mix 20 mL of triethylamine with 1000 mL of water and 680 mL of methanol, adjust with phosphoric acid to a pH of 4.0 ± 0.1, and mix.
Standard stock solution—Quantitatively dissolve an accurately weighed quantity of USP Bisoprolol Fumarate RS in water to obtain a solution having a known concentration of about twice the concentration of bisoprolol fumarate in the *Test solution.*
Standard solution—Dilute an accurately measured volume of *Standard stock solution* with an equal accurately measured volume of *Diluent.*

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Test solution—Withdraw a portion of the solution under test, filter, dilute with an equal volume of *Diluent,* and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 227-nm detector and a ~~3.9-mm × 30-cm~~ •4.6-mm × 33-cm•[1] column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas for bisoprolol. Calculate the quantity, in mg, of bisoprolol fumarate $[(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4]$ dissolved.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ is dissolved in 20 minutes.

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.5 M sodium chloride; 900 mL.

Apparatus 2: 75 rpm.

Time: 20 minutes.

Determine the amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ dissolved by employing the chromatographic method described in *Test 1*.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $(C_{18}H_{31}NO_4)_2 \cdot C_4H_4O_4$ is dissolved in 20 minutes.•[1]

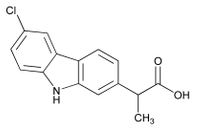
BRIEFING

Carprofen. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The test for *Limit of acetone and methylene chloride* uses a GC method in which the chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m capillary column coated with 3.0-µm G43 stationary phase. USP has received information indicating that the Agilent DB-624 brand of G43 column is suitable. The test for *Related compounds* and the *Assay* are HPLC methods validated with the Zorbax C18 brand of 4.6-mm × 25-cm column that contains 5-µm packing L1. Interested parties are invited to submit comments.

(VET: I. DeVeau) RTS—C44282

Add the following:

▲Carprofen



$C_{15}H_{12}ClNO_2$ 273.71

9*H*-Carbazole-2-acetic acid, 6-chloro-α-methyl-, (±)-.

(±)-6-Chloro-α-methylcarbazole-2-acetic acid [*53716-49-7*].

» Carprofen contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{12}ClNO_2$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Label it to indicate that it is intended for veterinary use only.

USP Reference standards ⟨11⟩—*USP Carprofen RS. USP Carprofen Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

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Limit of acetone and methylene chloride—

Standard solution—Transfer about 5.0 g of acetone and 0.6 g of methylene chloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *N*,*N*-dimethylacetamide to volume, and mix. Pipet 1 mL of this solution into a 100-mL volumetric flask, dissolve in and dilute with *N*,*N*-dimethylacetamide to volume, and mix.

Test solution—Transfer about 500 mg of Carprofen, accurately weighed, to a 5-mL volumetric flask, dissolve in and dilute with *N,N*-dimethylacetamide to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m capillary column coated with 3.0-µm G43 stationary phase. The carrier gas is nitrogen, flowing at a rate of about 4.9 mL per minute. The split flow ratio is about 10 : 1. Initially the column temperature is maintained at 80° for 4 minutes, then is increased at a rate of 30° per minute to a temperature of 190°, and maintained at 190° for at least 3 minutes. The injection port temperature is maintained at 210°, and the detector temperature is maintained at 220°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* acetone elutes before methylene chloride; the resolution, *R,* between them is not less than 1.5; and the relative standard deviation for replicate injections, determined from the peak responses of acetone, is not more than 10.0%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each residual solvent in the portion of Carprofen taken by the formula:

$$0.5(C_S / W)(r_U / r_S)$$

in which C_S is the concentration, in µg per mL, of the individual residual solvent in the *Standard solution; W* is the weight, in mg, of Carprofen taken to prepare the *Test solution;* r_U is the peak response of the individual residual solvent in the *Test solution;* and r_S is the peak response of the individual residual solvent in the *Standard solution:* not more than 5000 ppm of acetone is found; and not more than 600 ppm of methylene chloride is found.

Related compounds—

Mobile phase and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the responses for all the peaks. Calculate the percentage of each related compound in the portion of Carprofen taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the response of each individual peak other than the major peak of carprofen; and r_s is the sum of the peak responses: not more than 0.5% of each individual known related compound is found (see the relative retention times of these compounds in the table below); not more than 0.1% of each individual unknown related compound is found; and not more than 1.0% of total related compounds is found.

Known Related Compound	Approximate Relative Retention Time
Carprofen related compound A (carbazole)	0.9
2-[1,1-dimethoxy-2-hydroxypropyl]-6-chlorocarbazole	1.3
2-[2-chloropropionyl]-6-chloro-9-acetylcarbazole	3.3

Assay—

Mobile phase—Prepare a mixture of acetonitrile, water, methanol, and glacial acetic acid (40 : 35 : 25 : 0.2).

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Carprofen related compound A solution—[NOTE—Use low-actinic glassware.] Prepare a solution of USP Carprofen Related Compound A RS, accurately weighed, in *Mobile phase,* containing about 16 µg per mL, sonicating if necessary.

Standard preparation—[NOTE—Use low-actinic glassware.] Prepare a solution of USP Carprofen RS, accurately weighed, in *Mobile phase,* containing about 160 µg per mL, sonicating if necessary.

System suitability solution—[NOTE—Use low-actinic glassware.] Transfer 10 mL of the *Carprofen related compound A solution* and 10 mL of the *Standard preparation* into a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Assay preparation—[NOTE—Use low-actinic glassware.] Dissolve an accurately weighed quantity of Carprofen in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 160 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 239-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between carprofen and carprofen related compound A is not less than 2.0; the column efficiency for the carprofen peak is not less than 5000 theoretical plates; the tailing factor for the carprofen peak is not more than 2.0; and the relative standard deviation for replicate injections of carprofen is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the percentage of $C_{15}H_{12}ClNO_2$ in the portion of Carprofen taken by the formula:

$$100P(C_S / C_U)(R_U / R_S)$$

in which P is the purity, in µg per mg, of USP Carprofen RS; C_S and C_U are the concentrations, in µg per mL, of the *Standard preparation* and the *Assay preparation,* respectively; and R_U and R_S are the ratios of the carprofen peak response to the internal standard peak response obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Carprofen Tablets. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The tests for *Uniformity of dosage units* and *Related compounds* and the *Assay* use HPLC methods validated with the Phenomenex Prodigy C8 brand of 4.6-mm × 15-cm column that contains 5-µm packing L7. Interested parties are invited to submit comments.

(VET: I. DeVeau; BPC: M. Marques) RTS—C44780

Add the following:

▲Carprofen Tablets

» Carprofen Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of carprofen ($C_{15}H_{12}ClNO_2$).

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Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Carprofen RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Reference specimen—Mix about 2 mg of USP Carprofen RS with 200 mg of potassium bromide, and grind thoroughly for 10 to 15 minutes. Compress the mixture into a clear pellet. Record the IR spectrum of the pellet immediately after preparation.

Test specimen—Grind into powder not fewer than 4 Tablets. Transfer the powder, equivalent to about 100 mg of carprofen, to a 125-mL separatory funnel. Add 30 mL of water and 3 drops of hydrochloric acid, and shake for about 5 minutes. Add about 30 mL of methylene chloride, and shake for another 5 minutes. Allow the phases to separate. Carefully drain and collect the lower methylene chloride layer through anhydrous sodium sulfate that is placed on a cotton pledget into a suitable container. Evaporate the methylene chloride on a steam bath with the aid of a stream of nitrogen to dryness. Dry the residue in vacuum at 60° for about 30 minutes. Mix about 2 mg of the dried residue with 200 mg of potassium bromide, and grind thoroughly for 10 to 15 minutes. Compress the mixture into a clear pellet. Record the IR spectrum of the carprofen sample pellet immediately after preparation.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—[NOTE—Use low-actinic volumetric flasks, dissolution vessels, and evaporation covers.]

Medium: 0.05 M phosphate buffer, pH 7.5 (prepared by dissolving 6.8 g of monobasic potassium phosphate in 600 mL of water, mixing, adding 18 mL of 2 N sodium hydroxide, mixing, diluting with water to 1000 mL, and adjusting with 0.2 N sodium hydroxide or 0.2 N hydrochloric acid to a pH of 7.50 ± 0.05); 900 mL, degassed.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amount of $C_{15}H_{12}ClNO_2$ dissolved by employing the following method.

Standard solution—

FOR TABLETS LABELED TO CONTAIN 25 MG—Transfer about 25 mg of USP Carprofen RS, accurately weighed, to a 900-mL volumetric flask. Slowly add 10 mL of methanol. Dilute with *Medium* to volume, and mix.

FOR TABLETS LABELED TO CONTAIN 75 MG—Transfer about 75 mg of USP Carprofen RS, accurately weighed, to a 900-mL volumetric flask. Slowly add 30 mL of methanol. Dilute with *Medium* to volume, and mix.

FOR TABLETS LABELED TO CONTAIN 100 MG—Transfer about 100 mg of USP Carprofen RS, accurately weighed, to a 900-mL volumetric flask. Slowly add 40 mL of methanol. Dilute with *Medium* to volume, and mix.

Test solution—Pass a portion of the solution under test through a suitable 0.45-µm filter.

System suitability solution—Determine the absorbance of the *Standard solution,* as directed for *Procedure,* five times: the relative standard deviation is not more than 2.0%.

Procedure—Determine the amount of $C_{15}H_{12}ClNO_2$ dissolved by measuring the absorbance of the *Test solution* in comparison with the appropriate *Standard solution* at the wavelength of maximum absorbance at about 300 nm, using a 0.5-cm cell for Tablets labeled to contain 25 mg, a 0.2-cm cell for Tablets labeled to contain 75 mg, and a 0.1-cm cell for Tablets labeled to contain 100 mg. Use *Medium* as the blank. Calculate the percentage of $C_{15}H_{12}ClNO_2$ dissolved by the formula:

$$\frac{A_U \times W_S \times 100}{A_S \times LC}$$

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in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; W_S is the weight, in mg, of USP Carprofen RS used to prepare the *Standard solution;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{12}ClNO_2$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements for *Content Uniformity.*

Procedure for content uniformity—[NOTE—Use low-actinic glassware.]

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Prepare as directed for the *Standard preparation* in the *Assay.*

Test solution—Transfer 10 Tablets individually to 10 separate volumetric flasks of a suitable calibrated volume such that an interim concentration of 0.5 mg per mL of *Mobile phase* can be prepared. To each flask, add *Mobile phase* to 80% of the calibrated volume, sonicate for 10 minutes, then stir for 10 minutes. Sonicate again for 10 minutes, and stir for another 10 minutes or until the Tablets are completely disintegrated. Cool to room temperature, dilute with *Mobile phase* to volume to obtain an interim concentration of 0.5 mg of carprofen per mL, and mix. Quantitatively transfer 5.0 mL of the individual solutions to 10 separate 50.0-mL volumetric flasks, dilute with *Mobile phase* to volume, and mix. Pass the solution through a polyvinylidenefluoride (PVDF) filter having a 0.45-µm or finer porosity, discarding the first 5 mL of the filtrate. The final concentration is about 0.05 mg of carprofen per mL.

Procedure—Proceed as directed for *Procedure* in the *Assay.* Calculate the percentage of the labeled content of $C_{15}H_{12}ClNO_2$ in the portion of Tablets taken by the formula:

$$100(C_S/(C_U)(r_U/r_S)$$

in which the terms are as defined therein.

Chromatographic purity—

Mobile phase—Proceed as directed in the *Assay.*

Standard solution—[NOTE—Use low-actinic glassware.] Dissolve an accurately weighed quantity of USP Carprofen RS in *Mobile phase* to obtain a solution having a known concentration of 0.05 µg of carprofen per mL.

Sensitivity solution—[NOTE—Use low-actinic glassware.] Quantitatively dilute the *Standard solution* with *Mobile phase* to obtain a solution containing about 0.005 µg of carprofen per mL.

Test solution—Use the *Assay preparation.*

Blank solution—Transfer an accurately weighed portion of the Tablet base, equivalent to the weight of 1 Tablet, to a volumetric flask of the same calibrated volume as that used to prepare the *Test solution*. To each flask add *Mobile phase* to 80% of the calibrated volume. Sonicate for 10 minutes, then stir for 10 minutes. Sonicate again for 10 minutes, and stir for another 10 minutes. Cool to room temperature, dilute with *Mobile phase* to volume, and mix. Quantitatively transfer 5.0 mL of the solution to a 50.0 mL-volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass the solution through a PVDF filter having a 0.45-µm or finer porosity, discarding the first 5 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. Wash the column after each series of analyses with a mixture of acetonitrile and water (20 : 80) for 30 minutes; gradually change the composition of acetonitrile and water to 80 : 20 over 10 minutes; continue to wash at 80 : 20 for 30 minutes; gradually change the composition to 50 : 50 over 10 minutes; and continue to wash at 50 : 50 for another 30 minutes. Chromatograph the *Standard solution,* the *Sensitivity solution,* and the *Test solution,* and record the peak responses as directed for *Procedure:* for the *Standard solution,* the column efficiency is not less than 4000 theoretical plates, the tailing factor is not more than 2.0, and the relative standard deviation

for replicate injections is not more than 2.0%; for the *Sensitivity solution,* the carprofen peak should be defined and integratable; for the *Test solution,* the resolution, *R,* between carprofen and the nearest impurity peak is not less than 2.0. After every six injections of any solution, inject a *Standard solution* in duplicate. The ratio of the average response of the duplicate injections to that obtained from the initial five replicate injections is 0.95 to 1.05.

Procedure—Inject a volume (about 50 µL) of the *Standard solution,* the *Test solution,* and the *Blank solution* into the chromatograph, record the chromatograms, and measure all the peak areas. Calculate the percentage of carprofen-related compounds in the portion of Tablets taken by the formula:

$$0.1(C_S / C_U)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of carprofen in the *Standard solution;* C_U is the concentration, in mg per mL, of carprofen in the *Test solution;* r_i is the peak area of any peak other than carprofen obtained from the *Test solution;* and r_S is the peak area of carprofen obtained from the *Standard solution:* not more than 0.5% of any single impurity is found; and the sum of all impurities is not more than 2.0%. Disregard any peak also observed in the *Blank solution.*

Assay—

Mobile phase—Mix 500 mL of acetonitrile, 500 mL of water, and 1 mL of phosphoric acid. Degas before using. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—[NOTE—Use low-actinic glassware.] Dissolve an accurately weighed quantity of USP Carprofen RS in *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay preparation—[NOTE—Use low-actinic glassware.] Accurately weigh 20 Tablets, and calculate the average Tablet weight. Grind the Tablets into uniform powder. Transfer three accurately weighed portions of the powder, each equivalent to the weight of one Tablet, into three volumetric flasks of a suitable calibrated volume such that an interim concentration of 0.5 mg per mL of *Mobile phase* can be prepared. To each flask add *Mobile phase* to 80% of the calibrated volume, sonicate for 10 minutes, then stir for 10 minutes. Sonicate again for 10 minutes, and stir for another 10 minutes. Cool to room temperature, dilute with *Mobile phase* to volume to obtain an interim concentration of 0.5 mg of carprofen per mL, and mix. Quantitatively transfer 5.0 mL of the solution to a 50.0-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass the solution through a PVDF filter having a 0.45-µm or finer porosity, discarding the first 5 mL of the filtrate. The final concentration is about 0.05 mg of carprofen per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. Wash the column after each series of analyses with a mixture of acetonitrile and water (20 : 80) for 30 minutes; gradually change the composition of acetonitrile and water to 80 : 20 over 10 minutes; continue to wash at 80 : 20 for 30 minutes; gradually change the composition to 50 : 50 over 10 minutes; and continue to wash at 50 : 50 for another 30 minutes. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the column efficiency for carprofen is not less than 4000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for five replicate injections is not more than 2.0%. Inject the *Standard preparation* in duplicate after every 12 injections or fewer of any other solution. The ratio of the average area of the duplicate injections to that obtained from the initial five replicate injections is 0.95 to 1.05.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into

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the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of the labeled content of carprofen ($C_{15}H_{12}ClNO_2$) in the portion of Tablets taken by the formula:

$$100(C_S / C_U)(R_U / R_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of USP Carprofen RS in the *Standard preparation* and carprofen in the *Assay preparation,* respectively; and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Diltiazem Hydrochloride Extended-Release Capsules, *USP 29* page 715. It is proposed to add a *Dissolution Test 15* because FDA recently approved a new generic version of this product. In the absence of any negative comments, it is proposed to implement the inclusion of the *Dissolution Test 15* via the *Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of February 1, 2007.

(BPC: M. Marques) RTS—C42282; C45348

Change to read:

Dissolution ⟨711⟩—

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1.* Proceed as directed for *Extended-Release Dosage Forms.*

Medium: water; 900 mL.

Apparatus 2: 100 rpm.

Times: 3, 9, and 12 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to the *Acceptance Table* given.

Acceptance Table

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges, and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time. At 3 hours none of the units is outside the range of 10% to 35% of labeled content; at 9 hours none of the units is outside the range of 45% to 95% of labeled content; and at 12 hours none of the units is less than 65% of labeled content at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges and is not less than the stated amount at the final test time. At 3 hours not more than 2 of the 24 units are outside the range of 10% to 35% of labeled content, and these two units must be within the range of 5% to 45% of labeled content; at 9 hours not more than 2 of 24 of the units are outside the range of 45% to 95% of labeled content, and these two units must be within the range of 35% to 100% of labeled content; at 12 hours not more than 2 of the 24 units are less than 65% of labeled content at the final test time, and these two units cannot be less than 60% of labeled content at the final test time.

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4.*

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times: 4, 8, 12, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
4	between 10% and 25%
8	between 35% and 60%
12	between 55% and 80%
24	not less than 80%

TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5.*

Medium: 0.05 M phosphate buffer, pH 7.2; 900 mL.

Apparatus 2: 50 rpm.

Procedure—Proceed as directed under *Test 1.*

Times: 1, 3, and 8 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	not more than 15%
3	between 45% and 70%
8	not less than 80%

TEST 10—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 10.*

Medium: 0.05 M phosphate buffer, pH 6.5; 900 mL. Prepare the buffer employing the following method. Dissolve 7.1 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 6.5.

Apparatus 1: 100 rpm.

Procedure—Proceed as directed under *Test 1.*

Times: 1, 6, 9, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	not more than 10%
6	between 10% and 30%
9	between 34% and 60%
24	not less than 80%

FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times: 1, 4, 10, and 15 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	between 5% and 20%
4	between 30% and 50%
10	between 70% and 90%
15	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3.*

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 100 rpm.

Times: 6, 12, 18, 24, and 30 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
6	between 20% and 45%
12	between 25% and 50%
18	between 35% and 70%
24	not less than 70%
30	not less than 85%

TEST 6—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6.*

Medium and *Procedure*—Proceed as directed under *Test 1.*

Apparatus 1: 100 rpm.

Times: 2, 4, 8, 12, and 16 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	not more than 25%
4	between 25% and 50%
8	between 60% and 85%
12	not less than 70%
16	not less than 80%

TEST 7—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7.*

Medium: pH 4.2 acetate buffer; 900 mL. Prepare the buffer by employing the following method. Transfer 115 mL of acetic acid to a 10-L volumetric flask, dilute with water to volume, and mix *(Solution A)*. Transfer 165.4 g of anhydrous sodium acetate to a 10-L volumetric flask, dilute with water to volume, and mix *(Solution B)*. Mix 4410 mL of *Solution A* with 1590 mL of *Solution B*. Adjust, if necessary, with the addition of *Solution A* or *Solution B* to a pH of 4.2 ± 0.05.

Apparatus 2: 100 rpm.

Times: 1, 4, 10, and 15 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	not more than 10%
4	between 15% and 35%
10	between 65% and 85%
15	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8.*

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 1.*

Times: 1, 4, 10, and 15 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	between 5% and 20%
4	between 30% and 50%
10	between 60% and 90%
15	not less than 80%

TEST 9—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 9.*

NOTE—Perform the test separately in each of the two media.

Medium 1: 0.1 N hydrochloric acid; 900 mL.

Medium 2: simulated intestinal fluid TS, prepared without enzyme and adjusted to a pH of 7.5 ± 0.1; 900 mL.

Apparatus 2: 75 rpm.

Time for Medium 1: 2 hours.

Times for Medium 2: 2, 12, 18, and 24 hours.

Procedure—Determine the amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 237 nm on filtered portions of the solution under test, suitably diluted with the appropriate *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Diltiazem Hydrochloride RS in the same *Medium.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved (*Medium 1*)	Amount dissolved (*Medium 2*)
2	between 0% and 5%	between 20% and 45%
12		between 35% and 55%
18		not less than 60%
24		not less than 80%

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TEST 11—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11.*

Medium, Apparatus, and *Procedure*—Proceed as directed under *Test 3.*

Times: 1, 6, 12, and 18 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
1	not more than 10%
6	between 30% and 40%
12	between 36% and 58%
18	not less than 85%

TEST 12—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 12.* Proceed as directed for *Extended-Release Dosage Forms.*

Medium and *Procedure*—Proceed as directed under *Test 1.*

Apparatus 1: 100 rpm.

Times: 2, 8, 14, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	not more than 20%
8	between 30% and 55%
14	not less than 65%
24	not less than 80%

TEST 13—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 13.* Proceed as directed for *Extended-Release Dosage Forms.*

Medium and *Procedure*—Proceed as directed under *Test 1.*

Apparatus 1: 100 rpm.

Times: 2, 8, 14, and 24 hours.

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	not more than 20%
8	between 30% and 55%
14	between 60% and 80%
24	not less than 80%

TEST 14—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 14.* Proceed as directed for *Extended-Release Dosage Forms.*

Medium, Apparatus, Times, and *Procedure*—Proceed as directed under *Test 3.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
6	between 20% and 45%
12	between 25% and 50%
18	between 35% and 70%
24	not less than 70%
30	not less than 80%

•TEST 15—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 15.* Proceed as directed for *Extended-Release Dosage Forms.*

Medium: 0.05 M phosphate buffer, pH 7.5; 900 mL.

Apparatus 2: 75 rpm.

Times: 2, 4, 8, 12, and 16 hours.

Procedure—Proceed as directed for *Test 1.*

Tolerances—The percentages of the labeled amount of $C_{22}H_{26}N_2O_4S \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2.*

Time (hours)	Amount dissolved
2	not more than 25%
4	between 20% and 40%
8	between 60% and 85%
12	not less than 70%
16	not less than 80%

•1

BRIEFING

Divalproex Sodium, page 1362 of *PF* 31(5) [Sept.–Oct. 2005]. On the basis of comments received, it is proposed to revise this proposed new monograph. The specific changes include the following:

1. To eliminate the confusion of monomer vs. oligomer, reference to the chemical abstract number has been deleted. Also, the molecular weight has been designated to indicate the repeating unit.
2. The Definition has been modified to indicate that the content is calculated as available valproic acid. The need for content calculation on the "anhydrous basis" has been removed to reflect approved marketed product. Appropriate changes have been made in the *Assay* to reflect this.
3. The *Diluent* has been replaced with *Mobile phase* in the *Assay* to eliminate the problems caused by the presence of sodium lauryl sulfate.
4. *Stock solution A* and *Stock solution B* have been renamed as *Standard stock preparation* and *Impurity stock preparation,* respectively. A separate *System suitability preparation* has been introduced.
5. 2-Propanol has been replaced with acetonitrile as the solvent in the *Impurity stock preparation.*
6. The test for *Residual solvents* is no longer necessary because it is covered under the *General Notices.*

(MD-PP: R. Ravichandran) RTS—C44120

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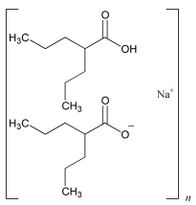
Add the following:

▲Divalproex Sodium



$(C_{16}H_{31}NaO_4)_n$, in which $n \geq 1$. Repeating unit molecular weight, 310.41

Pentanoic acid, 2-propyl-, sodium salt (2 : 1).

Sodium hydrogen bis(2-propylvalerate) ~~oligomer~~ [~~76584-70-8~~].

» ~~Divalproex Sodium contains not less than 98.0 percent and not more than 102.0 percent of $(C_{16}H_{31}NaO_4)_n$, calculated on the anhydrous basis.~~ Divalproex Sodium contains not less than 98.0 percent and not more than 102.0 percent of available valproic acid ($C_8H_{16}O_2$).

Packaging and storage—Preserve in tight containers. Store at room temperature.

USP Reference standards ⟨11⟩—*USP Divalproex Sodium RS. USP Valproic Acid RS. USP Valproic Acid Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: Ignite about 100 mg: the residue meets the requirements of the tests for *Sodium* ⟨191⟩.

Water, *Method I* ⟨921⟩**:** not more than 1.0%, determined on 3.0 g.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

~~**Residual solvents** ⟨467⟩**:** meets the requirements.~~

Assay—

Buffer—Dissolve 3.5 g of monobasic sodium phosphate monohydrate in 900 mL of water. Adjust with phosphoric acid to a pH of 3.5. Dilute with water to 1 L.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and acetonitrile (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Diluent*—Prepare a 0.5% solution of sodium dodecyl sulfate in water.~~

~~*Stock solution A*—Transfer an accurately weighed amount of USP Valproic Acid RS to a suitable volumetric flask, first dissolve in methanol, using 10% of the final volume, then dilute with *Diluent* to volume, and mix to obtain a solution having a known concentration of about 5.0 mg per mL.~~

Standard stock preparation—Transfer an accurately weighed amount of USP Valproic Acid RS to a suitable volumetric flask, and dissolve in *Mobile phase* to obtain a solution having a known concentration of about 5.0 mg per mL.

~~*Stock solution B*—Dissolve an accurately weighed amount of USP Valproic Acid Related Compound A RS in 2-propanol to obtain a solution having a known concentration of about 0.5 mg per mL.~~

Impurity stock preparation—Dissolve an accurately weighed amount of USP Valproic Acid Related Compound A RS in acetonitrile to obtain a solution having a known concentration of about 0.5 mg per mL of valproic acid related compound A.

~~*Standard preparation*—Accurately transfer 20 mL of *Stock solution A* and 1 mL of *Stock solution B* into a 100 mL volumetric flask, and dilute with *Mobile phase* to obtain a solution having 1.0 mg per mL of valproic acid and 0.005 mg per mL of valproic acid related compound A.~~

System suitability preparation—Accurately transfer 10 mL of *Standard stock preparation* and 1 mL of *Impurity stock preparation* to a 100-mL volumetric flask, and dilute with

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Mobile phase to obtain a solution having concentrations of 0.5 mg per mL of valproic acid and 0.005 mg per mL of valproic acid related compound A.

Standard preparation—Dilute quantitatively the *Standard stock preparation* with *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL of valproic acid.

Assay preparation—~~Transfer about 50 mg of Divalproex Sodium, accurately weighed, to a 100-mL volumetric flask; dissolve in 10 mL of methanol; and dilute with *Diluent* to volume. This solution has a concentration of about 0.5 mg per mL ofdivalproex sodium.~~ Transfer about 50 mg of Divalproex Sodium, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Mobile phase* to volume. This solution has a concentration of about 0.5 mg per mL of divalproex sodium.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the ~~*Standard preparation,*~~ *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention time for valproic acid related compound A is about 0.69, and that for valproic acid is 1.0; the resolution, *R,* between valproic acid related compound A and valproic acid is not less than 5.0; for the valproic acid peak, ~~the column efficiency is not less than 5000 theoretical plates;~~ the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about ~~15 µL~~ 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of ~~($C_{16}H_{24}NaO_4$),~~ available valproic acid ($C_8H_{16}O_2$) in the portion of Divalproex Sodium taken by the formula:

$$100(C_S / C_U)(r_U / r_S)(310.41/144.21)(½)$$

in which C_S is the concentration, in mg per mL, of valproic acid in the *Standard preparation;* C_U is the concentration of Divalproex Sodium, in mg per mL, in the *Assay preparation;* r_U and r_S are the peak areas for valproic acid obtained from the *Assay preparation* and the *Standard preparation;* 310.41 and 144.21 are the molecular weights for divalproex sodium repeating unit and valproic acid, respectively; and 2 is the number of moles of valproic acid per mole of divalproex sodium repeating unit.▲*USP31*

BRIEFING

Ensulizole, *USP 29* page 802, page 3719 of the *Second Supplement*, and page 1617 of *PF* 31(6) [Nov.–Dec. 2005]. It is proposed to correct the formula for the *Assay* calculation.

(HDQ: M. Marques) RTS—C47639

Change to read:

Assay—Transfer about 1200 mg of Ensulizole, accurately weighed, to a 300-mL iodine flask, and dissolve by stirring in 25 mL of 0.5 N sodium hydroxide. Add phenolphthalein TS, and titrate the excess with 0.5 N hydrochloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.5 N sodium hydroxide is equivalent to 137.15 mg of $C_{13}H_{10}N_2O_3S$. Calculate the percentage of $C_{13}H_{10}N_2O_3S$ in the portion of Ensulizole taken by the formula:

~~$$\frac{[(V_{NaOH} \times T_{NaOH}) - (V_{HCl} \times T_{HCl})] \times 0.5 \times 274.30 \times 100}{W \times LOD \times 10}$$~~

▲$$\frac{[(V_{NaOH} \times T_{NaOH}) - (V_{HCl} \times T_{HCl})] \times 0.5 \times 274.30 \times 100}{W \times (1 - LOD) \times 10}$$ ▲*USP30*

▲$$\frac{N_{HCl} \times (V_B - V_A) \times 274.30 \times 100}{W \times (1 - LOD)}$$ ▲*USP31*

~~in which V_{NaOH} is the volume, in mL, of 0.5 N sodium hydroxide added; T_{NaOH} is the titer of the 0.5 N sodium hydroxide; V_{HCl} is the volume, in mL, of 0.5 N hydrochloric acid used; T_{HCl} is the titer of 0.5 N hydrochloric acid; W is the weight, in g, of Ensulizole taken;~~

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~~★100 is the percentage conversion factor;▲USP30 *LOD* and is the percentage of loss on drying, as determined in the test for *Loss on drying*.~~

▲in which N_{HCl} is the actual normality of 0.5 N hydrochloric acid; V_B is the volume, in mL, of 0.5 N hydrochloric acid used in the titration of the blank; V_A is the volume, in mL, of 0.5 N hydrochloric acid used in the titration of the sample; W is the weight, in mg, of ensulizole taken, and LOD is the percentage of loss on drying expressed as a decimal fraction, as determined in the test for *Loss on drying*.▲USP31

BRIEFING

Esterified Estrogens, *USP 29* page 852. Because USP has received comments that Esterified Estrogens do not contain 17α-dihydroequilin, it is proposed to revise the *Identification* test, the test for *Free steroids,* and the *Assay* to remove all requirements for and references to 17α-dihydroequilin. In the absence of any significant adverse comments, it is proposed to implement this revision via an *Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of April 1, 2007.

(MD-PS: D. Bempong) RTS—C46968

Change to read:

Identification— ~~It responds to *Identification* test *A* under *Conjugated Estrogens*.~~

•The chromatogram of the *Assay preparation* exhibits distinctive peaks for estrone and equilin at relative retention times corresponding to those exhibited in the chromatogram of the *Standard preparation,* as obtained in the *Assay*.•2

Change to read:

Free steroids— ~~Proceed with Esterified Estrogens as directed in the test for *Limit of estrone, equilin, and 17α-dihydroequilin* (free steroids) under *Conjugated Estrogens*. The limit is 3.0% of free steroids.~~

•*pH 5.2 Acetate buffer, Stock solution, Internal standard solution, and System suitability solution*—Proceed as directed in the *Assay.*

Free steroids standard solution—Dilute the *Stock solution* tenfold. Pipet 1.0 mL of the resulting solution and 1.0 mL of the *Internal standard solution* into a suitable centrifuge tube fitted with a tight screw cap or stopper. Proceed as directed for *Standard preparation* in the *Assay*, beginning with "Evaporate the mixture".

Test solution—Proceed as directed for *Assay preparation* in the *Assay,* with the following exceptions: do not add the sulfatase enzyme preparation, and transfer 6.0 mL instead of 3.0 mL of the filtrate to the centrifuge tube. Prepare a reagent blank in the same manner.

Chromatographic system—Proceed as directed in the *Assay,* with the additional requirement that the relative standard deviation for the ratio of the peak response of estrone to that of the internal standard in the *Free steroids standard solution,* for not less than two replicate injections, is not greater than 5.5%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Free steroids standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the following ratio:

$$R_U / R_S$$

in which R_U is the ratio of the combined peak areas of equilin and estrone relative to the area of the internal standard in the *Test solution,* corrected for any reagent blank peaks; and R_S is the ratio of the peak area of estrone to that of the internal standard obtained from the *Free steroids standard solution:* the ratio is not more than 1.5 (3.0% of free steroids).•2

Change to read:

Assay—

~~*Internal standard solution, Stock solution, Acetate buffer, pH 5.2, System suitability solution, Standard preparation,* and *Chromatographic system*— Proceed as directed in the *Assay* under *Conjugated Estrogens*.~~

•*pH 5.2 Acetate buffer*—Mix 79 mL of sodium acetate TS with 21 mL of 1 N acetic acid, dilute with water to 500 mL, and mix. If necessary, adjust with the 1 N acetic acid or sodium acetate TS to a pH of 5.2 ± 0.1.

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Stock solution—Dissolve accurately weighed quantities of USP Equilin RS and USP Estrone RS in alcohol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 70 µg per mL and 160 µg per mL, respectively.

Internal standard solution—Prepare a solution of 3-*O*-methylestrone in methanol containing about 150 µg per mL.

System suitability solution—Dissolve a quantity of USP Estradiol RS (17β-estradiol) in alcohol to obtain a solution containing about 2 µg per mL. Pipet 1.0 mL of this solution, 1.0 mL of *Stock solution,* and 1.0 mL of *Internal standard solution* into a centrifuge tube fitted with a tight screw cap or stopper. Proceed as directed for *Standard preparation,* beginning with "Evaporate the mixture".

Standard preparation—Pipet 1.0 mL of *Stock solution* and 1.0 mL of *Internal standard solution* into a suitable centrifuge tube fitted with a tight screw cap or stopper. Evaporate the mixture with the aid of a stream of nitrogen to dryness, maintaining the temperature below 50°. To the dry residue add 15 µL of dried pyridine and 65 µL of bis(trimethylsilyl)-trifluoroacetamide containing 1% trimethylchlorosilane. Immediately cover the tube tightly, mix, and allow to stand for 15 minutes. Add 0.5 mL of toluene, and mix.•2

Assay preparation— ~~Using an accurately weighed quantity of Esterified Estrogens, equivalent to about 2 mg of total esterified estrogens, proceed as directed for *Assay preparation* in the *Assay* under *Conjugated Estrogens*.~~

•Transfer an accurately weighed quantity of Esterified Estrogens, equivalent to about 2 mg of total esterified estrogens, to a 50-mL centrifuge tube fitted with a polytef-lined screw cap and containing 15 mL of *pH 5.2 Acetate buffer* and 1 g of barium chloride. Cap the tube tightly, and shake for 30 minutes. If necessary, adjust the solution with 1 N acetic acid or sodium acetate TS to a pH of 5.0 ± 0.5. Place in a sonic bath for 30 seconds, then shake for an additional 30 minutes. Add a suitable sulfatase enzyme preparation equivalent to 2500 Units, and shake for 20 minutes in a water bath maintained at 50°. Add 15.0 mL of ethylene dichloride to the warm mixture, cap the tube again, and shake by mechanical means for 15 minutes. Centrifuge for 10 minutes or until the lower layer is clear. Transfer as much of the organic phase as possible, and dry by passing it rapidly through a filter consisting of a pledget of dry glass wool and about 5 g of anhydrous sodium sulfate in a small funnel. Protect from loss by evaporation. Transfer 3.0 mL of the solution to a suitable centrifuge tube fitted with a tight screw cap or stopper, and add 1.0 mL of *Internal standard solution.* Proceed as directed for *Standard preparation,* beginning with "Evaporate the mixture".

Chromatographic system (See *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector maintained at a temperature of 260° and contains a 0.25-mm × 15-m fused silica capillary column bonded with a 0.25-µm layer of phase G19, and a split injection system. The carrier gas is hydrogen flowing at a rate of 2 mL per minute, and the split flow rate is 40 to 60 mL per minute. The column temperature is maintained at 220°, and the injection port temperature is maintained at 260°. Adjust the operating conditions as necessary to maintain the elution time of the 3-*O*-methylestrone peak at between 17 and 25 minutes. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*: the relative retention times are about 0.29, 0.80, 0.87, and 1.00 for 17-estradiol, estrone, equilin, and 3-*O*-methylestrone, respectively; the resolution, *R,* between estrone and equilin is not less than 1.2; the tailing factor for the estrone peak is not more than 1.3; and the relative standard deviation of the estrone peak ratios, for not fewer than four injections of the *Standard preparation,* is not greater than 2.0%.•2

Procedure— ~~Proceed as directed in the *Assay* under *Conjugated Estrogens*.~~

•Separately inject equal volumes (about 1 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks.•2

Calculate the quantity, in mg, of each sodium estrogen sulfate (equilin and estrone) in the portion of Esterified Estrogens taken by the formula:

$$(0.005)(F)C_i(R_U/R_S)$$

in which F is the conversion factor of free estrogen to the conjugate sodium salt (1.380 for equilin and 1.377 for estrone); C_i is the concentration, in µg per mL, of USP Equilin RS or USP Estrone RS, as appropriate, in the ~~alcohol solution;~~

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•*Standard solution;*•2
and R_U and R_S are the ratios of the estrone or equilin peak areas to the 3-*O*-methylestrone peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Esterified Estrogens Tablets, *USP 29* page 853. Because USP has received comments that Esterified Estrogens do not contain 17α-dihydroequilin, it is proposed to revise the *Assay* to remove all requirements for and references to 17α-dihydroequilin by replacing the cross-reference to *Conjugated Estrogens* in the *Assay* with a cross-reference to *Esterified Estrogens.* It is also proposed to delete USP Testosterone RS from the *USP Reference standards* section because this Reference Standard is not used in any test in the monograph. In the absence of any significant adverse comments, it is proposed to implement this revision via an *Interim Revision Announcement* pertaining to *USP 29–NF 24,* with the official date of April 1, 2007.

(MD-PS: D. Bempong) RTS—C46968

Change to read:

USP Reference standards ⟨11⟩—*USP Equilin RS. USP Estrone RS.* ~~*USP Testosterone RS.*~~

••2

Change to read:

Assay—Weigh and finely powder not fewer than 20 Tablets. Using a suitable portion of the powder, proceed as directed in the *Assay* under ~~*Conjugated Estrogens*~~

•*Esterified Estrogens.*•2

BRIEFING

Famotidine Tablets, *USP 29* page 883. In the *Dissolution* test, it is proposed to add a quantitation method by HPLC and a *Time* and *Tolerances* for Tablets labeled as chewable. The chromatographic procedure was validated using Inertsil ODS-2 brand of L1 packing. An alternative column for this procedure is Hypersil C18.

(BPC: M. Marques) RTS—C48375

Change to read:

Dissolution ⟨711⟩—
Medium: pH 4.5, 0.1 M phosphate buffer; prepared by dissolving 13.6 g of monobasic potassium phosphate in 1 L of water; 900 mL.
Apparatus 2: 50 rpm.
Time: 30 minutes.
~~*Procedure*—Determine the amount of $C_8H_{15}N_7O_2S_3$ dissolved from UV absorption at the wavelength of maximum absorbance at about 265 nm, using filtered portions of the solution under test, suitably diluted with *Medium* if necessary, in comparison with a Standard solution having a known concentration of USP Famotidine RS in the same *Medium.*~~

▲Determine the amount of $C_8H_{15}N_7O_2S_3$ dissolved employing one of the following methods.

SPECTROPHOTOMETRIC METHOD—Determine the amount of $C_8H_{15}N_7O_2S_3$ dissolved from UV absorption at the wavelength of maximum absorbance at about 265 nm, using filtered portions of the solution under test, suitably diluted with *Medium* if necessary, in comparison with a Standard solution having a known concentration of USP Famotidine RS in the same *Medium.*

CHROMATOGRAPHIC METHOD—

Buffer solution and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Famotidine RS in *Medium* to obtain a solution having a known concentration of about 0.14 mg per mL. Dilute this solution with *Medium* to obtain a solution containing *L*/900 mg per mL, *L* being the famotidine tablet label claim, in mg.

Test solution—Use filtered portions of the solution under test.

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′*, is greater than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the

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peak responses. Calculate the amount of $C_8H_{15}N_7O_2S_3$ dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the *Standard solution* and the *Test solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the tablet label claim, in mg.▲*USP31*

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_8H_{15}N_7O_2S_3$ is dissolved in 30 minutes.

▲FOR TABLETS LABELED AS CHEWABLE—Proceed as directed for either of the methods specified above, except for the following:

Time: 45 minutes.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_8H_{15}N_7O_2S_3$ is dissolved in 45 minutes.▲*USP31*

BRIEFING

Finasteride Tablets, *USP 29* page 908. It is proposed to update the system suitability requirements in the *Dissolution* test to reflect the validation report.

(BPC: M. Marques) RTS—C43215

Change to read:

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

FOR PRODUCTS LABELED AS 5-MG TABLETS—

Time: 45 minutes.

Determine the amount of $C_{23}H_{36}N_2O_2$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (29 : 21). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluting solution—Prepare a solution of acetonitrile and water (7 : 3).

Standard solution—Dissolve an accurately weighed quantity of USP Finasteride RS in *Diluting solution,* and dilute quantitatively, and stepwise if necessary, with *Diluting solution* to obtain a solution having a known concentration approximately equivalent to the sample under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The column temperature is maintained at 45°. The flow rate is about 2 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′*, is not less than 2.0; the column efficiency is ~~not less~~

▲greater▲*USP31*
than 1000 theoretical plates; the tailing factor is ~~not more than 2.0;~~

▲less than 2;▲*USP31*
and the relative standard deviation for replicate injections is ~~not more~~

▲less▲*USP31*
than 2.0%.

Procedure—Separately inject equal volumes (about 200 µL) of the solution under test and the *Standard solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of $C_{23}H_{36}N_2O_2$ dissolved.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{23}H_{36}N_2O_2$ is dissolved in 45 minutes.

FOR PRODUCTS LABELED AS 1-MG TABLETS—

Time: 30 minutes.

Mobile phase—Prepare a degassed mixture of acetonitrile and water (11 : 9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluting solution—Prepare a solution of water and acetonitrile (7 : 3).

Standard solution—Dissolve an accurately weighed quantity of USP Finasteride RS in *Diluting solution,* to obtain a solution having a known concentration of 0.1 mg per mL. Dilute this solution quantitatively, and stepwise if necessary, in 0.5% sodium lauryl sulfate to obtain a solution containing 0.001 mg of finasteride per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L11. The column temperature is maintained at 45°. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than ~~2.0;~~

▲2;▲*USP31*
and the relative standard deviation for replicate injections is not more than ~~2.0%~~

▲2%.▲*USP31*

Procedure—Separately inject equal volumes (about 100 µL) of the solution under test and the *Standard solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of finasteride ($C_{23}H_{36}N_2O_2$) dissolved.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{23}H_{36}N_2O_2$ is dissolved in 30 minutes.

In-Process Revision

BRIEFING

Fluvastatin Sodium, *USP 29* page 961 and page 103 of *PF* 32(1) [Jan.–Feb. 2006]. The previously proposed replacement of the test for *Water* with the test for *Loss on drying* is now canceled.

It is proposed to add hydrated forms of Fluvastatin Sodium to the monograph. This proposal is consistent with the policy relating to inclusion of different degrees of hydration which was approved by the Council of Experts Executive Committee in January 2005 and published in *PF* 31(3), page 690, under *Policies and Announcements*. As per this policy, this proposal may become official "... only when the FDA has approved, or has not given any indication that it will not approve, a new drug application for a drug product with a different polymorphic form of the active ingredient than the form used to manufacture the reference listed drug."

The test for *Water* is revised to provide a separate requirement for the hydrated forms of the drug and to add a *Note* to clarify that for this monograph, the term "hydrated form" covers several known forms of Fluvastatin Sodium that are not stoichiometric hydrates. The actual range for the *Water* content for each hydrated form, included in the manufacturer's specifications, may be tighter than the one proposed in the monograph.

It is also proposed to add a *Labeling* requirement. In addition, *Identification* test *A* is revised to add a detailed procedure for a polymorphic equalization.

Interested parties are encouraged to submit their comments to the MD-GRE Expert Committee.

(MD-GRE: E. Gonikberg) RTS—C43519

Change to read:

Packaging and storage—Preserve in tight, light-resistant containers, protected from moisture. ~~Store between 15° and 30°.~~

▲Store at a temperature not exceeding 40°.▲*USP30*

Add the following:

▲**Labeling**—Where it is a hydrated form, the label so indicates.▲*USP31*

Change to read:

USP Reference standards ⟨11⟩—*USP Fluvastatin Sodium RS.* ~~*USP Fluvastatin Related Compound A RS.*~~

▲▲*USP30*
USP Fluvastatin Related Compound B RS. USP Fluvastatin for System Suitability RS.

▲[NOTE—*USP Fluvastatin for System Suitability RS* contains 1% to 2% of the fluvastatin sodium anti-isomer.]▲*USP30*

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩. ▲[NOTE—If a difference appears in the IR spectra of the analyte and the standard, dissolve equal portions of the test specimen and the USP Reference Standard in equal volumes of methanol. Evaporate the solutions to dryness on a steam bath, protecting the solutions from light, and dry at 105° for 30 minutes. Repeat the test on the residues.]▲*USP31*

~~**B:** *Ultraviolet Absorption* ⟨197U⟩.~~

▲▲*USP30*
~~**C:**~~
▲**B:**▲*USP30*
A solution (0.2 in 1) meets the requirements of the flame test for *Sodium* ⟨191⟩.

Change to read:

Water, *Method I* ⟨921⟩**:** not more than 4.0%;

▲if labeled as a hydrated form: not more than 12.0%. [NOTE—For this monograph, the term "hydrated form" refers to several known forms of Fluvastatin Sodium that are not stoichiometric hydrates.]▲*USP31*

Change to read:

Chromatographic purity—[NOTE—Protect all solutions from light, and use amber autosampler vials and low-actinic glassware.]

Solution A, Solution B, and *Mobile phase*—Proceed as directed in the *Assay.*

~~*System suitability stock solution*—Prepare a solution in a mixture of methanol and acetonitrile (3 : 2) containing about 0.1 mg of USP Fluvastatin Related Compound A RS and about 0.1 mg of USP Fluvastatin Related Compound B RS per mL.~~

▲▲*USP30*
System suitability solution—~~Transfer about 50 mg of USP Fluvastatin for System Suitability RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in 35 mL of *Solution B.* Add 5.0 mL of *System suitability stock solution* into the flask, dilute with *Solution A* to volume, and mix.~~

▲Prepare a solution in a mixture of methanol and acetonitrile (3 : 2) containing about 0.1 mg of USP Fluvastatin Related Compound B RS per mL. Transfer about 0.5 mL of this solution to a 10-mL volumetric flask, and dilute to volume with the *System suitability preparation*, prepared as directed in the *Assay.*▲*USP30*
[NOTE—The ~~*System suitability stock solution* and the~~

▲▲*USP30*
System suitability solution is stable for up to 6 months if stored in a refrigerator.]

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

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Chromatographic system—Proceed as directed in the *Assay,* except use the liquid chromatograph equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 305 nm and at 365 nm. Chromatograph the *System suitability solution,* and record the peak responses at 305 nm as directed for *Procedure.* Identify the peaks corresponding to fluvastatin, fluvastatin anti-isomer, ~~fluvastatin hydroxydiene,~~

▲▲*USP30*
and fluvastatin *t*-butyl ester. The resolution, *R,* between fluvastatin anti-isomer and fluvastatin is not less than 1.6; the column efficiency is not less than 700 theoretical plates for the fluvastatin peak; and the tailing factor is not more than 3.0. Chromatograph the *Standard solution,* and record the peak responses at 305 nm as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms at 305 nm and 365 nm, identify the impurities listed in *Table 1,* and measure the peak responses. [NOTE—3-Hydroxy-5-keto fluvastatin is monitored using a wavelength of 365 nm, and all other compounds are monitored at 305 nm.] Calculate the percentage of each impurity, except for 3-hydroxy-5-keto fluvastatin, in the portion of Fluvastatin Sodium taken by the formula:

~~$100F(C_S/C_T)(r_{i\,(305)}/r_{S\,(305)})$~~

▲$100(1/F)(C_S/C_T)(r_{i\,(305)}/r_{S\,(305)})$▲*USP30*

in which F is the relative response factor as listed in *Table 1* [NOTE—Use F equal to 1.0 for unknown impurities]; C_S is the concentration, in mg per mL, of USP Fluvastatin Sodium RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Fluvastatin Sodium in the *Test solution;* $r_{i\,(305)}$ is the peak response at 305 nm for each impurity obtained from the *Test solution;* and $r_{S\,(305)}$ is the peak response at 305 nm for the fluvastatin peak obtained from the *Standard solution.*

Calculate the percentage of 3-hydroxy-5-keto fluvastatin in the portion of Fluvastatin Sodium taken by the formula:

~~$100F(C_S/C_T)(r_{i\,(365)}/r_{S\,(365)})$~~

▲$100(1/F)(C_S/C_T)(r_{i\,(365)}/r_{S\,(365)})$▲*USP30*

in which F, C_S, and C_T are as defined above; $r_{i\,(365)}$ is the peak response at 365 nm for 3-hydroxy-5-keto fluvastatin obtained from the *Test solution;* and $r_{S\,(365)}$ is the peak response at 365 nm for the fluvastatin peak obtained from the *Standard solution.* In addition to not exceeding the limits for each impurity in *Table 1,* not more than 0.1% of any other individual impurity is found; and not more than 1.0% of total impurities is found.

Table 1

Name	Relative Retention Time	Relative Response Factor *(F)*	Limit (%)
Fluvastatin *N*-ethyl analog ▲[2]▲*USP30*	0.7	~~0.9~~ ▲1.2▲*USP30*	0.1
Fluvastatin anti-isomer ▲[3]▲*USP30*	1.2	1.0	0.8
3-Hydroxy-5-keto fluvastatin ▲[4]▲*USP30*	1.5	~~0.037~~[1] ▲27.0[1]▲*USP30*	0.1
3-Keto-5-hydroxy fluvastatin ▲[5]▲*USP30*	1.6	~~1.6~~ ▲0.63▲*USP30*	0.1
Fluvastatin hydroxydiene[2] ▲[6]▲*USP30*	2.0	~~1.1~~ ▲0.92▲*USP30*	0.1
Fluvastatin short chain aldehyde ▲[7]▲*USP30*	3.0	~~0.7~~ ▲1.4▲*USP30*	0.1
Fluvastatin *t*-butyl ester ▲(fluvastatin related compound B)▲*USP30* [3] ▲[8]▲*USP30*	3.4	~~1.1~~ ▲0.94▲*USP30*	0.2

[1] At 365 nm

[2] ~~Fluvastatin related compound A~~
▲[*R**,*S**-*E*]-(±)-7-[3-(4-Fluorophenyl)-1-ethyl-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt▲*USP30*

[3] ~~Fluvastatin related compound B~~
▲[*R**,*R**-*E*]-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid monosodium salt▲*USP30*

▲[4] *E*-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3-hydroxy-5-oxo-6-heptenoic acid monosodium salt▲*USP30*

▲[5] *E*-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3-oxo-5-hydroxy-6-heptenoic acid monosodium salt▲*USP30*

▲[6] [*E,E*]-(±)-7-[3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indol-2-yl]-3-hydroxy-4,6-heptadienoic acid monosodium salt▲*USP30*

▲[7] 3-(4-Fluorophenyl)-1-(methylethyl)-1*H*-indole]-2-carboxaldehyde▲*USP30*

▲[8] [*R**,*S**-*E*]-(±)-7-[3-(4-Fluorophenyl)-1-methylethyl-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1-dimethylethyl ester▲*USP30*

In-Process Revision

BRIEFING

Fluvoxamine Maleate Tablets, page 3568 of the *First Supplement* and page 1622 of *PF* 30(5) [Sept.–Oct. 2004]. In the *Procedure* section of the *Dissolution* test, it is proposed to add a statement allowing corrections, as needed, to eliminate the effect of interference caused by excipients.

(BPC: M. Marques) RTS—C48262

Change to read:

Dissolution ⟨711⟩—

Medium: water; 900 mL, degassed.
Apparatus 2: 50 rpm.
Time: 30 minutes.
Procedure—Determine the amount of $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 246 nm on portions of the solution under test centrifuged at 2000 rpm for 10 minutes, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Fluvoxamine Maleate RS in the same *Medium*.

▲When there are known interferences due to excipients, excipient interference corrections may be applied, as necessary.▲*USP31*
Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{21}F_3N_2O_2 \cdot C_4H_4O_4$ is dissolved in 30 minutes.

Add the following:

■**Related compounds—**

Buffer solution, Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Identification solution—Dissolve a quantity of maleic acid in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.35 mg per mL.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay stock preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution,* the *Test solution,* and the *Identification solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of impurities in the portion of Tablets taken by the formula:

$$100(C/D)F(r_i/r_S)$$

in which C is the concentration, in mg per mL, of USP Fluvoxamine Maleate RS in the *Standard solution; D* is the expected concentration, in mg per mL, of fluvoxamine maleate taking into account the labeled amount and the amount of sample taken to prepare the *Test solution; F* is the response factor of each impurity as given in *Table 1;* r_i is the individual peak area of each impurity in the *Test solution;* and r_S is the peak area of fluvoxamine maleate in the *Standard solution.* The limits of impurities are specified in *Table 1.* [NOTE—Disregard any peak due to maleic acid or to the reagent blank.]

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Table 1

Compound name	Relative retention time	Response Factor	Limit %
Maleic acid	about 0.19	—	—
5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-[2-[(2-succinyl)amino]ethyl]oxime	about 0.50	1.0	0.8
5-Methoxy-4′-(trifluoromethyl)valerophenone(*E*)-*O*-(2-aminoethyl)aminoethyl oxime maleate	about 0.67	1.4	0.2
Z-isomer	about 0.79	1.0	0.5
Fluvoxamine	1.0	—	—
4′-(Trifluoromethyl)valerophenone(*E*)-*O*-2-(2-aminoethyl)aminoethyl oxime maleate	about 1.18	1.0	0.2
(*E*)-*O*-2-(2-Aminoethyl)-4-(trifluoromethyl)-α-phenylacetophenone oxime maleate	about 1.74	1.0	0.2
4′-(Trifluoromethyl)valerophenone(*E*)-*O*-(2-aminoethyl) oxime maleate	about 2.00	1.0	0.2
5-Methoxy-4′-(trifluoromethyl)valerophenone oxime	about 3.45	0.6	0.2
5-Methoxy-1-[4-(trifluoromethyl)phenyl]-1-pentanone-(*E*)-*O*-(2-aminoethyl] oxime maleic acid monoamide	about 4.3	1.0	0.2
5-Methoxy-4′-(trifluoromethyl)valerophenone ketone	about 4.2	0.3	0.2
Unknown impurities	—	1.0	0.1
Total	—	—	1.8

■1S (*USP30*)

In-Process Revision

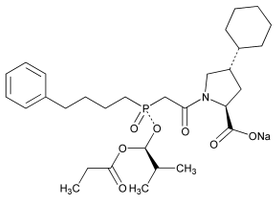
BRIEFING

Fosinopril Sodium, page 789 of *PF* 32(3) [May–June 2006]. On the basis of comments received, it is proposed to revise the chemical names of fosinopril related compound B and fosinopril related compound F in the footnotes under *Table 1*.

(MD-CV: S. Ramakrishna) RTS—C48880

Add the following:

■Fosinopril Sodium



$C_{30}H_{45}NNaO_7P$ 585.64

L-Proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, [1[*S*(R*)*],2α,4*β*]-.

(4*S*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt [*88889-14-9*].

» Fosinopril Sodium contains not less than 97.5 percent and not more than 102.0 percent of $C_{30}H_{45}NNaO_7P$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Fosinopril Sodium RS. USP Fosinopril Related Compound A RS. USP Fosinopril Related Compound B RS. USP Fosinopril Related Compound C RS. USP Fosinopril Related Compound D RS. USP Fosinopril Related Compound E RS. USP Fosinopril Related Compound F RS.*

Identification, *Infrared Absorption* ⟨197M⟩.

Water, ~~*Method II*~~ *Method I* ⟨921⟩**:** not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Change to read:

Related compounds—

TEST 1—

Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure—Proceed as directed in the *Assay,* and measure the areas for each component in the chromatogram obtained, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentage of each individual related compound by the formula:

$$100(r_i / r_s)$$

in which r_i is the response of any individual peak, other than the fosinopril sodium peak; and r_s is the sum of the responses of all the peaks. [NOTE—If present, two more diastereomers may not be resolved from fosinopril related compound B by this method. These peaks, appearing at a relative retention

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time of 0.7, should be integrated together to determine conformance with the limit in *Table 1*.]

Table 1

Relative Retention Time	Fosinopril Related Compound	Test	Limit (%)
2.0	A[1]	1	0.3
0.7	B[2]	1	1.0
1.2	C[3]	2	0.3
1.3	D[4]	2	0.3
0.8	E[5]	3	0.3
0.9	F[6]	3	0.3
0.12	Impurity 1[7]	1	0.3
0.24	Impurity 2[8]	1	0.2

[1] (4*S*)-4-Cyclohexyl-1-[(4-phenylbutyl)phosphinyl]acetyl-L-proline

[2] (4~~*R*~~▲*S*▲*USP31*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-D-proline propionate (ester)

[3] Mixture of (4*S*)-4-Cyclohexyl-1-[*(S)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt and (4*S*)-4-Cyclohexyl-1-[[*(R)*-[*(R)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt

[4] (4*R*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt

[5] (4*S*)-4-~~Cyclohexyl~~ Phenyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt

[6] (4*S*)-4-Cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-~~ethoxy~~▲propoxy▲*USP31*](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), ▲sodium salt▲*USP31*

[7] (2*S*,4*S*)-4-Cyclohexyl-1-pivaloylpyrrolidine-2-carboxylic acid

[8] 2-(*(RS)*-(*(SR)*-2-Methyl-1-(propionyloxy)propoxy)(4-phenylbutyl)-phosphinyl)acetic acid

TEST 2—

Mobile phase—Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (4000 : 15 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Resolution solution—Transfer about 1 mg each of USP Fosinopril Sodium RS, USP Fosinopril Related Compound C RS, and USP Fosinopril Related Compound D RS to a 100-mL volumetric flask. Dissolve in and dilute with the *Standard solution* to volume, and mix.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains packing L12. The column temperature is maintained at 45°. The flow rate is about 0.9 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fosinopril sodium and fosinopril related compound C is not less than 1.5.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to two times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compound C and fosinopril related compound D only by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of fosinopril related compound C or fosinopril related compound D; and r_s is the sum of the responses of all the peaks.

TEST 3—

0.2% Phosphoric acid solution—Prepare a 1 in 500 solution of phosphoric acid.

Mobile phase—Prepare a degassed mixture of acetonitrile and *0.2% Phosphoric acid solution* (560 : 440). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Transfer about 1 mg each of USP Fosinopril Sodium RS, USP Fosinopril Related Compound E RS, and USP Fosinopril Related Compound F RS to a 100-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer about 10 mg of Fosinopril Sodium, accurately weighed, to a 50-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 25-cm column that contains packing L11. The column temperature is maintained at 45°. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fosinopril related compound F and fosinopril sodium is not less than 1.5, and the resolution between fosinopril related compound E and fosinopril related compound F is not less than 1.5.

Procedure—Inject about 20 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak areas, carrying out the chromatography to four times the retention time of the fosinopril sodium peak. Calculate the percentages of fosinopril related compound E and fosinopril related compound F only, ~~by~~ using the formula below:

$$100(r_i / r_s)$$

in which r_i is the peak response of fosinopril related compound E or fosinopril related compound F; and r_s is the sum of the responses of all the peaks. In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.1% of any other individual impurity is found (calculated as directed for the *Procedure* in *Test 1*); and not more than 1.5% of total impurities is found.

~~**Organic volatile impurities,** *Method I* **Residual solvents** ⟨467⟩**:** meets the requirements.~~

Assay—

Mobile phase—Prepare a degassed mixture of acetonitrile, water, and phosphoric acid (2000 : 10 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 10 mg of USP Fosinopril Sodium RS, and about 1 mg each of USP Fosinopril Related Compound A RS and USP Fosinopril Related Compound B RS to a 100-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Fosinopril Sodium RS in *Mobile phase* to obtain a solution having a known concentration of about 0.10 mg per mL.

Assay preparation—Transfer about 25 mg of Fosinopril Sodium, accurately weighed, to a 250-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 3.9-mm × 15-cm column that contains packing L3. The column temperature is maintained at 33°. The flow rate is about 1.2 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between fosinopril related compound B and fosinopril sodium is not less than 2.0; and the relative standard deviation of the fosinopril sodium peak response for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in mg, of $C_{30}H_{45}NNaO_7P$ in the portion of Fosinopril Sodium taken by the formula:

$$250C_S(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Fosinopril Sodium RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP30*)

In-Process Revision

BRIEFING

Gabapentin, page 3569 of the *First Supplement* and page 50 of *PF* 31(1) [Jan.–Feb. 2005]. On the basis of comments received, it is proposed to make the following changes in the test for *Related compounds*.

1. It is proposed to delete *Test 2* because it monitors only gabapentin related compound A and *Test 1, Method 1* also monitors this related compound.
2. *Test 1, Method 1* is renamed as *Limit of early eluting impurities,* and *Test 1, Method 2* is renamed as *Limit of late eluting impurities.*
3. The *System suitability solution* in the current *Assay* is moved to *Limit of early eluting impurities* because the criteria are more relevant for this test.
4. In the *Procedure,* the limit of total impurities is revised to reflect the currently approved products on the market.

In addition, the proposed *Labeling* section is deleted, based on the changes made in the test for *Related compounds*. The test for *Limit of chloride* is also deleted because it does not provide any specific value-added information related to the quality of the drug substance.

(MD-PP: R. Ravichandran) RTS—C47073

~~**Labeling**—Label it to indicate with which impurity tests the article complies.~~

Delete the following:

▲~~**Limit of chloride**—Transfer about 1500 mg of Gabapentin, accurately weighed, to a 100-mL beaker, and dissolve in 50 mL of a mixture of water, methanol, and acetic acid (60 : 39 : 1). Titrate with 0.01 N silver nitrate VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections (see *Titrimetry* ⟨541⟩). Each mL of 0.01 N silver nitrate is equivalent to 0.3545 mg of chloride: not more than 0.01% is found.~~▲*USP31*

Add the following:

▲**Related compounds**—~~[NOTE—Perform all related impurity tests unless the manufacturer has assurance, based on knowledge of the manufacturing process, that one of the tests is not relevant to the manufacturer's material.]~~

~~TEST 1, METHOD 1~~ LIMIT OF EARLY ELUTING IMPURITIES—

Diluent, Buffer solution, Mobile phase, ~~*Impurities solution, System suitability solution,*~~ and *Chromatographic system*—Proceed as directed in the *Assay.*

Impurities solution—Dissolve suitable quantities of USP Gabapentin RS, USP Gabapentin Related Compound A RS, and USP Gabapentin Related Compound B RS in methanol to obtain a solution containing about 1.4 mg per mL and 0.84 mg per mL, respectively.

System suitability solution—Dissolve a suitable quantity of USP Gabapentin RS in *Diluent,* and add an appropriate volume of *Impurities solution* to obtain a solution containing about 14.0 mg per mL, 0.014 mg per mL, and 0.0084 mg per mL of USP Gabapentin RS, USP Gabapentin Related Compound A RS, and USP Gabapentin Related Compound B RS, respectively.

Test solution—Use the *Assay preparation*.

Standard solution—~~Use the *Standard preparation,* prepared as directed in the *Assay.*~~ Dissolve a suitable quantity of USP Gabapentin Related Compound E RS in *Diluent* to obtain a solution having a known concentration of 8.4 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution* (about 20 µL), and record the peak responses as directed for *Procedure:* identify the major peaks using the relative retention times given in *Table 1:* the resolution, *R,* between gabapentin related compound A and gabapentin related compound B is not less than 2.3; and the relative standard deviation for gabapentin is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of any impurity in the portion of Gabapentin taken by the formula:

$$\sim\sim 2500F(C/W)(r_i/r_S)\sim\sim$$

$$100(1/F)C_S/C_T)(r_i/r_S)$$

~~in which *F* is the relative response factor of the impurity according the table below; *C* is the concentration, in mg per mL, of USP Gabapentin Related Compound E RS in the *Standard solution; W* is the weight, in mg, of Gabapentin, on an anhydrous basis, used to prepare the *Test solution;*~~ in

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which F is the relative response factor of the impurity (relative to gabapentin related compound E) according to *Table 1;* C_S is the concentration, in mg per mL, of USP Gabapentin Related Compound E RS in the *Standard solution;* C_T is the concentration of Gabapentin, in mg per mL, in the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for gabapentin related compound E in the *Standard solution:* the impurities meet the requirements given in ~~table~~ *Table 1*.~~.~~

~~Compound Name~~	~~Relative Response Factor~~	~~Limit (%)~~
~~Gabapentin related compound A~~	~~1.0~~	~~0.10~~
~~Gabapentin related compound B~~	~~1.0~~	~~0.06~~
~~Gabapentin related compound E~~	~~1.0~~	~~0.10~~
~~Individual unknown impurity~~	~~0.025~~	~~0.10~~

~~TEST 1, METHOD 2~~ LIMIT OF LATE ELUTING IMPURITIES—

Diluent—Dissolve 2.32 g of ammonium phosphate monobasic in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Buffer solution—Proceed as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* ~~methanol, and acetontrile (35 : 30 : 30)~~ acetonitrile, and methanol (35 : 35 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Gabapentin Related Compound D RS in a small amount of methanol, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.0028 mg per mL.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 13,600 theoretical plates for the gabapentin related compound D peak; and the relative standard deviation for replicate injections is not more than 7.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. [NOTE—Disregard all the peaks having relative retention times of 0.35 or less relative to

Table 1

Compound Name	Relative Retention Time[1] (approximate)	Relative Response Factor[2]	Limit (%)
Gabapentin related compound E	2.9	1.0	0.10
Gabapentin related compound A	3.5	5.3	0.1
Gabapentin related compound B	3.8	0.35	0.06
Individual unknown impurity	—	0.41	0.10

[1] The relative retention times are calculated based on the retention time of gabapentin. [NOTE—This information is for identification purposes only.]
[2] The relative response factors are calculated based on the response of gabapentin related compound E due to the low absorptivity of gabapentin at the monitoring wavelength (215 nm).

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gabapentin related compound D as these are quantified in the test for *Related compounds*.] Calculate the percentage of any impurity in the portion of Gabapentin taken by the formula:

~~$2500(C/W)(r_i/r_s)$,~~

$$100(1/F)(C_S/C_T)(r_i/r_S)$$

~~in which *C* is the concentration, in mg per mL, of USP Gabapentin Related Compound D RS in the *Standard solution; W* is the weight, in mg, of Gabapentin, on the anhydrous basis, used to prepare the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_s is the peak area for gabapentin related compound D in the *Standard solution:* not more than 0.02% of gabapentin related compound D is found; not more than 0.10% of any other impurity is found; and not more than 0.35% of total impurities is found (including the impurities quantified in *Test 1* and *Test 2*) [NOTE—Disregard all the peaks having relative retention times of 0.35 or less.]~~ in which F is the relative response factor of the impurity (relative to gabapentin related compound D) which is 1.0 for gabapentin related compound D and 0.025 for all other impurities, respectively; C_S is the concentration, in mg per mL, of USP Gabapentin Related Compound D RS in the *Standard solution;* C_T is the concentration of Gabapentin, in mg per mL, in the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for gabapentin related compound D in the *Standard solution:* not more than 0.10% of any impurity is found, and not more than 0.5% of total impurities (including the impurities quantified in *Limit of early eluting impurities*) is found.

~~TEST 2—~~

~~*Diluent*—Dissolve 1.2 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 5 N potassium hydroxide to a pH of 6.9.~~

~~*Blank solution*—Use the *Diluent.*~~

~~*Solution A*—Dissolve 1.2 g of monobasic potassium phosphate in 940 mL of water, and adjust with 5 N potassium hydroxide to a pH of 6.9, add 60 mL of acetonitrile, mix, filter, and degas.~~

~~*Solution B*—Dissolve 1.2 g of monobasic potassium phosphate in 700 mL of water, adjust with 5 N potassium hydroxide to a pH of 6.9, add 300 mL of acetonitrile, mix, filter, and degas.~~

~~*Mobile phase*—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard solution*—Dissolve accurately weighed quantities of USP Gabapentin RS and USP Gabapentin Related Compound A RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.04 mg per mL.~~

~~*Test solution*—Transfer about 500 mg of Gabapentin, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.3 mL per minute. The chromatograph is programmed as follows. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 4.8 for gabapentin related compound A and 1.0 for gabapentin; and the relative standard deviation for replicate injections in both peaks is not more than 10.0%.~~

~~Time (minutes)~~	~~*Solution A* (%)~~	~~*Solution B* (%)~~	~~Elution~~
~~0~~	~~100~~	~~0~~	~~equilibration~~
~~0–7~~	~~100~~	~~0~~	~~isocratic~~
~~7–45~~	~~100→0~~	~~0→100~~	~~linear gradient~~
~~45–45.1~~	~~0→100~~	~~100→0~~	~~linear gradient~~
~~45.1–48~~	~~100~~	~~0~~	~~re-equilibration~~

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~~*Procedure*—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. [NOTE—Disregard any peaks obtained from the *Blank solution.*] Calculate the percentage of gabapentin related compound A in the portion of Gabapentin taken by the formula:~~

~~$2500(C/W)(r_u/r_s)$,~~

~~in which C is the concentration, in mg per mL, of USP Gabapentin Related Compound A RS in the *Standard solution*; W is the amount, in mg, of Gabapentin taken to prepare the *Test solution*; r_u is the peak area of gabapentin related compound A in the *Test solution;* and r_s is the peak area of USP Gabapentin Related Compound A RS in the *Standard solution:* not more than 0.10% of gabapentin related compound A is found. Calculate the percentage of each impurity in the portion of Gabapentin taken by the formula:~~

~~$2500(C/W)(r_u/r_s)$,~~

~~in which C is the concentration, in mg per mL, of USP Gabapentin RS in the *Standard solution*; W is the amount, in mg, of Gabapentin taken to prepare the *Test solution*; r_u is the peak area of any impurity different from gabapentin related compound A in the *Test solution;* and r_s is the peak area of USP Gabapentin RS in the *Standard solution:* not more than 0.10% of any individual impurity is found, and the sum of all impurities is not more than 0.50%.~~ ▲*USP31*

Change to read:

Assay—

Diluent—Dissolve 2.32 g of monobasic ammonium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.0.

Buffer solution—Dissolve 0.58 g of monobasic ammonium phosphate and 1.83 g of sodium perchlorate in 1000 mL of water. Adjust with perchloric acid to a pH of 1.8.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (76 : 24). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Impurities solution*—Dissolve suitable quantities of USP Gabapentin Related Compound A RS and USP Gabapentin Related Compound B RS in methanol to obtain a solution containing about 1.4 mg per mL and 0.84 mg per mL, respectively.~~

~~*System suitability solution*—Dissolve suitable quantities of USP Gabapentin RS in *Diluent,* and add an appropriate volume of *Impurities solution* to obtain a solution containing about 14.0 mg per mL, 0.014 mg per mL, and 0.0084 mg per mL of USP Gabapentin RS, USP Gabapentin Related Compound A RS, and USP Gabapentin Related Compound B RS, respectively.~~

▲ ▲*USP31*

Standard preparation—Dissolve ~~accurately weighed quantities of *USP Gabapentin RS* and *USP Gabapentin Related Compound E* RS~~ ▲an accurately weighed quantity of USP Gabapentin RS▲*USP31* in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 14.0 mg per mL and 0.0084 mg per mL, respectively.

Assay preparation—Transfer about 350 mg of Gabapentin, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. ~~Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 2.75 for gabapentin related compound A, about 3.3 for gabapentin related compound B, and 1.0 for gabapentin; and the resolution, *R,* between gabapentin related compound A and gabapentin related compound B is not less than 2.3.~~

▲ ▲*USP31*

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are about 2.9 for gabapentin related compound E and 1.0 for gabapentin; and~~

▲ ▲*USP31*

the relative standard deviation for replicate injections is not more than 2.0% for the gabapentin peak.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the ~~quantity, in mg,~~ ▲percentage▲*USP31* of $C_9H_{17}NO_2$ in the portion of Gabapentin taken by the formula:

~~$25C(r_U/r_S)$~~

$$▲100(C_S/C_U)(r_U/r_S)▲_{USP31}$$

in which ~~C is the concentration, in mg per mL, of USP Gabapentin RS in the *Standard preparation;*~~ ▲C_S and C_U are the concentrations of gabapentin, in mg per mL, in the *Standard preparation* and the *Assay preparation,* respectively;▲*USP31* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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BRIEFING

Gabapentin Capsules. A monograph for Gabapentin Capsules had been proposed in *PF* 28(2) [Mar.–Apr. 2002] but was recently canceled. A new monograph is now being proposed for this dosage form. The liquid chromatographic procedures in the tests for *Related compounds* and *Dissolution* and in the *Assay* are based on analyses performed with the Spherisorb S5 brand of L7 column. In the test for *Related compounds,* a gradient elution method is used in which the typical retention time for gabapentin related compund A is 33 minutes. In the *Assay,* an isocratic method is used in which the typical retention time for gabapentin is 6 minutes.

(MD-PP: R. Ravichandran; BPC: M. Marques) RTS—C44434

Add the following:

▲Gabapentin Capsules

» Gabapentin Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of gabapentin ($C_9H_{17}NO_2$).

Packaging and storage—Preserve in well-closed containers. Store at conrolled room temperature.

USP Reference standards ⟨11⟩—*USP Gabapentin RS. USP Gabapentin Related Compund A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

Test specimen—Empty the contents of not fewer than 10 Capsules, and grind to a fine powder. Use an amount of the powder, equivalent to 2 mg of gabapentin, and 200 mg of potassium bromide.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩**—**

Medium: 0.06 N hydrochloric acid (prepared by adding 51 mL of hydrochloric acid to 10 L of water); 900 mL.

Apparatus 2: 50 rpm.

Time: 20 minutes.

Determine the amount of gabapentin ($C_9H_{17}NO_2$) dissolved by employing the following method.

Mobile phase—Proceed as directed in the *Assay.*

Standard stock solution—Transfer about 111 mg of USP Gabapentin RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Medium* to volume.

Working standard solution—

FOR CAPSULES LABELED TO CONTAIN 100 MG—Transfer 10.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, and dilute with *Medium* to volume.

FOR CAPSULES LABELED TO CONTAIN 300 MG—Transfer 30.0 mL of *Standard stock solution* to a 100-mL volumetric flask, and dilute with *Medium* to volume.

FOR CAPSULES LABELED TO CONTAIN 400 MG—Transfer 20.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, and dilute with *Medium* to volume.

Test solution—Pass a portion of the solution under test through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to use the *Working standard solution*.

Procedure—Separately inject equal volumes (about 100 µL) of the appropriate *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the amount of gabapentin ($C_9H_{17}NO_2$) dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the *Working standard solution* and the *Test solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution*; 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Capsule label claim in mg.

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Tolerances—Not less than 80% *(Q)* of the labeled amount of gabapentin ($C_9H_{17}NO_2$) is dissolved in 20 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Diluent—Prepare as directed in the *Assay.*

Solution A—Dissolve 1.2 g of monobasic potassium phosphate in 940 mL of water. Adjust with 5 N potassium hydroxide to a pH of 6.9, add 60 mL of acetonitrile, and stir. Filter, and degas.

Solution B—Dissolve 1.2 g of monobasic potassium phosphate in 700 mL of water. Adjust with 5 N potassium hydroxide to a pH of 6.9, add 300 mL of acetonitrile, and stir. Filter, and degas.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities of USP Gabapentin RS and USP Gabapentin Related Compound A RS in *Diluent* to obtain a solution having a known concentration of about 0.04 mg of each per mL.

Test solution—Weigh and finely powder not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg of gabapentin, to a suitable volumetric flask, and dissolve the contents in *Diluent* with sonication, if necessary, for about 30 seconds. Dilute with *Diluent* to volume, and mix to obtain a final solution having a known concentration of about 20 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0.0–4.0	100	0	isocratic
4.0–45.0	100→0	0→100	linear gradient
45.0–45.1	0→100	100→0	linear gradient
45.1–50.0	100	0	re-equilibration

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor for the gabapentin peak is not more than 2.0; and the relative standard deviation for replicate injections for both gabapentin and gabapentin related compound A is not more than 5.0%.

Procedure—Separately inject a volume (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of gabapentin related compound A in the portion of Capsules taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Gabapentin Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of gabapentin in the *Test solution;* and r_U and r_S are the individual peak responses for gabapentin related compound A obtained from the *Test solution* and *Standard solution,* respectively: not more than 0.4% of gabapentin related compound A is found. Calculate the percentage of any other unspecified impurity using the formula:

$$100(C_S/C_T)(r_i/r_S)$$

in which C_S and C_T are the concentrations, in mg per mL, of gabapentin in the *Standard solution* and the *Test solution,* respectively; r_i is the response for each unspecified impurity in the *Test solution;* and r_S is the peak response for gabapentin

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in the *Standard solution:* not more than 0.1% of any indivdiual unspecified impurity is found, and not more than 1.0% of total impurities is found.

Assay—

Diluent—Dissolve 1.2 g of monobasic potassium phosphate in 1 L of water. Adjust with 5 N potassium hydroxide to a pH of 6.9.

Mobile phase—Dissolve 1.2 g of monobasic potassium phosphate in 940 mL of water. Adjust with 5 N potassium hydroxide to a pH of 6.9, add 60 mL of acetonitrile, and stir. Filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Gabapentin RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 4.0 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of gabapentin, to a suitable volumetric flask, and dissolve the contents in *Diluent* with sonication, if necessary, for about 60 seconds. Dilute with *Diluent* to volume, and mix to obtain a final solution having a known concentration of about 4.0 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 7,000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the gabapentin peak. Calculate the percentage of gabapentin ($C_9H_{17}NO_2$) in the portion of Capsules taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of gabapentin in the *Standard preparation* and *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Gabapentin Tablets. Because there is no existing *USP* monograph for this dosage form, a new monograph is being proposed. The liquid chromatographic procedures in the tests for *Related compounds* and *Dissolution* and in the *Assay* are based on analyses performed with the Spherisorb S5 brand of L7 column. In the test for *Related compounds,* a gradient elution method is used in which the typical retention time for gabapentin related compound A is 33 minutes. In the *Assay,* an isocratic method is used in which the typical retention time for gabapentin is 6 minutes.

(MD-PP: R. Ravichandran; BPC: M. Marques) RTS—C44435

Add the following:

▲Gabapentin Tablets

» Gabapentin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of gabapentin ($C_9H_{17}NO_2$).

Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

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USP Reference standards ⟨11⟩—*USP Gabapentin RS. USP Gabapentin Related Compund A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

Test specimen—Grind at least 20 Tablets to a fine powder. Use an amount of powder, equivalent to about 2 mg of gabapentin, and about 200 mg of dry potassium bromide.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: 0.06 N hydrochloric acid (prepared by adding 51 mL of hydrochloric acid to 10 L of water); 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amount of gabapentin ($C_9H_{17}NO_2$) dissolved by the following method.

Mobile phase—Proceed as directed in the *Assay.*

Standard stock solution—Transfer about 111 mg of USP Gabapentin RS, accurately weighed, to a 50-mL volumetric flask, and dissolve in and dilute with *Medium* to volume.

Working standard solutions—Dilute aliquots of the *Standard stock solution* with *Medium* to obtain solutions having the following concentrations: 110 µg per mL for Tablets labeled to contain 100 mg; 330 µg per mL for Tablets labeled to contain 300 mg; 440 µg per mL for Tablets labeled to contain 400 mg; 660 µg per mL for Tablets labeled to contain 600 mg; and 880 µg per mL for Tablets labeled to contain 800 mg.

Test solution—Pass a portion of the solution under test through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to use the *Working standard solutions*: the column efficency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 3%.

Procedure—Separately inject equal volumes (about 100 µL for the Tablets labeled to contain 100, 300, or 400 mg; and about 50 µL for Tablets labeled to contain 600 or 800 mg) of the appropriate *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the amount of gabapentin ($C_9H_{17}NO_2$) dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the *Working standard solution* and the *Test solution,* respectively; C_S is the concentration, in mg per mL, of the *Working standard solution;* 900 is the volume, in mL, of *Medium*; 100 is the conversion factor to percentage; and *LC* is the Tablet label claim in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of gabapentin ($C_9H_{17}NO_2$) is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Diluent—Prepare as directed in the *Assay.*

Solution A—Dissolve 1.2 g of monobasic potassium phosphate in 940 mL of water, Adjust with 5 N potassium hydroxide to a pH of 6.9, add 60 mL of acetonitrile, and stir. Filter, and degas.

Solution B—Dissolve 1.2 g of monobasic potassium phosphate in 700 mL of water, adjust with 5 N potassium hydroxide to a pH of 6.9, add 300 mL of acetonitrile, and stir. Filter, and degas.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Standard solution—Dissolve accurately weighed quantities of USP Gabapentin RS and USP Gabapentin Related Compound A RS in *Diluent* to obtain a solution having a known concentration of about 0.04 mg of each per mL.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 500 mg of gabapentin, to a suitable volumetric flask, and dissolve the contents in *Diluent* with sonication, if necessary, for about 30 seconds. Dilute with *Diluent* to volume, and mix to obtain a final solution having a known concentration of about 20 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0.0–4.0	100	0	isocratic
4.0–45.0	100→0	0→100	linear gradient
45.0–45.1	0→100	100→0	linear gradient
45.1–50.0	100	0	re-equilibration

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor for the gabapentin peak is not more than 2.0; and the relative standard deviation for replicate injections for both gabapentin and gabapentin related compound A is not more than 5.0%.

Procedure—Separately inject a volume (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of gabapentin related compound A in the portion of Tablets taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Gabapentin Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of gabapentin in the *Test solution;* and r_U and r_S are the individual peak responses for gabapentin related compound A obtained from the *Test solution* and *Standard solution,* respectively: not more than 0.4% of gabapentin related compound A is found. Calculate the percentage of any other unspecified impurity using the formula:

$$100(C_S / C_T)(r_i / r_S)$$

in which C_S and C_T are the concentrations, in mg per mL, of gabapentin in the *Standard solution* and *Test solution,* respectively; r_i is the response for each unspecified impurity in the *Test solution;* and r_S is the peak response for gabapentin in the *Standard solution:* not more than 0.1% of any indivdiual unspecified impurity is found; and not more than 1.0% of total impurities is found.

Assay—

Diluent—Dissolve 1.2 g of monobasic potassium phosphate in 1 L of water. Adjust with 5 N potassium hydroxide to a pH of 6.9.

Mobile phase—Dissolve 1.2 g of monobasic potassium phosphate in 940 mL of water. Adjust with 5 N potassium hydroxide to a pH of 6.9, add 60 mL of acetonitrile, and stir. Filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Gabapentin RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 4.0 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of gabapentin, to a suitable volumetric flask, and dissolve the contents in *Diluent* with sonication, if necessary, for about 60 seconds. Dilute with *Diluent* to volume, and mix to obtain a final solution having a known concentration of about 4.0 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 7,000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0 %.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the gabapentin peak. Calculate the percentage of gabapentin ($C_9H_{17}NO_2$) in the portion of Tablets taken by the formula:

$$100(C_S/C_U)(r_U/r_S)$$

in which C_S and C_U are the concentrations, in mg per mL, of gabapentin in the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

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BRIEFING

Imipenem and Cilastatin for Injection, *USP 29* page 1110; **Imipenem and Cilastatin for Injectable Suspension,** *USP 29* page 1111. It is proposed to add a *Uniformity of dosage units* requirement in order to provide a further measure of quality for marketed products.

(MD-ANT: B. Gilbert) RTS—C47565

Add the following:

▲**Uniformity of dosage units** ⟨905⟩: meets the requirements.▲*USP31*

BRIEFING

Imipenem and Cilastatin for Injectable Suspension, *USP 29* page 1111—See briefing under *Imipenem and Cilastatin for Injection*.

(MD-ANT: B. Gilbert) RTS—C47566

Add the following:

▲**Uniformity of dosage units** ⟨905⟩: meets the requirements.▲*USP31*

BRIEFING

Indium In 111 Chloride Solution, *USP 29* page 1119. On the basis of comments received, it is proposed to revise the *Radiochemical purity* section to replace the descending paper chromatography method with an ITLC method using SG glass microfiber strips.

(RMI: A. Wilk) RTS—C41565

Change to read:

Radiochemical purity~~— Dispense about 50 µL of Solution into 1 mL of 0.04 M hydrochloric acid, taking care to use polypropylene tips prewashed in 0.04 M hydrochloric acid for all dispensings. Draw a line approximately 10 cm from one end of a Whatman No. 1 paper strip (5 × 25 cm). Using dispensers with polypropylene tips prewashed in 0.04 M hydrochloric acid, spot 10 µL of 0.5 N sodium carbonate at the start position followed by 2 µL of the test specimen. Allow the strip to air-dry, place in a chromatography jar, and elute downwards using 1 M sodium chloride as the eluent. The indium chloride will remain at the origin. After allowing the strip to air-dry, interpret the chromatogram using an appropriate scanner, and determine the percentage of radiochemical purity of the test specimen. Not less than 95% indium is present as ionic In.~~

▲*Adsorbent:* instant thin-layer chromatography (ITLC) strips (2.5 cm × 10 cm).[1]

Test solution—Dispense about 50 µL of Solution into 1 mL of 0.05 M hydrochloric acid, taking care to use polypropylene tips prewashed in 0.05 M hydrochloric acid for all dispensings.

Application volume: 2 µL. The amount of ^{111}In spotted should be between 0.5 and 30 µCi as of the day of the test.

Developing solvent system: a mixture of a 1 in 10 solution of ammonium acetate and methanol (1 : 1).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Examine the plate with an appropriate scanner, and determine the percentage of radiochemical purity of the *Test solution.* The indium chloride will remain at the origin. Not less than 95% of indium is present as ionic indium.▲*USP31*

BRIEFING

Diluted Isosorbide Mononitrate, *USP 29* page 1205 and page 3727 of the *Second Supplement.* It is proposed to use USP Diluted Isosorbide Mononitrate Related Compound A RS instead of the previously proposed reference standard, USP Isosorbide Mononitrate Related Compound A RS. The currently proposed reference standard is a dry mixture of an active component and a suitable excipient.

(MD-CV: S. Ramakrishna) RTS—C49076

[1] Type SG impregnated glass microfiber sheet (Gelman Sciences, Ann Arbor, MI).

Change to read:

USP Reference standards ⟨11⟩—*USP Isosorbide RS.* ■[NOTE—The following Reference Standards are dry mixtures of an active component with suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component on the basis of the content stated on the label.]■2S *(USP29)*
USP Diluted Isosorbide Dinitrate RS. USP ■*Diluted*■2S *(USP29)*
Isosorbide Mononitrate RS. USP

▲*Diluted*▲*USP31*
Isosorbide Mononitrate Related Compound A RS.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (95 : 5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer an accurately weighed quantity of USP ■Diluted■2S *(USP29)* Isosorbide Mononitrate RS to a suitable volumetric flask, dissolve in water, add a volume of methanol equivalent to 4% of the flask volume, and dilute with water to volume to obtain a solution having a known concentration of about 2.0 mg ■of isosorbide mononitrate■2S *(USP29)* per mL.

Isosorbide mononitrate related compound A standard preparation—Dissolve an accurately weighed quantity of USP

▲Diluted▲*USP31*
Isosorbide Mononitrate Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 1.0 mg of

▲isosorbide mononitrate related compound A▲*USP31*
per mL. Quantitatively dilute a portion of this solution with water to obtain a solution having a known concentration of about 0.05 mg per mL.

Resolution solution—Transfer 10.0 mL of *Isosorbide mononitrate related compound A standard preparation,* 1.0 mL of the *Standard preparation,* and 4.0 mL of methanol to a 100-mL volumetric flask, and dilute with water to volume. Filter a portion of the solution, discarding the first few mL of the filtrate.

Assay preparation—Transfer ■an accurately weighed amount of Diluted Isosorbide Mononitrate, equivalent to 100 mg of isosorbide mononitrate,■2S *(USP29)* to a 50-mL volumetric flask, dissolve in about 25 mL of water, add 2 mL of methanol, dilute with water to volume, and mix. Filter a portion of the solution, discarding the first few mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4-mm × 12.5-cm column that contains packing L1. The flow rate is about 1.5 mL per minute, increasing to 3.0 mL per minute at about 8.5 minutes to ensure that the isosorbide mononitrate peak has completely eluted. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for isosorbide mononitrate related compound A, 1.0 for isosorbide mononitrate, and 4.1 for isosorbide dinitrate; and the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the isosorbide mononitrate peaks. Calculate the quantity, in mg, of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$\blacksquare CV(r_U / r_S)_{\blacksquare 2S\ (USP29)}$$

in which C is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;* $\blacksquare V$ is the volume, in mL, of the *Assay preparation;* $\blacksquare_{2S\ (USP29)}$ and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Isosorbide Mononitrate Tablets, page 1513 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Isosorbide Mononitrate Extended-Release Tablets*.

(MD-CV: S. Ramakrishna) RTS—C49075

Add the following:

■Isosorbide Mononitrate Tablets

» Isosorbide Mononitrate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$).

Packaging and storage—Preserve in tight containers. Store at a temperature between 20° and 30°.

Change to read:

USP Reference standards ⟨11⟩—*USP Isosorbide RS.* ▲[NOTE—The following Reference Standards are dry mixtures of an active component and suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component based on the content stated on the label.]▲*USP31* *USP Diluted Isosorbide Dinitrate RS. USP* ▲*Diluted*▲*USP31* *Isosorbide Mononitrate RS. USP* ▲*Diluted*▲*USP31* *Isosorbide Mononitrate Related Compound A RS.*

Change to read:

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 120 mg of isosorbide mononitrate, to a suitable container, add 50.0 mL of absolute alcohol, sonicate for 10 minutes, and then centrifuge. Quantitatively dilute the supernatant (10 in 50) with absolute alcohol.

Standard solution: ~~0.5 mg~~ ▲a solution of▲*USP31* USP ▲Diluted▲*USP31* Isosorbide Mononitrate RS in absolute alcohol ▲containing 0.5 mg of isosorbide mononitrate per mL.▲*USP31*

Application volume: 20 µL.

Developing solvent system: a mixture of chloroform and methanol (95 : 5).

Spray reagent—Dissolve 1 g of soluble starch in 100 mL of boiling water. Cool, add 0.5 g of potassium iodide, and mix to dissolve.

Procedure—Examine the plate under short-wavelength UV light, marking any observed spots. Visualize nitrates on the plate by spraying with *Spray reagent* and illuminating with short-wavelength UV light for about 10 minutes. Isosorbide mononitrate and other nitrates appear as a violet spot on a white to light violet background.

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B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—[To come.]

Uniformity of dosage units ⟨905⟩**:** meet the requirements for *Content Uniformity.*

Change to read:

Related compounds—

TEST 1—

Adsorbent, Standard solution 1, Standard solution 2, Standard solution 3, Application volume, and *Developing solvent system*—Prepare as directed in *Related compounds, Test 1* under *Diluted Isosorbide Mononitrate.*

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of isosorbide mononitrate, to a suitable container, add 20.0 mL of absolute alcohol, sonicate for 10 minutes, and then centrifuge. Use the supernatant.

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. After developing, dry the plate with warm air for about 10 minutes, dip the plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at 105° for 5 minutes. Any spot in the chromatogram obtained from the *Test solution* and corresponding to the R_F value of the spots obtained from the *Standard solutions* is not more intense than the spot in the chromatogram obtained from *Standard solution 3:* not more than 1.0% of any individual impurity is found. If the spot in the chromatogram obtained from the *Test solution* is nearly as intense as the spot obtained from *Standard solution 3,* further dilute the *Test solution* (1 : 1) with absolute alcohol, repeat the test, and compare the intensity of the isosorbide spot in the diluted *Test solution* with the intensity of the spots obtained from the *Standard solutions,* correcting the percent level for the additional dilution of the *Test solution.*

TEST 2—

Mobile phase and *Resolution solution*—Proceed as directed in the *Assay.*

Isosorbide mononitrate related compound A standard stock solution—Dissolve an accurately weighed quantity of USP ▲Diluted▲*USP31* Isosorbide Mononitrate Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg of isosorbide mononitrate related compound A per mL.

Isosorbide dinitrate standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg of isosorbide dinitrate per mL.

Standard solution—Transfer a quantity of USP ▲Diluted▲*USP31* Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, quantitatively add a volume of *Isosorbide mononitrate related compound A standard stock solution* and a volume of *Isosorbide dinitrate standard stock solution,* and dilute with water to volume to obtain a solution having a known concentration of about 0.1 mg of ~~USP Isosorbide Mononitrate RS~~ ▲isosorbide mononitrate▲*USP31* per mL, 0.0005 mg of isosorbide mononitrate related compound A per mL, and 0.0005 mg of isosorbide dinitrate per mL. Filter a portion of the solution, discarding the first few mL of the filtrate.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed

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for *Procedure:* the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10% for the isosorbide mononitrate related compound A and isosorbide dinitrate peaks.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Compare the peak areas of the corresponding impurity obtained from the *Test solution* and the *Standard solution,* respectively. The average peak area of the impurity in the *Test solution* is less than or equal to the average peak area of the corresponding peak in the *Standard solution:* not more than 0.5% of isosorbide mononitrate related compound A is found; and not more than 0.5% of isosorbide dinitrate is found.

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (7 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution of USP ▲Diluted▲*USP31* Isosorbide Mononitrate RS and USP ▲Diluted▲*USP31* Isosorbide Mononitrate Related Compound A RS having a concentration of 0.0005 mg of each ▲of isosorbide mononitrate and isosorbide mononitrate related compound A▲*USP31* per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP ▲Diluted▲*USP31* Isosorbide Mononitrate RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg ▲of isosorbide mononitrate▲*USP31* per mL. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of isosorbide mononitrate, to a 200-mL volumetric flask, add 100 mL of water, and sonicate for about 10 minutes. Dilute with water to volume, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Tablets taken by the formula:

$$200C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP30*)

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BRIEFING

Isosorbide Mononitrate Extended-Release Tablets, page 1082 of *PF* 31(4) [July–August 2005]. It is proposed to use USP Diluted Isosorbide Mononitrate RS instead of the previously proposed Reference Standard, USP Isosorbide Mononitrate RS. A *Note* is also added to the *USP Reference standards* section to identify the Reference Standards that are dry mixtures of an active component and a suitable excipient. It is proposed to update the *Tolerances* in *Dissolution Test 1* to be in accordance with those approved by FDA. Also, *Dissolution Test 2* and *Dissolution Test 3* are being added. The chromatographic method in *Dissolution Test 2* was developed with a MicroBondpak C18 brand of L1 column. With this column the retention time of isosorbide mononitrate is between 4.5 and 6.5 minutes. The chromatographic procedure in *Dissolution Test 3* was developed using a Supelcosil LC brand of L1 column. An alternative column is the Kromasil C18 brand. With either of these two columns the retention time of isosorbide mononitrate is about 4.5 minutes.

(MD-CV: S. Ramakrishna; BPC: M. Marques) RTS—C43144; C42561; C42562; C48982

Add the following:

▲Isosorbide Mononitrate Extended-Release Tablets

» Isosorbide Mononitrate Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$).

Packaging and storage—Preserve in tight containers. Store at a temperature between 20° and 30°.

Labeling— ~~[To come.]~~ When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

USP Reference standards ⟨11⟩—*USP Isosorbide RS.* [NOTE—The following Reference Standards are dry mixtures of an active component and suitable excipients to permit safe handling. For quantitative applications, calculate the concentration of the active component based on the content stated on the label.] *USP Diluted Isosorbide Dinitrate RS. USP Diluted Isosorbide Mononitrate RS. USP Diluted Isosorbide Mononitrate Related Compound A RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—Proceed as directed for *Identification* test *A* under *Isosorbide Mononitrate Tablets.*

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

~~**Drug release** ⟨724⟩ **—** [To come.]~~

Dissolution ⟨711⟩—

TEST 1—

Medium: water; 900 mL.

Apparatus 2: 50 rpm. The Tablets are placed in a metal helix, prepared by winding 10 inches of a 0.8-mm stainless steel wire around a 9/32-inch shaft and pulling the coils to form a helix 1 inch long.

Times: 1, 2, 4, 8, and 12 hours.

Determine the amount of $C_6H_9NO_6$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (7 : 3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Standard solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Mononitrate RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of about 0.06 mg of isosorbide mononitrate per mL.

Test solution—Use portions of the solution under test passed through a 0.45-µm nylon filter, discarding the first 4 to 6 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the chromatogram as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Determine the amount, in mg, of isosorbide mononitrate dissolved at each interval by the formula:

$$\frac{r_U \times C_S \times V}{r_S}$$

in which r_U and r_S are the peak responses for the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* and V is the volume, in mL, of *Medium* in the vessel at each time point.

Calculate the amount, in mg, of isosorbide mononitrate removed by sampling at the previous time points by the formula:

$$\sum AD \times \frac{V_S}{V}$$

in which AD is the amount, in mg, of isosorbide mononitrate dissolved at each time point; V_S is the volume, in mL, of the sample taken; and V is the volume, in mL, of *Medium* in the vessel at each time point.

Calculate the percentage of isosorbide mononitrate dissolved at each time point by the formula:

$$\frac{(AD + AR) \times 100}{LC}$$

in which AD is the amount, in mg, of isosorbide mononitrate dissolved at a given time point; AR is the amount, in mg, of isosorbide mononitrate removed at the previous time point; 100 is the conversion factor to percentage; and LC is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_6H_9NO_6$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between ~~12% and 32%~~ 15% and 35%
2	between ~~23% and 43%~~ 28% and 48%
4	between ~~39% and 59%~~ 43% and 68%
8	between 65% and ~~85%~~ 90%
12	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: Simulated gastric fluid (without enzymes); 500 mL.

Apparatus 2: 50 rpm.

Times: 1, 2, 6, and 12 hours.

Determine the amount of $C_6H_9NO_6$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (3 : 2). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).

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Standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Mononitrate RS in *Medium,* and dilute quantitatively, and stepwise if necessary, with *Medium* to obtain a solution having a known concentration of about 1.2 mg of isosorbide mononitrate per mL.

Working standard solution—Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of 60 µg per mL for Tablets labeled to contain 30 mg and a final concentration of 120 µg per mL for Tablets labeled to contain 60 mg.

Test solution—Use portions of the solution under test passed through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 10-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution,* and record the chromatogram as directed for *Procedure:* the tailing factor is not more than 2.0, and the relative standard deviation for replicate injections is not more than 2.0%

Procedure—Separately inject equal volumes (about 20 µL) of the appropriate *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the concentration (C_i), in mg per mL, of isosorbide mononitrate removed at each time point by the formula:

$$C_i = \frac{r_{U(i)}}{r_S} \times C_S$$

in which $r_{U(i)}$ is the peak response for the *Test solution* at time point *i;* r_S is the peak response for the *Working standard solution;* and C_S is the concentration, in mg per mL, of the *Working standard solution*. Calculate the total amount, in percentage, of drug release at each time point *i* by the formula:

$$\{C_i \times [V_0 - ((i-1)V_t)] + (\sum_{j=1}^{i-1} C_j V_t)\} \times \frac{100}{LC}$$

in which C_i is the concentration, in mg per mL, of drug removed at time point *i;* V_0 is the initial volume, in mL, of *Medium;* V_t is the volume, in mL, of sample removed at each sampling time, C_j is the concentration, in mg per mL, of drug released at time *j;* V_t is the volume, in mL, removed at each sampling time *t*; 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_6H_9NO_6$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	30-mg Tablet, Amount dissolved	60-mg Tablet, Amount dissolved
1	between 25% and 40%	between 25% and 45%
2	between 35% and 60%	between 35% and 60%
6	between 72% and 90%	between 72% and 90%
12	not less than 80%	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Medium: Simulated gastric fluid (without enzymes); 500 mL.

Apparatus 2: 50 rpm.

Times: 1, 2, 6, and 12 hours.

Determine the amount of $C_6H_9NO_6$ dissolved by employing the following method.

Buffer solution—Transfer 15.4 g of ammonium acetate and 11.5 mL of acetic acid to a 1-L volumetric flask containing about 500 mL of water. Adjust with acetic acid to a pH of 4.7. Dilute with water to volume.

Standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Mononitrate RS in *Medium,* and dilute quantitatively, and stepwise if necessary,

with *Medium* to obtain a solution having a known concentration of about 0.12 mg of isosorbide mononitrate per mL.

Working standard solution—For Tablets labeled to contain 60 mg, use the *Standard stock solution* with no further dilution. For Tablets labeled to contain 30 mg, transfer 25.0 mL of the *Standard stock solution* to a 50-mL volumetric flask. Dilute with *Medium* to volume.

Test solution—Use portions of the solution under test passed through a suitable 0.45-µm filter.

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and *Buffer solution* (6 : 3 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution,* and record the chromatogram as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the appropriate *Working standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the concentration (C_i), in mg per mL, of isosorbide mononitrate removed at each time point by the formula:

$$C_i = \frac{r_{U(i)}}{r_S} \times C_S$$

in which $r_{U(i)}$ is the peak response for the *Test solution* at time point *i;* r_S is the peak response for the *Working standard solution;* and C_S is the concentration, in mg per mL, of the *Working standard solution*. Calculate the total amount, in percentage, of drug release at each time point *i* by the formula:

$$\{C_i \times [V_0 - ((i-1)V_t)] + (\sum_{j=1}^{i-1} C_j V_t)\} \times \frac{100}{LC}$$

in which C_i is the concentration, in mg per mL, of drug removed at time point *i;* V_0 is the initial volume, in mL, of *Medium;* V_t is the volume, in mL, of sample removed at each sampling time; C_j is the concentration, in mg per mL, of drug released at time *j;* V_t is the volume, in mL, removed at each sampling time *t;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of isosorbide mononitrate dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 30% and 50%
6	between 70% and 90%
12	not less than 85%

Uniformity of dosage units ⟨905⟩**:** meet the requirements for *Content Uniformity.* Proceed as directed in the *Assay,* except to use 1 Tablet instead of the portion of powdered Tablets used in the *Assay preparation.*

~~**Water,** *Method I* ⟨921⟩**:** not more than 5.0%.~~

~~*Test solution*—Weigh and finely powder 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to one Tablet, accurately weighed, to a suitable container. Add 5.0 mL of methanol, shake for 45 minutes, and then centrifuge at about 4000 rpm for 10 minutes. Use 0.25 mL of the resulting supernatant, correcting for the blank.~~

Related compounds—

TEST 1—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

In-Process Revision

Standard solution 1—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.0125 mg of isosorbide per mL.

Standard solution 2—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.025 mg of isosorbide per mL.

Standard solution 3—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.05 mg of isosorbide per mL.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of isosorbide mononitrate, to a suitable flask containing 20.0 mL of acetonitrile. Sonicate for 10 minutes and then centrifuge. Use the supernatant.

Application volume: 20 µL.

Developing solvent system: a mixture of toluene, ethyl acetate, and isopropyl alcohol (53 : 32 : 15).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. After developing, dry the plate with warm air for about 10 minutes, dip the plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at 105° for 5 minutes. Any spot in the chromatogram obtained from the *Test solution* and corresponding to the R_F value of the spots obtained from the *Standard solutions* is not more intense than the spot in the chromatogram obtained from *Standard solution 3:* not more than 1% of any individual impurity is found. [NOTE—The R_F values of isosorbide and isosorbide mononitrate are about 0.2 and 0.6, respectively.] If the spot in the chromatogram obtained from the *Test solution* is nearly as intense as the spot obtained from *Standard solution 3,* further dilute the *Test solution* with acetonitrile (1 : 1), repeat the test, and compare the intensity of the isosorbide spot in the diluted *Test solution* with the intensity of the spots obtained from the *Standard solutions,* correcting the percentage level for the additional dilution of the *Test solution.*

TEST 2—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (75 : 25). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Isosorbide mononitrate related compound A standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Mononitrate Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.3 mg of isosorbide mononitrate related compound A per mL.

Isosorbide dinitrate standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.15 mg of isosorbide dinitrate per mL.

Standard stock solution—Transfer 2.0 mL of *Isosorbide mononitrate related compound A standard stock solution* and 4.0 mL of *Isosorbide dinitrate standard stock solution* to a 100-mL volumetric flask. Dilute with water to volume, and mix.

~~*Standard*~~ *Resolution solution*—Transfer ~~about 24 mg~~ a quantity of USP Diluted Isosorbide Mononitrate RS, ~~accurately weighed~~ equivalent to about 24 mg of isosorbide mononitrate, to a 100-mL volumetric flask, add 10.0 mL of *Standard stock solution,* add 20 mL of methanol, and dilute with water to volume.

~~*Resolution*~~ *Standard solution*—Transfer 10.0 mL of *Standard stock solution* and 20 mL of methanol to a 100-mL volumetric flask. Dilute with water to volume, and mix.

In-Process Revision

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of isosorbide mononitrate, to a 50-mL volumetric flask, add 40 mL of methanol, and sonicate for about 30 minutes with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 minutes. Quantitatively dilute the supernatant with water (10 in 50). Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.0. [NOTE—The relative retention times are about 0.9 for isosorbide mononitrate related compound A, 1.0 for isosorbide mononitrate, and 5.6 for isosorbide dinitrate.] Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10% for the isosorbide mononitrate related compound A and isosorbide dinitrate peaks.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of isosorbide mononitrate related compound A and isosorbide dinitrate in the portion of Tablets taken by the formula:

$$25(C/W)(r_U / r_S)$$

in which C is the concentration, in µg per mL, of the appropriate Standard, USP Diluted Isosorbide Mononitrate Related Compound A RS or USP Diluted Isosorbide Dinitrate RS, in the *Standard solution; W* is the weight, in mg, of isosorbide mononitrate in the sample used to prepare the *Test solution;* and r_U and r_S are the peak areas of the corresponding component obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.25% of isosorbide mononitrate related compound A is found, and not more than 0.25% of isosorbide dinitrate is found. Calculate the percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak area for each other impurity obtained from the *Test solution;* and r_s is the sum of the areas of all the peaks: not more than 0.25% of total other impurities is found, and not more than 0.5% of total impurities is found, including isosorbide mononitrate related compound A and isosorbide dinitrate.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (8 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Isosorbide mononitrate related compound A standard preparation—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Mononitrate Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.15 mg of isosorbide mononitrate related compound A per mL.

Resolution solution—Transfer a quantity of USP Diluted Isosorbide Mononitrate RS, accurately weighed and equivalent to about 30 mg of isosorbide mononitrate, to a 250-mL volumetric flask. Dissolve in water, add 10.0 mL of *Isosorbide mononitrate related compound A standard preparation,* add 50 mL of methanol, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a concentration of about 0.12 mg of isosorbide mononitrate per mL and about 0.006 mg of isosorbide mononitrate related compound A per mL.

In-Process Revision

Standard preparation—Transfer a quantity of USP Diluted Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, add a portion of methanol equivalent to about 20% of the flask volume, and dilute with water to volume to obtain a solution having a known concentration of about 0.12 mg of isosorbide mononitrate per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of isosorbide mononitrate, to a 100-mL volumetric flask, add 50 mL of methanol, and sonicate for about 30 minutes with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 minutes. Quantitatively dilute the supernatant with water (10 in 50). Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4-mm × 12.5-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5, and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about ~~50 µL)~~ 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Tablets taken by the formula:

$$500C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Lactulose Concentrate, *USP 29* page 1224. On the basis of comments received, it is proposed to revise the *Procedure* in the test for *Related compounds* to add a *Table* with the names and relative retention times of the related compounds. The test for *Related compounds* and the *Assay* are also being revised to clarify the numeric coefficients in the formulas.

(MD-GRE: E. Gonikberg) RTS—C48759

Change to read:

Related compounds—

Phosphate buffer solution and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution—Transfer accurately weighed quantities of USP Galactose RS, USP Anhydrous Lactose RS, USP Epilactose RS, and USP Fructose RS to a 10-mL volumetric flask, and dissolve in and dilute with a mixture of water and acetonitrile (1 : 1) to volume to obtain a solution having known concentrations of about 6.4 mg per mL, 4.8 mg per mL, 3.2 mg per mL and 0.4 mg per mL, respectively.

Test solution—Prepare as directed for the *Assay preparation* in the *Assay.*

Chromatographic system—Proceed as directed in the *Assay.* To evaluate the system suitability requirements, use the *Standard preparation* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses.

▲Identify the peaks based on their relative retention times given in *Table 1.*

Table 1

Name	Relative Retention Time
Fructose	0.30
Galactose	0.42
Epilactose	0.85
Lactulose	1.0
Lactose	1.1

▲*USP31*

In-Process Revision

Calculate the percentages of galactose, lactose, epilactose, and fructose, if found, in the portion of Concentrate taken by the formula:

~~*5000(C/W)(r_u / r_s),*~~

▲100(*CV/W*)(r_U / r_S)▲*USP31*

in which *C* is the concentration, in mg per mL, of the relevant USP Reference Standard in the *Standard solution;*

▲*V* is the volume, in mL, of the *Test solution;*▲*USP31*
W is the weight, in mg, of lactulose in the *Test solution;* and r_U and r_S are the peak responses for the relevant related compounds obtained from the *Test solution* and the *Standard solution,* respectively: relative to lactulose, not more than 16% of galactose is found, not more than 12% of lactose is found, not more than 8% of epilactose is found, and not more than 1% of fructose is found.

Change to read:

Assay—

Phosphate buffer solution—Dissolve 1.15 g of monobasic sodium phosphate in 1000 mL of water.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Phosphate buffer solution* (82 : 18). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—Ensure that the concentration of acetonitrile in the *Mobile phase* is between 78% and 85% to obtain appropriate retention times.]

Standard preparation—Transfer accurately weighed quantities of USP Lactulose RS, USP Anhydrous Lactose RS, and USP Epilactose RS to a 10-mL volumetric flask, and dissolve in and dilute with a mixture of water and acetonitrile (1 : 1) to volume, to obtain a solution having known concentrations of 40 mg per mL, 4.8 mg per mL, and 3.2 mg per mL, respectively.

Assay preparation—Transfer an accurately weighed quantity of Concentrate containing about 2.0 g of lactulose to a 50-mL volumetric flask, and dissolve in 20 mL of water. Add 25.0 mL of acetonitrile, mix, allow the solution to reach ambient temperature, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector maintained at a temperature of 40 ± 1° and a 4.6-mm × 15-cm column that contains 3-µm packing L8. The column temperature is maintained at 40 ± 1°. The flow rate is about 1.3 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure.* ~~the relative retention times are about 0.30 for fructose, 0.42 for galactose, 0.85 for epilactose, 1.0 for lactulose, and 1.1 for lactose;~~

▲Identify the components based on their relative retention times given in *Table 1:*▲*USP31*
the resolution, *R,* between lactulose and lactose is not less than 1.5, and that between lactulose and epilactose is not less than 0.9; and the relative standard deviation for replicate injections determined from the main peak is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg, of lactulose ($C_{12}H_{22}O_{11}$) in the portion of Concentrate taken by the formula:

~~*50C(r_u / r_s),*~~

▲*CV*(r_U / r_S)▲*USP31*

in which *C* is the concentration, in mg per mL, of USP Lactulose RS in the *Standard preparation;*

▲*V* is the volume, in mL, of the *Assay preparation;*▲*USP31* and r_U and r_S are the peak responses for lactulose obtained from the *Assay preparation* and the *Standard preparation*, respectively.

BRIEFING

Lansoprazole, *USP 29* page 1229. On the basis of information received, it is proposed to make the following changes:

1. Add the chemical names of impurities B and C to *Table 1* in the *Chromatographic purity* test.
2. Add a "disregard" limit of 0.05% to the *Chromatographic purity* test.
3. To increase the stability of the solutions in the *Chromatographic purity* test, it is proposed to use a basic *Diluent,* instead of the currently used *Diluent* with pH 7.0.
4. To further increase the stability of the solutions, it is proposed to specify the use of a cooled autosampler. A *Note* is added that the lansoprazole solutions are stable for about 24 hours at 5°.
5. Report the limit of the *Water* and *Residue on ignition* tests rounded off to one decimal place. The MD-GRE Expert Committee is aware that the water, when present even in small amounts, may affect the stability of Lansoprazole, and encourages interested manufacturers to submit stability data for lots with differing initial levels of water.
6. Change the acceptance criteria in the *Definition* from "not less than 99.0 percent and not more than 101.0 percent" to "not less than 98.0 percent and not more than 102.0 percent", which are typical for chromatographic assay procedures. On the basis of comments received, the relative standard deviation in the *Assay* is also revised.
7. The relative response factors under *Chromatographic purity* are revised to implement a uniform and consistent approach as proposed in the *Stimuli* article, *The Use of Relative Response Factors to Determine Impurities,* published on page 960 of *PF* 31(3) [May–June 2005].
8. Change the format of the formulas under *Chromatographic purity* and *Assay,* as recommended in the *Stimuli* article, *Common Pharmacopeial Calculations in USP Monographs,* published on page 626 of *PF* 31(2) [Mar.–Apr. 2005].

(MD-GRE: E. Gonikberg) RTS— C48691

Change to read:

» Lansoprazole contains not less than ~~99.0~~

▲98.0▲*USP31*
percent and not more than ~~101.0~~

▲102.0▲*USP31*
percent of $C_{16}H_{14}F_3N_3O_2S$.

Change to read:

Water, *Method Ia* ⟨921⟩**:** not more than ~~0.10%,~~

▲0.1%,▲*USP31*
determined on a 1.0-g specimen, 50 mL of a dehydrated mixture of pyridine and ethylene glycol (9 : 1 to 8 : 2) being used as the solvent.

In-Process Revision

Change to read:

Residue on ignition ⟨281⟩**:** not more than ~~0.10%.~~

▲0.1%.▲*USP31*

Change to read:

Chromatographic purity—

▲[NOTE—Store and inject the lansoprazole solutions at or below 5° using a cooled autosampler. The solutions are stable for about 24 hours when stored at 5°.]▲*USP31*

Solution A: water.

Solution B—Prepare a filtered and degassed mixture of acetonitrile, water, and triethylamine (160 : 40 : 1). Adjust with phosphoric acid to a pH of 7.0.

Diluent—~~Prepare a mixture of *Solution A* and *Solution B* (9 : 1).~~

▲Prepare a mixture of 0.1 N sodium hydroxide solution and methanol (75 : 25).▲*USP31*

Blank solution—Prepare a mixture of *Diluent* and methanol (9 : 1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—~~[NOTE—Prepare immediately before using.]~~

▲
▲*USP31*
Dissolve 5 mg each of USP Lansoprazole RS and USP Lansoprazole Related Compound A RS in 200 mL of methanol. Pipet 1 mL of this solution into a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

System suitability solution—Dissolve a suitable quantity of USP Lansoprazole Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.025 mg per mL. Pipet 1 mL of this solution into a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard solution—~~[NOTE—Inject within 10 minutes of preparation.]~~

▲
▲*USP31*
Dissolve an accurately weighed quantity of USP Lansoprazole RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 25 µg per mL. Pipet 1 mL of this solution into a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix. The final concentration of the *Standard solution* is about 2.5 µg per mL.

Test solution—~~[NOTE—Inject within 10 minutes of preparation.]~~

▲
▲*USP31*
Transfer about 125 mg of Lansoprazole, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Pipet 1 mL of this solution into a 10-mL volumetric flask, and dilute with *Diluent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 0.8 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–40	90→20	10→80	linear gradient
40–50	20	80	isocratic
50–51	20→90	80→10	linear gradient
51–60	90	10	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between lansoprazole and lansoprazole related compound A is not less than 6. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 3%.

Procedure—Separately inject equal volumes (about 40 µL) of the *Blank solution,* the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify the lansoprazole peak and the peaks due to the impurities listed in *Table 1*. Measure the areas for the major peaks, excluding the peaks obtained from the *Blank solution.* Calculate the percentage of each impurity in the portion of Lansoprazole taken by the formula:

~~$50(CF/W)(r_i/r_s)$~~

▲$100 \times 0.001(1/F)(C_S/C_T)(r_i/r_S)$▲*USP31*

in which F is the relative response factor for each impurity peak (see *Table 1* for values); ~~*C* is the concentration, in µg per mL, of USP Lansoprazole RS in the *Standard solution; W* is the weight, in mg, of Lansoprazole taken for the Test solution;~~

▲0.001 is the conversion factor from µg per mL to mg per mL; C_S is the concentration, in µg per mL, of USP Lansoprazole RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Lansoprazole in the *Test solution;*▲*USP31*

r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for lansoprazole obtained from the *Standard solution:* In addition to not exceeding the limits for impurities in *Table 1,* not more than 0.6% of total impurities is found.

▲Disregard any peak below 0.05%.▲*USP31*

Change to read:

Assay—

Diluent—Prepare a mixture of water, acetonitrile, and triethylamine (60 : 40 : 1), and adjust with phosphoric acid to a pH of 10.0.

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and triethylamine (60 : 40 : 1). Adjust with phosphoric acid to a pH of 7.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve suitable quantities of USP Lansoprazole RS and USP Lansoprazole Related Compound A RS in *Diluent* to obtain a solution containing about 0.1 mg of each per mL.

Internal standard solution—Dissolve an accurately weighed quantity of 4′-ethoxyacetophenone in *Diluent* to obtain a solution having a known concentration of about 2.5 mg per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Lansoprazole RS in *Internal standard solution* to obtain a solution having a known concentration of about 5.0 mg per mL. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Assay preparation—Transfer about 50 mg of Lansoprazole, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Internal standard solution* to volume, and mix. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between lansoprazole and lansoprazole related

In-Process Revision

Table 1

Name	Relative Response Factor (*F*)	Approximate Relative Retention Time	Limit (%)
Lansoprazole ~~related compound A~~	~~1.22~~	1.1	0.4
▲sulfone[1]▲*USP31*	▲0.82▲*USP31*		
~~Impurity B~~	~~0.76~~	0.8	0.1
▲Lansoprazole *N*-oxide[2]▲*USP31*	▲1.3▲*USP31*		
~~Impurity C~~	~~1.27~~	1.2	0.1
▲Lansoprazole sulfide[3]▲*USP31*	▲0.79▲*USP31*		
Other individual impurity	1.00	—	0.1

▲1 Lansoprazole related compound A: (2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole)▲*USP31*

▲2 [[(1*H*-benzimidazole-2-yl)sulfinyl]methyl]-3-methyl-4-(2,2,2-trifluoroethoxy)-pyridine 1-oxide▲*USP31*

▲3 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-pyridin-2-yl]methyl]sulfanyl]-1*H*-benzimidazole▲*USP31*

compound A is not less than 5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than ~~0.5%.~~

▲1.0%.▲*USP31*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the ~~quantity, in mg,~~

▲percentage▲*USP31* of $C_{16}H_{14}F_3N_3O_2S$ in the portion of Lansoprazole taken by the formula:

~~$500C(R_U / R_S)$~~

▲$100(C_S / C_U)(R_U / R_S)$▲*USP31*

in which ~~*C* is the concentration, in mg per mL, of USP Lansoprazole RS in the *Standard preparation;*~~

▲C_S and C_U are the concentrations, in mg per mL, of lansoprazole in the *Standard preparation* and the *Assay preparation,* respectively;▲*USP31* and R_U and R_S are the peak response ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Leflunomide Tablets, page 1383 of *PF* 31(5) [Sept.–Oct. 2005]. It is proposed to add a *Dissolution* test to this monograph. The chromatographic procedure in this test was validated using the Hypersil BDS C18 brand of L1 column. The retention time for the leflunomide peak is about 5 minutes.

(BPC: M. Marques) RTS—C43057; C44097

Add the following:

▲Leflunomide Tablets

» Leflunomide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of leflunomide ($C_{12}H_9F_3N_2O_2$).

Packaging and storage—Preserve in tight, light- and humidity-resistant containers.

In-Process Revision

USP Reference standards ⟨11⟩—*USP Leflunomide RS. USP Leflunomide Related Compound A RS. USP Leflunomide Related Compound B RS. USP Leflunomide Related Compound C RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Spectral range: 220 to 360 nm.

Solution: 0.01 mg per mL.

Medium: methanol.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩ ~~[To come.]~~

Medium: For Tablets labeled to contain 10 mg or 20 mg: water, 1000 mL, deaerated. For Tablets labeled to contain 100 mg: water containing 0.6 % of polyoxyethylene lauryl ether; 1000 mL, deaerated.

Apparatus 2: 100 rpm.

Time: 30 minutes.

Determine the amount of $C_{12}H_9F_3N_2O_2$ dissolved employing one of the following methods.

SPECTROPHOTOMETRIC METHOD—

Procedure—Determine the amount of $C_{12}H_9F_3N_2O_2$ dissolved from ultraviolet absorbances at the wavelength of maximum absorbance at about 262 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted with *Medium* if necessary, in comparison with a Standard solution having a known concentration of USP Leflunomide RS in the same *Medium*. [NOTE—A volume of methanol not exceeding 2% of the final volume of the Standard solution may be used to dissolve leflunomide.]

CHROMATOGRAPHIC METHOD—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (1 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 22 mg of USP Leflunomide RS, accurately weighed, to a 100-mL volumetric flask. Add 40 mL of acetonitrile, and sonicate until dissolved. Add about 40 mL of water, and cool to room temperature. Dilute with water to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, and dilute with water to volume.

Test solution—Use portions of the solution under test passed through a suitable 0.45-µm filter.

Chromatographic system—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the amount of leflunomide ($C_{12}H_9F_3N_2O_2$) dissolved by the formula:

$$\frac{r_U \times C_S \times 1000 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the *Standard solution* and the *Test solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution;* 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{12}H_9F_3N_2O_2$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Mobile phase, Standard preparation, System suitability preparations, and *Chromatographic system*—Prepare as directed in the *Assay.*

In-Process Revision

Test solution—Transfer 1 Tablet to a suitable volumetric flask, and prepare a solution having a concentration of about 1 mg of leflunomide per mL. Add *Mobile phase* 50% by volume, and shake to disintegrate the Tablet. After the Tablet is completely disintegrated, add acetonitrile 20% by volume, dilute with *Mobile phase* to volume, and shake again. Pass through a membrane filter.

Procedure—Proceed as directed in the *Assay,* except to use the *Test solution* instead of the *Assay preparation.*

Water, *Method Ic* ⟨921⟩**:** not more than 9.0%.

Related compounds—

Mobile phase, System suitability preparations, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution and *Test solution*—Prepare as directed for *Standard preparation* and *Assay preparation,* respectively, in the *Assay.*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each individual impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response of each individual impurity in the chromatogram obtained from the *Test solution;* and r_s is the sum of all the related compounds and the leflunomide peak responses in the chromatogram obtained from the *Test solution:* not more than 0.1% of leflunomide related compound A is found; not more than 3.5% of leflunomide related compound B is found; not more than 0.1% of any other individual impurity is found; and not more than 4.0% of total impurities is found.

Assay—

Mobile phase—Prepare a mixture of water, acetonitrile, and triethylamine (65 : 35 : 05), filter, and degas. Adjust with phosphoric acid to a pH of 4.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Leflunomide RS in a minimum volume of acetonitrile, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1 mg per mL.

System suitability preparation 1—Transfer 20.0 mg of USP Leflunomide Related Compound A RS, accurately weighed, to a 20-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

System suitability preparation 2—Transfer 100.0 mg of USP Leflunomide Related Compound B RS and 10.0 mg of USP Leflunomide Related Compound C RS, each accurately weighed, to a 100-mL volumetric flask. Add 1 mL of *System suitability preparation 1,* 5 mL of acetonitrile, and 80 mL of *Mobile phase,* and shake by mechanical means for 10 minutes. Dilute with *Mobile phase* to volume, and mix.

System suitability preparation 3—Transfer about 100.0 mg of USP Leflunomide RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in 2 mL of acetonitrile, add 1 mL of *System suitability preparation 2* and 80 mL of *Mobile phase,* and shake by mechanical means for 10 minutes. Dilute with *Mobile phase* to volume, and mix.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of leflunomide, to a 100.0-mL volumetric flask. Add 20 mL of acetonitrile, dilute with *Mobile phase* to volume, and shake by mechanical means for 10 minutes. Pass through a membrane filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.0-mm × 12.5-cm column containing packing L1. The flow rate is about 1 mL per minute. Chromatograph *System suitability preparation 3* and the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times for leflunomide related compound A, leflunomide related compound B, leflunomide related compound C, and leflunomide are about 0.4, 0.2, 0.9, and 1.0, respectively; the resolution, *R,* between leflunomide related compound C and leflunomide is not less than 1.5; the tailing factor for leflunomide is not more than 3.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of leflunomide ($C_{12}H_9F_3N_2O_2$) in the portion of Tablets taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Leflunomide RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets. Because there is no existing *USP* monograph for this dosage form, a new monograph is being proposed. The reverse-phase HPLC method used in the test for *Loratadine chromatographic purity* and in the *Assay for loratadine* was validated using the Inertsil ODS(3) brand of L1 column. Loratadine elutes at approximately 6.5 minutes. The normal-phase HPLC method used in the test for *Pseudoephedrine sulfate chromatographic purity* and in the *Assay for pseudoephedrine sulfate* was validated using the Prodigy Silica brand of L3 column. Pseudoephedrine sulfate elutes at approximately 6.8 minutes.

(MD-PS: D. Bempong) RTS—C41808

Add the following:

▲Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets

» Loratadine and Pseudoephedrine Sulfate Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of loratadine ($C_{22}H_{23}ClN_2O_2$) and pseudoephedrine sulfate [$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$].

Packaging and storage—Preserve in light-resistant containers in a dry place. Store between 2° and 25°.

USP Reference standards ⟨11⟩—*USP Loratadine RS. USP Pseudoephedrine Sulfate RS.*

Identification—

A: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for loratadine*.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay for pseudoephedrine sulfate*.

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Dissolution ⟨711⟩—[To come.]

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Loss on drying ⟨731⟩**—**Dry about 5 g of finely ground Tablets, accurately weighed, at 105° for 2 hours: it loses not more than 3.0% of its weight.

Loratadine chromatographic purity—

Buffer solution and *Mobile phase*—Proceed as directed in the *Assay for loratadine*.

Standard solution—Dissolve an accurately weighed quantity of USP Loratadine RS in *Mobile phase,* and dilute quantitatively and stepwise, if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.25 µg per mL.

Sensitivity test solution—Transfer 5 mL of the *Standard solution* into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—Prepare as directed for *Assay preparation* in the *Assay for loratadine,* except instead of passing the final solution through a suitable filter, centrifuge the solution at a speed of at least 3000 rpm for about 10 minutes. Use the supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that containing 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Sensitivity test solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and record the peak responses. Calculate the percentage of individual impurities in the portion of Tablets taken by the formula:

$$0.1(D/F)(C/W)(r_i/r_S)$$

in which D is the dilution factor used in the preparation of the *Test solution; F* is the relative response factor (equal to 0.63 for the impurity with a relative retention time of about 0.5 and 1.0 for all other impurity peaks [NOTE—The impurity with a relative retention time of about 0.5 is 8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[l,2-*b*]pyridin-11-one.]); C is the concentration, in µg per mL, of USP Loratadine RS in the *Standard solution; W* is the weight, in mg, of loratadine in the portion of powdered Tablets taken to prepare the *Test solution;* r_i is the peak response obtained for each individual unknown impurity in the *Test solution;* and r_S is the peak response for loratadine obtained from the *Standard solution:* not more than 0.2% of the impurity with a relative retention time of about 0.5 is found; not more than 0.2% of any other impurity is found; and not more than 0.3% of total impurities is found. [NOTE—Disregard peaks due to pseudoephedrine sulfate and peaks due to excipients.]

Pseudoephedrine sulfate chromatographic purity—

Ammonium acetate solution and *Mobile phase*—Proceed as directed in the *Assay for pseudoephedrine sulfate*.

Standard solution—Dissolve an accurately weighed quantity of USP Pseudoephedrine Sulfate RS in *Mobile phase,* and dilute quantitatively and stepwise, if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 9.6 µg per mL.

Sensitivity test solution—Transfer 5 mL of *Standard solution* into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

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Test solution—Accurately weigh and finely powder at least 20 Tablets, and transfer a portion of the powdered Tablets, equivalent to 480 mg of pseudoephedrine, into a 50-mL volumetric flask. Add 40 mL of methanol, and stir vigorously for 30 minutes or longer, if necessary, until the powder is finely dispersed. Dilute with methanol to volume, and mix. Transfer 2 mL of the resulting suspension into a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Centrifuge the solution in a plastic centrifuge tube at a speed of at least 3000 rpm for about 10 minutes. Use the supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 10-µm packing L3. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 3.0%. Chromatograph the *Sensitivity test solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and record the peak responses. Calculate the percentage of individual impurities in the portion of Tablets taken by the formula:

$$0.1D(C/W)(r_i / r_S)$$

in which D is the dilution factor used in the preparation of the *Test solution;* C is the concentration, in µg per mL, of USP Pseudoephedrine Sulfate RS in the *Standard solution;* W is the weight, in mg, of pseudoephedrine sulfate in the portion of powdered Tablets taken to prepare the *Test solution;* r_i is the peak response obtained for each individual impurity in the *Test solution;* and r_S is the peak response obtained for pseudoephedrine sulfate in the *Standard solution:* not more than 0.1% of ephedrine sulfate (with a relative retention time of 0.78) is found; not more than 0.2% of any individual unknown impurity is found; and not more than 0.5% of total impurities is found. [NOTE—Disregard peaks due to loratadine and peaks due to excipients.]

Assay for loratadine—

Buffer solution—Dissolve 2.72 g of monobasic potassium phosphate in 1 L of water, and adjust with 5 N sodium hydroxide to a pH of 6.50 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (70 : 30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Loratadine RS in *Mobile phase,* and dilute quantitatively and stepwise, if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Assay preparation—Crush a number of Tablets, equivalent to 100 mg of loratadine, and accurately transfer the crushed Tablets into a 1000-mL volumetric flask. Add 800 mL of methanol, and stir vigorously for 30 minutes or longer, if necessary, until the Tablets are completely disintegrated and the powder is finely dispersed. Dilute with methanol to volume, and mix. Transfer 5 mL of the resulting suspension into a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass the solution through a suitable filter, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 3000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the loratadine peak. Calculate the quantity, in mg, of loratadine ($C_{22}H_{23}ClN_2O_2$) in the portion of Tablets taken by the formula:

$$DC(r_U / r_S)$$

in which D is the dilution factor, in mL, for the *Assay preparation;* C is the concentration, in mg per mL, of USP Loratadine RS in the *Standard preparation,* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Assay for pseudoephedrine sulfate—

Ammonium acetate solution—Dissolve 4 g of ammonium acetate in 1000 mL of water.

Mobile phase—Prepare a filtered and degassed mixture of dehydrated alcohol and *Ammonium acetate solution* (85 : 15). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Pseudoephedrine Sulfate RS in *Mobile phase,* and dilute quantitatively and stepwise, if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.2 mg per mL.

Assay preparation—Crush a number of Tablets, equivalent to 2.4 g of pseudoephedrine sulfate, and accurately transfer the crushed Tablets into a 1000-mL volumetric flask. Add 80 mL of methanol, and stir vigorously for 30 minutes or longer, if necessary, until the Tablets are completely disintegrated and the powder is finely dispersed. Dilute with methanol to volume, and stir for an additional 10 minutes. Transfer 5 mL of the resulting suspension into a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass the solution through a suitable filter, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 10-µm packing L3. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the pseudoephedrine sulfate peak. Calculate the quantity, in mg, of pseudoephedrine sulfate $[(C_{10}H_{15}NO)_2 \cdot H_2SO_4]$ in the portion of Tablets taken by the formula:

$$DC(r_U / r_S)$$

in which D is the dilution factor, in mL, for the *Assay preparation;* C is the concentration, in mg per mL, of USP Pseudoephedrine Sulfate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

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BRIEFING

Magnesium Carbonate, *USP 29* page 1292; **Magnesium Chloride,** *USP 29* page 1294; **Magnesium Oxide,** *USP 29* page 1299 and page 3730 of the *Second Supplement*. Comments were received that the use of an air–acetylene flame in the test for *Limit of calcium* could lead to an underestimation of calcium content in magnesium products. Calcium may form refractory compounds that do not completely decompose at the temperatures achieved by an air–acetylene flame. To address this problem, it is proposed to use a nitrous oxide–acetylene flame which has a higher temperature. Additionally, it is proposed to modify the standard curve, add a *Note* to clarify the use of commercially available atomic absorption standard solutions for calcium, and to add a formula for the final calculation. It is also proposed to add formulas to clarify correction for the content of calcium and other calculations in the *Assay.*

(MD-GRE: E. Gonikberg) RTS—C44339

Change to read:

Limit of calcium—

▲[NOTE—A commercially available atomic absorption standard solution for calcium may be used where preparation of a calcium standard stock solution is described below. Concentrations of the *Standard preparations* and the *Test preparation* may be modified to fit the linear or working range of the instrument.]▲*USP31*

Dilute hydrochloric acid—Dilute 100 mL of hydrochloric acid with water to 1000 mL.

Lanthanum solution—To 58.65 g of lanthanum oxide add 400 mL of water, and add, gradually with stirring, 250 mL of hydrochloric acid. Stir until dissolved, dilute with water to 1000 mL, and mix.

Standard preparations—Transfer 249.7 mg of calcium carbonate, previously dried at 300° for 3 hours and cooled in a desiccator for 2 hours, to a 100-mL volumetric flask, dissolve in a minimum amount of hydrochloric acid, dilute with water to volume, and mix. Transfer

▲1.0,▲*USP31*
5.0, 10.0, and 15.0 mL of this stock solution to separate 1000-mL volumetric flasks, each containing 20 mL of *Lanthanum solution* and 40 mL of *Dilute hydrochloric acid,* add water to volume, and mix. These *Standard preparations* contain

▲1.0,▲*USP31*
5.0, 10.0, and 15.0 µg of calcium in each mL, respectively.

Blank solution—Transfer 4 mL of *Lanthanum solution* and 10 mL of *Dilute hydrochloric acid* to a 200-mL volumetric flask, dilute with water to volume, and mix.

Test preparation—Transfer 250 mg of Magnesium Carbonate to a beaker, add 30 mL of *Dilute hydrochloric acid,* and stir until dissolved, heating if necessary. Transfer the solution so obtained to a 200-mL volumetric flask containing 4 mL of *Lanthanum solution,* dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparations* and the *Test preparation* at the calcium emission line at 422.7 nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a calcium hollow-cathode lamp and ~~an air–acetylene~~

▲a nitrous oxide–acetylene▲*USP31*
flame, using the *Blank solution* as the blank. ~~Plot the absorbances of the *Standard preparations* versus their concentrations of calcium, in µg per mL, and draw a straight line through the three points. From the line so obtained and the absorbance of the *Test preparation,* determine the concentration, in µg per mL, of calcium in the *Test preparation*. Calculate the percentage of calcium in the specimen by multiplying this value by 0.08:~~

▲Determine the concentration, C, in µg per mL, of calcium in the *Test preparation* using the calibration graph. Calculate the content of calcium, in percentage, in the portion of Magnesium Carbonate taken by the formula:

$$100(0.001CV/W)$$

in which C is as defined above; the multiplier of 0.001 is for conversion of µg per mL to mg per mL; V is the volume, in mL, of the *Test preparation;* and W is the amount of Magnesium Carbonate, in mg, taken to prepare the *Test preparation:*▲*USP31*
the limit is 0.45%.

Change to read:

Assay—Dissolve about 1 g of Magnesium Carbonate, accurately weighed, in 30.0 mL of 1 N sulfuric acid VS, add methyl orange TS, and titrate the excess acid with 1 N sodium hydroxide VS. ~~From the volume of 1 N sulfuric acid consumed, deduct the volume of 1 N sulfuric acid corresponding to the content of calcium in the weight of Magnesium Carbonate taken for the assay. The difference is the volume of 1 N sulfuric acid equivalent to the magnesium oxide present. Each mL of 1 N sulfuric acid is equivalent to 20.15 mg of MgO and to 20.04 mg of Ca.~~

▲Record the volume, V_A, in mL, of 1 N sodium hydroxide consumed. Perform the blank determination, and record the volume, V_B, in mL, of 1 N sodium hydroxide consumed. Calculate the volume, V_S, of 1 N sulfuric acid, in mL, consumed by the sample, by the formula:

$$(V_B - V_A) \times N_{NaOH}$$

in which N_{NaOH} is the exact normality of the sodium hydroxide solution. Calculate the volume of 1 N sulfuric acid, V_{Ca}, in mL, consumed by calcium which is present in the Magnesium Carbonate taken for the *Assay,* by the formula:

$$(W \times L_{Ca})/(100 \times 20.04)$$

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in which W is the weight, in mg, of Magnesium Carbonate taken; L_{Ca} is the content of calcium, in percentage, as determined in the test for *Limit of calcium;* and 20.04 is the weight, in mg, of Ca that is equivalent to each mL of 1 N sulfuric acid.

Calculate the percentage of MgO in the portion of Magnesium Carbonate taken by the formula:

$$100(V_S - V_{Ca}) \times 20.15/W$$

in which 20.15 is the weight, in mg, of MgO that is equivalent to each mL of 1 N sulfuric acid; and the other terms are as defined above.▲*USP31*

BRIEFING

Magnesium Chloride, *USP 29* page 1294—See briefing under *Magnesium Carbonate.*

(MD-GRE: E. Gonikberg) RTS—C44339

Change to read:

Limit of calcium—

Dilute hydrochloric acid, Lanthanum solution, Standard preparations, and *Blank solution*—Proceed as directed in the test for *Limit of calcium* under *Magnesium Carbonate*.

Test preparation—Transfer 10.0 g of Magnesium Chloride to a 200-mL volumetric flask, add water to dissolve it, add 4 mL of *Lanthanum solution,* dilute with water to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the test for *Limit of calcium* under *Magnesium Carbonate*. ~~Calculate the percentage of calcium in the Magnesium Chloride taken by multiplying the concentration, in µg per mL, of calcium found in the *Test preparation* by 0.002:~~

▲Determine the concentration, C, in µg per mL, of calcium in the *Test preparation* using the calibration graph. Calculate the content of calcium, in percentage, in the portion of Magnesium Chloride taken by the formula:

$$100(0.001CV/W)$$

in which C is as defined above; the multiplier of 0.001 is for conversion of µg per mL to mg per mL; V is the volume, in mL, of the *Test preparation;* and W is the amount of Magnesium Chloride, in mg, taken to prepare the *Test preparation:*▲*USP31*
the limit is 0.01%.

BRIEFING

Magnesium Oxide, *USP 29* page 1299 and page 3730 of the *Second Supplement*—See briefing under *Magnesium Carbonate.*

(MD-GRE: E. Gonikberg) RTS—C44340

Change to read:

Limit of calcium—

Dilute hydrochloric acid, Lanthanum solution, Standard preparations, and *Blank solution*—Prepare as directed in the test for *Limit of calcium* under *Magnesium Carbonate*.

Test preparation—Transfer 250 mg of Magnesium Oxide, freshly ignited, to a beaker, add 30 mL of *Dilute hydrochloric acid,* and stir until dissolved, heating if necessary. Transfer the solution so obtained to a 200-mL volumetric flask containing 4 mL of *Lanthanum solution,* dilute with water to volume, and mix.

Procedure—Proceed as directed in the test for *Limit of calcium* under *Magnesium Carbonate*.

▲Determine the concentration, C, in µg per mL, of calcium in the *Test preparation* using the calibration graph. Calculate the content of calcium, in percentage, in the portion of Magnesium Oxide taken by the formula:

$$100(0.001CV/W)$$

in which C is as defined above; the multiplier of 0.001 is for conversion of µg per mL to mg per mL; V is the volume, in mL, of the *Test preparation;* and W is the amount of Magnesium Oxide, in mg, taken to prepare the *Test preparation:*▲*USP31*
the limit is 1.1%.

Change to read:

Assay—Ignite about 500 mg of Magnesium Oxide to constant weight in a tared platinum crucible, weigh the residue accurately, dissolve it in 30.0 mL of 1 N sulfuric acid VS, add methyl orange TS, and titrate the excess acid with 1 N sodium hydroxide VS. ~~From the volume of 1 N sulfuric acid consumed, deduct the volume of 1 N~~

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~~sulfuric acid corresponding to the content of calcium in the Magnesium Oxide taken for the assay. The difference is the volume of 1 N sulfuric acid equivalent to the MgO in the portion of Magnesium Oxide taken. Each mL of 1 N sulfuric acid is equivalent to 20.15 mg of MgO and to 20.04 mg of Ca.~~

▲Record the volume, V_A, in mL, of 1 N sodium hydroxide consumed. Perform the blank determination, and record the volume, V_B, in mL, of 1 N sodium hydroxide consumed. Calculate the volume, V_S, of 1 N sulfuric acid, in mL, consumed by the sample, by the formula:

$$(V_B - V_A) \times N_{NaOH}$$

in which N_{NaOH} is the exact normality of the sodium hydroxide solution. Calculate the volume of 1 N sulfuric acid, V_{Ca}, in mL, consumed by calcium which is present in the Magnesium Oxide taken for the *Assay,* by the formula:

$$(W \times L_{Ca})/(100 \times 20.04)$$

in which W is the weight, in mg, of Magnesium Oxide taken; L_{Ca} is the content of calcium, in percentage, as determined in the test for *Limit of calcium;* and 20.04 is the weight, in mg, of Ca that is equivalent to each mL of 1 N sulfuric acid.

Calculate the percentage of MgO in the portion of Magnesium Oxide taken by the formula:

$$100(V_S - V_{Ca}) \times 20.15/W$$

in which 20.15 is the weight, in mg, of MgO that is equivalent to each mL of 1 N sulfuric acid; and the other terms are as defined above.▲*USP31*

BRIEFING

Meloxicam Oral Suspension. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The liquid chromatographic procedures in the *Assay* and in the test for *Chromatographic purity* are based on analyses performed with the Kromasil brand of L1 column. The typical retention time for meloxicam is 10.5 minutes.

(MD-CCA: C. Anthony; MSA: R. Tirumalai; BPC: M. Marques) RTS—C44069

Add the following:

▲Meloxicam Oral Suspension

» Meloxicam Oral Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of meloxicam ($C_{14}H_{13}N_3O_4S_2$).

Packaging and storage—Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Meloxicam RS. USP Meloxicam Related Compound B RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Transfer a volume of Oral Suspension, equivalent to about 2.5 mg of meloxicam, to a 10-mL volumetric flask. Dilute with acetone to volume, and mix for 10 minutes. If necessary, pass through fluted filter paper.

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Standard solution: 0.25 mg per mL, prepared by dissolving USP Meloxicam RS in 1 mL of water and diluting with acetone to volume.

Developing solvent solution: a mixture of chloroform, methanol, and ammonium hydroxide (80 : 20 : 1)

Procedure—Proceed as directed in the chapter. After removing the plate from the chamber and drying, examine the chromatograms under UV light at 254-nm: the R_F value (approximately 0.45) of the principal dark spot obtained from the *Test solution* corresponds to that obtained from the *Standard solution.*

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

pH ⟨791⟩**:** between 3.5 and 4.5.

Viscosity ⟨911⟩—Determine using a shear rate programmable rotational viscometer: between 40 and 100 centipoises, determined at 20°.

Dissolution ⟨711⟩—

Medium: pH 7.5 phosphate buffer; 900 mL.

Apparatus 2: 25 rpm.

Time: 15 minutes.

Determine the amount of $C_{14}H_{13}N_3O_4S_2$ dissolved by employing the following method.

Standard solution—Transfer about 20.83 mg of USP Meloxicam RS, accurately weighed, into a 100-mL volumetric flask. Dissolve in 5 mL of methanol and 1 mL of 0.1 M sodium hydroxide, and dilute with *Medium* to volume. Dilute with *Medium* to a final concentration of about 8.3 µg per mL of meloxicam.

Test solution—Shake each sample for 15 minutes. Weigh six portions, equivalent to 7.5 mg of the Oral Suspension, into separate tared 10-mL beakers, and record each weight. Introduce each of the samples to the middle of the dissolution vessels, and rinse each beaker with about 20 mL of the *Medium* withdrawn from the vessel. Carefully lower the paddle to the appropriate height and start the rotation. After completion of the dissolution, pass a 20-mL aliquot through a nylon filter having a 0.45-µm porosity, discarding the first 3 mL of the filtrate.

Procedure—Determine the amount of $C_{14}H_{13}N_3O_4S_2$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 362 nm on the *Test solution* in comparison with the *Standard solution,* using *Medium* as the blank. Calculate the percentage of $C_{14}H_{13}N_3O_4S_2$ released by the formula:

$$\frac{A_U \times C_S \times 900 \times d \times 100}{A_S \times W_U \times LC}$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of the *Standard solution; d* is the density, in g per mL, of the Oral Suspension; W_U is the weight, in mg, of the Oral Suspension taken; 900 is the volume, in mL of the *Medium;* 100 is the conversion factor to percentage; and *LC* is the label claim, in mg per mL.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{14}H_{13}N_3O_4S_2$ is dissolved in 15 minutes.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 100 cfu per g or 100 cfu per mL. The total yeasts and molds count does not exceed 50 cfu per g or 50 cfu per mL. It meets the requirements of the test for the absence of *Escherichia coli.*

Chromatographic purity—

Buffer, Mobile phase, and *Diluent*—Proceed as directed in the *Assay.*

Related compound standard stock solution—Proceed as directed for *Related compound standard stock preparation* in the *Assay.*

Sensitivity solution—Dilute the *Related compound standard stock solution* with *Diluent* to a final concentration of about 0.08 µg per mL.

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Related compound standard solution—Dilute *Related compound standard stock preparation* with *Diluent* to a final concentration of about 0.5 µg per mL.

Test solution—Proceed as directed for *Assay preparation* in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.* Chromatograph the *Sensitivity solution* (about 10 µL), and record the peak responses as directed for *Procedure* at 260 nm: the relative standard deviation of three replicate injections is not more than 10% for meloxicam related compound B. Chromatograph the *Related compound standard solution* (about 10 µL), and record the peak responses as directed for *Procedure* at 260 nm: the tailing factor for meloxicam related compound B is not more than 2.0.

Procedure—Separately inject equal volumes (about 10 µL) of the *Related compound standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and record the peak areas at 260 nm and 360 nm. The run time is about 20 minutes or two times the retention time of meloxicam. Calculate the percentage of meloxicam related compound B in the portion of Oral Suspension taken by the formula:

$$(5000/L)(C/V)(r_U/r_S)$$

in which L is the label claim, in mg per mL; C is the concentration, in mg per mL, of USP Meloxicam Related Compound B RS in the *Related compound standard solution;* V is the volume, in mL, of Oral Suspension taken to prepare the *Test solution;* r_U is the peak area obtained for meloxicam related compound B in the *Test solution* at 260 nm; and r_S is the peak area for meloxicam related compound B in the *Related compound standard solution* at 260 nm. Calculate the percentage of each unknown degradation product in the portion of Oral Suspension taken by the formula:

$$100(r_i/r_s)$$

in which r_i is the area of any unknown degradant at 360 nm; r_s is the sum of areas of meloxicam and all impurities in the *Test solution* at 360 nm. Not more than 0.15% of meloxicam related compound B is found; not more than 0.2% of any individual unknown degradation product is found; and not more than 0.5% of total degradation products is found.

Assay—

Buffer—Dissolve 2 g of monohydrate citric acid and 2 g of boric acid in 1000 mL of water, and adjust with dihydrate trisodium citrate to a pH of 2.9.

Mobile phase—Mix 565 mL of *Buffer,* 260 mL of methanol, and 200 mL of acetonitrile. Degas the solution, and then dissolve 200 mg of sodium dodecyl sulfate in 1000 mL of the resulting solution.

Diluent—Dissolve 3 g of boric acid and 1.5 g of dihydrate trisodium citrate in 1000 mL of water, and adjust with 2 M sodium hydroxide to a pH of 8.3. Mix 420 mL of the resulting buffer with 420 mL of methanol and 160 mL of acetonitrile.

Standard stock preparation—Transfer about 67 mg of USP Meloxicam RS, accurately weighed, into a 100-mL volumetric flask. Add 3.0 mL of dimethylformamide. Swirl the flask, and allow to stand for about 5 minutes. Add 15 mL of methanol. Dilute with *Diluent* to just below volume. Sonicate for 30 minutes, and mix until dissolved. Cool to room temperature. Dilute with *Diluent* to volume.

Standard preparation—Dilute *Standard stock preparation* with *Diluent* to a final concentration of about 0.27 mg per mL.

Related compound standard stock preparation—Transfer about 21 mg of USP Meloxicam Related Compound B RS, accurately weighed, into a 100-mL volumetric flask. Add 3.0 mL of dimethylformamide, 15 mL of methanol, and about 60 mL of *Diluent.* Sonicate, and mix until dissolved. Cool to room temperature. Dilute with *Diluent* to volume. Dilute further with *Diluent* to a concentration of about 8.4 µg per mL.

System suitability solution—Transfer a volume of Oral Suspension, equivalent to about 15 mg of meloxicam, accurately weighed, to a 50-mL volumetric flask. Add 3.0 mL of *Related compound standard stock preparation.* Add 3.0 mL of dimethylformamide. Swirl the flask, and allow to stand for about 5 minutes. Add 15 mL of methanol. Dilute with *Diluent* to just below volume. Sonicate for 30 minutes, mixing the flask vigorously about every 5 minutes. Cool to room temperature. Dilute with *Diluent* to volume. Mix, and allow particulates to settle. Pass through a 0.45-µm membrane filter with a fiberglass prefilter.

Assay preparation—Transfer an accurately meaured volume of Oral Suspension, equivalent to about 15 mg of meloxicam, to a 50-mL volumetric flask. Add 3.0 mL of dimethylformamide. Swirl the flask, and allow to stand for about 5 minutes. Add 15 mL of methanol. Dilute with *Diluent* to just below volume. Sonicate for 30 minutes, mixing the flask vigorously about every 5 minutes. Cool to room temperature. Dilute with *Diluent* to volume. Mix, and allow particulates to settle. Pass through a 0.45-µm membrane filter with a fiberglass prefilter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a programmable dual wavelength detector, a single wavelength detector in series, or a photodiode array detector capable of detecting wavelengths from 190 nm to 400 nm, or equivalent, and a 4-mm × 12.5-cm analytical column that contains 5-µm packing L1. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. The run time is about 20 minutes or two times the retention time of meloxicam. Chromatograph the *System suitability solution* (about 10 µL), and record the peak responses as directed for *Procedure* at 360 nm and 260 nm: at 360 nm the resolution, *R,* between meloxicam and any other adjacent peak is not less than 1.5. The tailing factor for the meloxicam peak is not more than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure* at 360 nm: the relative standard deviation for replicate injections of the *Standard preparation* is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and record the peak areas at 360 nm. Calculate the amount of meloxicam ($C_{14}H_{13}N_3O_4S_2$), in mg per mL, in the portion of Oral Suspension taken by the formula:

$$50(C/V)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Meloxicam RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken to prepare the *Assay preparation;* r_U is the peak area obtained for meloxicam in the *Assay preparation* at 360 nm; and r_S is the peak area for meloxicam in the *Standard solution* at 360 nm.▲*USP31*

BRIEFING

Meropenem for Injection, *USP 29* page 1351. It is proposed to clarify the dilution scheme for *Assay preparation 2* in the *Assay.*

(MD-ANT: B. Gilbert) RTS—C46973

Change to read:

Assay—

Mobile phase—Dilute 15 mL of tetrabutylammonium hydroxide solution (25% in water) with water to 750 mL. Adjust with dilute phosphoric acid (1 in 10) to a pH of 7.5 ± 0.1. Add 150 mL of acetonitrile and 100 mL of methanol, mix, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed portion of USP Meropenem RS quantitatively in *Mobile phase* to obtain a solution having a known concentration of about 0.11 mg per mL. This solution contains the equivalent of about 0.1 mg of meropenem per mL. [NOTE—Immediately after preparation, store this solution in a refrigerator and use within 24 hours.]

Assay preparation 1 (where it is represented as being a single-dose container)—Constitute a container of Meropenem for Injection with a volume of water, accurately measured, corresponding to the amount of solvent specified in the labeling. Withdraw all of the withdrawable contents, using a suitable hypodermic needle and syringe, and transfer to a 100-mL volumetric flask. Dilute with water

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to volume, and mix. Dilute an accurately measured volume of this stock solution quantitatively with *Mobile phase* to obtain a solution having a concentration of about 0.1 mg of meropenem per mL. Hold this *Assay preparation 1* for 2 hours at 25 ± 1° before testing.

Assay preparation 2 (where the label states the quantity of meropenem in a given volume of constituted solution)—Constitute a container of Meropenem for Injection with a volume of water, accurately measured, corresponding to the amount of solvent specified in the labeling. Transfer an accurately measured volume of the constituted solution, equivalent to about 100 mg of meropenem to a 100-mL volumetric flask,

▲and dilute with water to volume.▲*USP31*
Transfer 5.0 mL of this stock solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Hold this *Assay preparation 2* for 2 hours at 25 ± 1° before testing.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 300-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Adjust the flow rate to obtain a retention time for meropenem of about 6 to 8 minutes. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2500 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of *Standard preparation, Assay preparation 1,* and *Assay preparation 2* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of meropenem ($C_{17}H_{25}N_3O_5S$) withdrawn from the container or in the portion of constituted solution taken by the formula:

$$100(L/D)(CP)(r_U/r_S)$$

in which L is the labeled quantity, in mg, of meropenem in the container or in the volume of constituted solution taken; D is the concentration, in mg per mL, of meropenem in *Assay preparation 1* or *Assay preparation 2*, based on the labeled quantity in the container or in the portion of constituted solution taken, respectively; C is the concentration, in mg per mL, of USP Meropenem RS in the *Standard preparation,* calculated on the anhydrous basis; P is the stated percentage, on the anhydrous basis, of meropenem in USP Meropenem RS; and r_U and r_S are the peak responses of meropenem obtained from *Assay preparation 1* or *Assay preparation 2*, as appropriate, and the *Standard preparation,* respectively.

BRIEFING

Metformin Hydrochloride Tablets, *USP 29* page 1365 and page 3732 of the *Second Supplement.* It is proposed to add *Dissolution Test 3* to this monograph because FDA approved a new generic version of this product. The chromatographic procedure in this test was validated using the Prodigy C18 brand of L1 column. The retention time of the metformin peak is about 13 minutes. A suitable alternative column is the Aqua C18 brand. In the absence of any significant adverse comments, it is proposed to implement this revision via the *Interim Revision Announcement* pertaining to *USP 29–NF 24,* with an official date of April 1, 2007.

(BPC: M. Marques) RTS—C43191

Change to read:

Dissolution ⟨711⟩—

TEST 1—
Medium: pH 6.8 phosphate buffer; 1000 mL.
Apparatus 1: 100 rpm.
Time: 45 minutes.
Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 233 nm on filtered portions of the solution under test, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium.*
Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 45 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

FOR PRODUCTS LABELED TO CONTAIN 500 MG OF METFORMIN—
Medium: pH 6.8 phosphate buffer; 1000 mL.
Apparatus 2: 50 rpm.
Time: 30 minutes.
Procedure—Proceed as directed for *Test 1.*
Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 minutes.

FOR PRODUCTS LABELED TO CONTAIN 850 MG OR 1000 MG OF METFORMIN—
Medium: pH 6.8 phosphate buffer; 1000 mL.
Apparatus 2: 75 rpm.
Time: 30 minutes.
Procedure—Proceed as directed for *Test 1.*
Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 minutes.

•TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3.*

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 1: 100 rpm.

Time: 60 minutes.

Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by employing the following method.

0.05 M Sodium phosphate with 1-pentanesulfonic acid solution—Dissolve 1.38 g of monobasic sodium phosphate in about 1800 mL of water. Add 3.484 g of 1-pentanesulfonic acid sodium salt, and mix. Adjust with diluted phosphoric acid to a pH of 3.00 ± 0.05. Add water to make 2000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.05 M Sodium phosphate with 1-pentanesulfonic acid solution* and acetonitrile (19 : 1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 25 mg, accurately weighed, of USP Metformin Hydrochloride RS to a 100-mL volumetric flask, and add about 50 mL of *Medium*. Sonicate until dissolved, and dilute with *Medium* to volume.

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Standard solution—Transfer 10.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, and dilute with *Medium* to volume.

Test solution—Withdraw a portion of the solution under test, and pass through a 0.45-µm nylon filter. Dilute with *Medium,* if necessary, to obtain a concentration similar to that of the *Standard solution*.

Chromatographic system—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph replicate injections of the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; the column efficiency is not less than 1500 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of metformin released by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times D \times LC}$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of metformin in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; D is the dilution factor of the *Test solution;* and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 60 minutes.•2

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BRIEFING

Metformin Hydrochloride Extended-Release Tablets, page 772 of *PF* 31(3) [May–June 2005].

1. On the basis of comments received, the limit of total impurities under the *Chromatographic purity* test is changed from "not more than 0.5%" to "not more than 0.6%". This limit is representative of marketed products.
2. Small variations in the acetonitrile content or differences in the performances of chromatographic columns may result in poor separation of metformin impurities from the analyte. To address this issue, it is proposed to add a *Note* to indicate that the composition of the *Mobile phase* may be changed to 95 : 5, if necessary, to improve the separation.
3. It is proposed to add *Test 7* and *Test 8* to the *Dissolution* tests in this monograph.

(MD-GRE: E. Gonikberg; BPC: M. Marques) RTS—C44063; C43520; C45557; C45559; C45557

Add the following:

▲Metformin Hydrochloride Extended-Release Tablets

» Metformin Hydrochloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in well-closed, light-resistant containers, and store at controlled room temperature.

Labeling—When more than one *Dissolution Test* is given, the labeling states the *Dissolution Test* used only if *Test 1* is not used.

USP Reference standards ⟨11⟩—*USP Metformin Hydrochloride RS. USP Metformin Related Compound B RS. USP Metformin Related Compound C RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

TEST 1—

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1; 1000 mL.

Apparatus 2: 100 rpm, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 3, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45-µm hydrophilic polyethylene filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S)] \times 100}{L}$$

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{180} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 22% and 42%
3	between 45% and 65%	between 49% and 69%
10	not less than 85%	not less than 85%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: Prepare as directed for *Medium* in *Test 1;* 1000 mL.

Apparatus 2: 100 rpm.

Times: 1, 2, 6, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45-µm polyethylene filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in mg per mL, in the *Medium* at each time point, *t,* by the formula:

$$\frac{A_U \times C_s \times D_U}{A_s}$$

in which A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; C_S is the concentration of metformin hydrochloride, in mg per mL, in the Standard solution; and D_U is the dilution factor of the solution under test. Calculate the percentage of metformin

hydrochloride ($C_4H_{11}N_5 \cdot HCl$) dissolved at each time point by the following formulas:

Percentage dissolved at the first time point (1 hour):

$$\frac{C_1 \times 1000 \times 100}{L}$$

in which C_1 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the first time interval; 1000 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Percentage dissolved at the second time point (2 hours):

$$\frac{C_2 \times (1000 - SV_1) + C_1 \times SV_1 \times 100}{L}$$

in which C_2 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the second time interval; 1000 is the volume, in mL, of *Medium;* SV_1 is the volume, in mL, of the sample withdrawn at 1 hour; C_1 is the content of metformin hydrochloride, in mg per mL, in the *Medium* at 1 hour; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Percentage dissolved at the *n*th time point:

$$\frac{C_n \times [1000 - (n-1)SV] + (C_1 + C_2 + ... + C_{n-1}) \times SV \times 100}{L}$$

in which C_n is the content of metformin hydrochloride, in mg per mL, in the *Medium* at the *n*th time interval; n is the time interval of interest; SV is the volume, in mL, of sample withdrawn at each time interval; C_1, C_2, C_3, ... C_{n-1} is the content of metformin hydrochloride, in mg per mL, in the *Medium* at each time interval; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 35% and 55%
6	between 65% and 85%
10	not less than 85%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1*.

Times: 1, 2, 5, and 12 hours for Tablets labeled to contain 500 mg; and 1, 3, and 10 hours for Tablets labeled to contain 750 mg.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a 0.45-µm hydrophilic polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{120} \times V_S) + (C_{300} \times V_S)] \times 100}{L}$$

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1

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hour; C_{120} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 2 hours; C_{300} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 5 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 500 MG

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 35% and 55%
5	between 60% and 80%
12	not less than 85%

FOR TABLETS LABELED TO CONTAIN 750 MG

Time (hours)	Amount dissolved
1	between 22% and 42%
3	between 49% and 69%
10	not less than 85%

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: Prepare as directed for *Medium* in *Test 1;* 1000 mL.

Apparatus 2: 100 rpm.

Times: 1, 3, 6, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 250 nm (shoulder) on portions of the solution under test passed through a 0.45-µm polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in mg per mL, in the *Medium* at each time point, *t,* by the formulas specified in *Test 2*.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	Amount dissolved
1	between 20% and 40%
3	between 45% and 65%
6	between 65% and 85%
10	not less than 85%

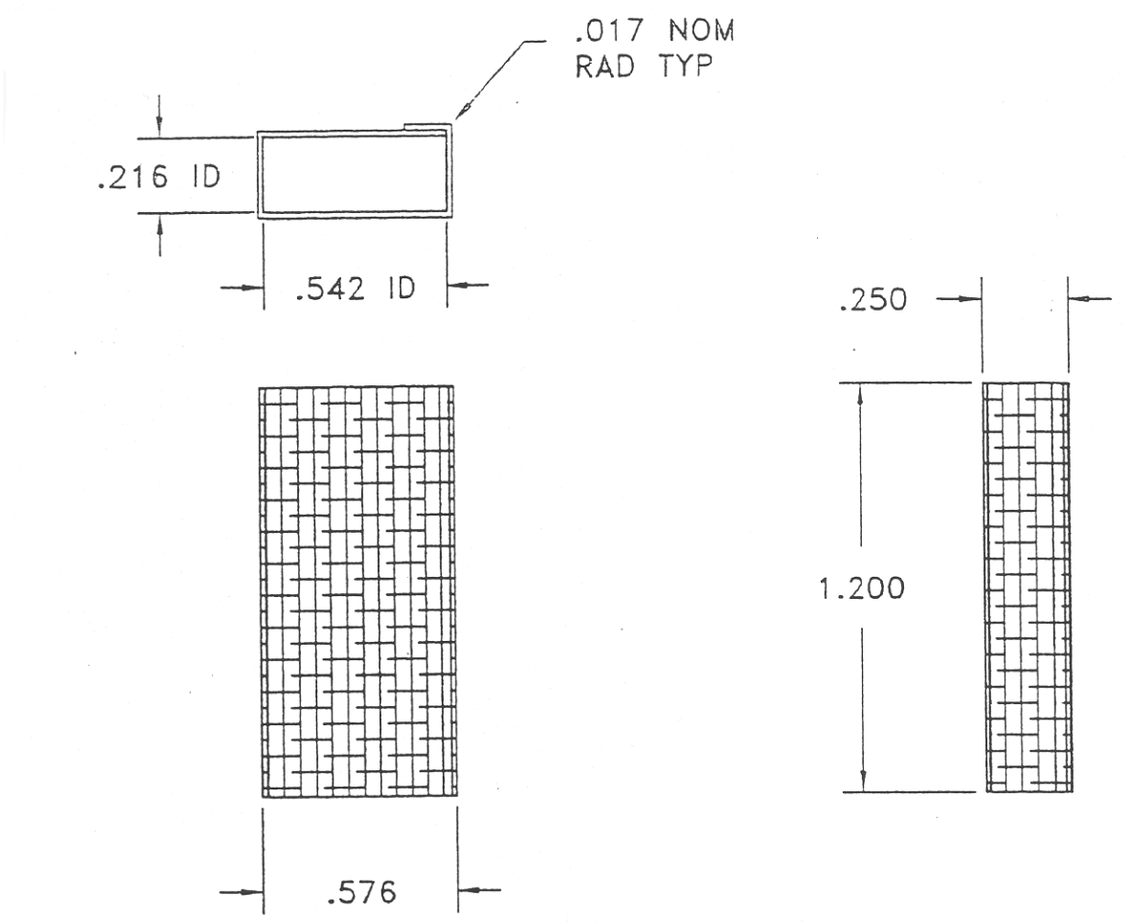
TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.1; 900 mL, deaerated.

Apparatus 1: 100 rpm, with the vertical holder described below.

Times: 2, 8, and 16 hours.

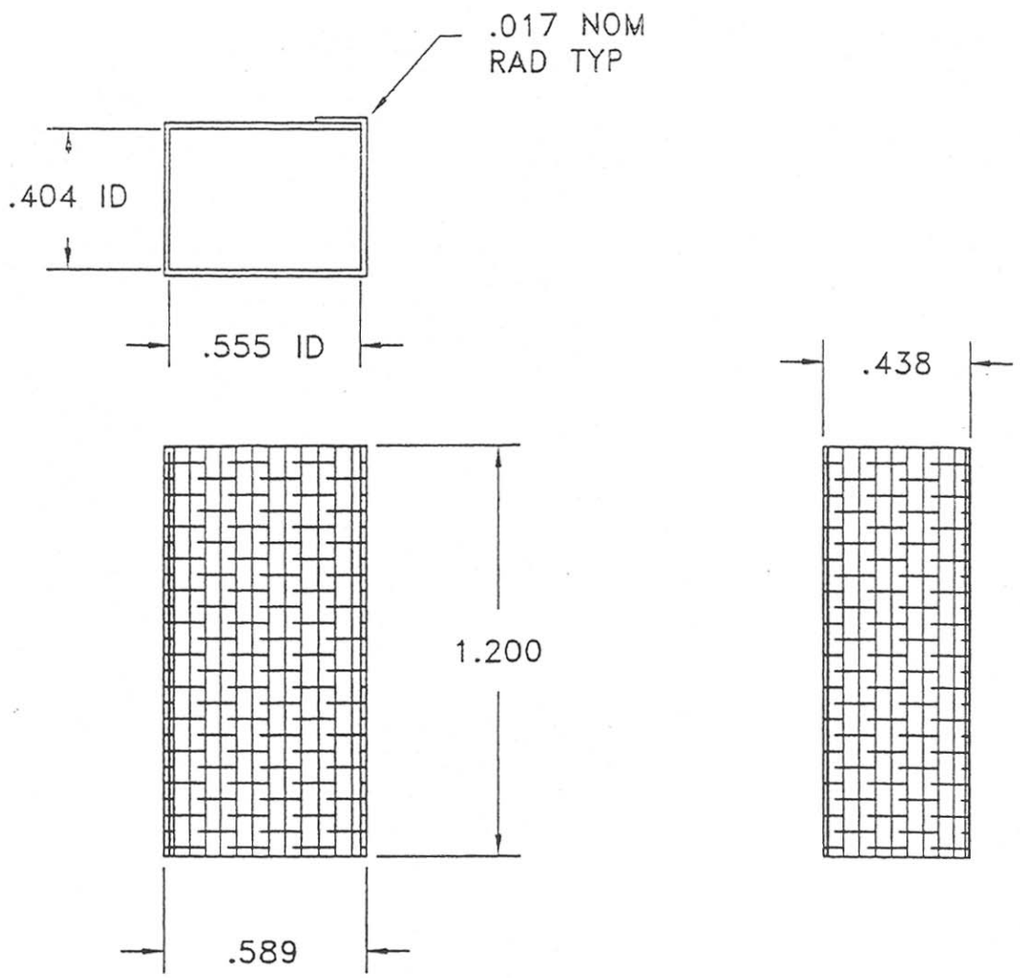
Procedure—Place a vertical sample holder into each basket (see *Figures 1* and *2*). Place one Tablet inside the sample holder, making sure that the Tablets are vertical at the bottom of the baskets. Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 250 nm on portions of the solution under test passed through a 0.45-µm polyethylene filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the content of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), C_t, in mg per mL, in the *Medium* at each time point, *t,* by the formulas specified in *Test 2*.



NOTES:

1. MATERIAL: 316SS OR EQUIVALENT .017 WIRE VERTICAL MEAS SQUARE WEAVE WITH .039 SQUARE OPENINGS.
2. ALL DIMENSIONS ARE IN INCHES. TOLERANCES TO BE +/-.010

Figure 1



NOTES:

1. MATERIAL: OR EQUIVALENT .017 WIRE VERTICAL MEAS SQUARE WEAVE WITH .039 SQUARE OPENINGS.
2. ALL DIMENSIONS ARE IN INCHES. TOLERANCES TO BE +/-.010

Figure 2

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	1000-mg Tablet, Amount dissolved
2	not more than 30%	not more than 30%
8	between 60% and 85%	between 65% and 90%
16	not less than 90%	not less than 90%

TEST 6—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6.*

Medium: pH 6.8 phosphate buffer prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 0.2 N sodium hydroxide to a pH of 6.8 ± 0.05; 1000 mL, deaerated.

Apparatus 2: 100 rpm, with USP sinker, if necessary.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 233 nm on portions of the solution under test passed through a 0.45-µm hydrophilic polyethylene filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S) + (C_{600} \times V_S)] \times 100}{L}$$

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{180} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; C_{600} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 10 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 20% and 40%
3	between 45% and 65%	between 45% and 65%
10	not less than 85%	not less than 85%

TEST 7—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7.*

Medium—Prepare as directed for *Medium* in *Test 1;* 1000 mL.

Apparatus 2: 50 rpm, with USP sinker, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 3, and 10 hours.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted with *Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula:

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{180} \times V_S) + (C_{600} \times V_S)] \times 100}{L}$$

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in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{180} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 3 hours; C_{600} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 10 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 20% and 40%
3	between 45% and 65%	between 40% and 60%
10	not less than 85%	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8.*

Medium—Prepare as directed for *Medium* in *Test 1;* 1000 mL.

Apparatus 2: 100 rpm, with sinker, for Tablets labeled to contain 500 mg.

Apparatus 1: 100 rpm, for Tablets labeled to contain 750 mg.

Times: 1, 2, 6, and 10 hours

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by UV absorption at the wavelength of maximum absorbance at about 232 nm on portions of the solution under test passed through a suitable 0.45-µm filter, suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium*. Calculate the amount of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$), in percentage, released at each time point by the formula (1):

in which C is the concentration, in mg per mL, of the Standard solution; A_U and A_S are the absorbances of the solution under test and the Standard solution, respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_{60} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 1 hour; C_{120} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 2 hours; C_{360} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 6 hours; C_{600} is the concentration, in mg per mL, of metformin hydrochloride in the *Medium* determined at 10 hours; 100 is the conversion factor to percentage; and L is the tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 2*.

Time (hours)	500-mg Tablet, Amount dissolved	750-mg Tablet, Amount dissolved
1	between 20% and 40%	between 20% and 40%
2	between 30% and 50%	between 35% and 55%
6	between 65% and 85%	between 75% and 95%
10	not less than 85%	not less than 85%

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Chromatographic purity—

Mobile phase and *Chromatographic system*—Prepare as directed in the *Assay.*

$$\frac{[C \times (A_U / A_S) \times (V - V_S) + (C_{60} \times V_S) + (C_{120} \times V_S) + (C_{360} \times V_S) + (C_{600} \times V_S)] \times 100}{L} \qquad (1)$$

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Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.1% of any individual impurity is found, and not more than ~~0.5%~~ 0.6% of total impurities is found. Disregard any peak less than 0.05%, and disregard any peak observed in the blank.

Assay—

Buffer solution—Transfer 1.0 g each of sodium heptanesulfonate and sodium chloride to a 2000-mL volumetric flask, add 1800 mL of water, and mix. Adjust with 0.06 M phosphoric acid to a pH of 3.85, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (90 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). [NOTE—To improve the separation, the composition may be changed to 95 : 5, if necessary.]

Diluent—Use a 1.25% solution of acetonitrile in water.

Standard preparation—Dissolve an accurately weighed quantity of USP Metformin Hydrochloride RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about (*L*/4000) mg per mL, where *L* is the labeled quantity, in mg, of metformin hydrochloride in each Tablet.

System suitability preparation—Dissolve suitable quantities of USP Metformin Related Compound B RS and USP Metformin Related Compound C RS in *Diluent* to obtain a solution containing about 12.5 µg of each per mL. Pipet 0.5 mL of this solution into a 50-mL volumetric flask, and dilute with the *Standard preparation* to volume.

Assay stock preparation—Weigh and finely powder not fewer than 10 Tablets. Transfer an accurately weighed portion of the powder, equivalent to the average Tablet weight, to a homogenization vessel, and accurately add 500 mL of 10% acetonitrile solution. Alternately, homogenize and allow to soak until the sample is fully homogenized.

Assay preparation—Pass a portion of the *Assay stock preparation* through a filter having a 0.45-µm porosity, discarding the first 3 mL of filtrate. Transfer 25 mL of the filtrate to a 200-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 3.9-mm × 30-cm column that contains 10-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.86 for metformin related compound B, 1.0 for metformin, and about 2.1 to 2.3 for metformin related compound C [NOTE—This impurity can have a variable retention time; the composition of the *Mobile phase* may be changed to 95 : 5, if metformin related compound C elutes at a relative retention time of less than 2.1.]; the resolution, *R,* between peaks due to metformin related compound B and metformin is not less than 1.5; the tailing factor for the metformin peak is not less than 0.8 and not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5% for the metformin peak and not more than 10% for each of the peaks due to metformin related compound B and metformin related compound C.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, carrying out the run until after the elution locus of metformin related compound C; record the

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chromatograms; and measure the responses for the major peaks. Calculate the quantity, in mg per Tablet, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) by the formula:

$$C(V/W)TD(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation; V* is the volume, in mL, of the *Assay stock preparation; W* is the weight, in mg, of sample used to prepare the *Assay stock preparation; T* is the average Tablet weight, in mg; D is the dilution factor of the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Morantel Tartrate, *USP 29* page 1455 and page 355 of *PF* 32(2) [Mar.–Apr. 2006]. On the basis of comments received, the following changes are proposed. In the Definition, it is proposed to decrease the lower limit of the allowed percentage range. In the *Related compounds* test, in the *Chromatographic system,* it is proposed to add relative rention times for morantel and two of its isomers; in the *Procedure,* it is proposed to add a specific limit for the 4-methyl isomer impurity of morantel tartrate (1-methyl-2-[(*E*)-2-(4-methylthiophen-2-yl)ethenyl]-1,4,5,6 tetrahydropyrimidine). These changes also result in a lower allowable limit in the *Assay.* Interested parties are encouraged to submit comments.

(VET: I. DeVeau) RTS—C46101

Change to read:

» Morantel Tartrate contains not less than ~~98.5~~ ▲96.4▲*USP31* percent and not more than 101.5 percent of $C_{12}H_{16}N_2S \cdot C_4H_6O_6$, calculated on the dried basis.

Change to read:

pH ⟨791⟩**:** between 2.8 and ~~3.2~~ ■3.9.■1S (*USP30*)

Solution—Dissolve and dilute 0.25 g to 25.0 mL of it in carbon dioxide-free water.

Change to read:

Related compounds—[NOTE—Conduct this test without exposure to daylight, and with the minimum necessary exposure to artificial light.]

Mobile phase—Mix 3.5 mL of triethylamine and 850 mL of water. Adjust with phosphoric acid to a pH of 2.5. Add 50 mL of tetrahydrofuran and 100 mL of methanol, and mix.

Tartrate solution—Prepare a solution containing about 0.15 mg of tartaric acid per mL in *Mobile phase*.

Standard solution 1—Dissolve an accurately weighed quantity of USP Morantel Tartrate RS in *Mobile phase* to obtain a solution having a known concentration of about 5.0 µg per mL.

Standard solution 2—Dilute 2.0 mL of *Standard solution 1* to 100.0 mL with *Mobile phase*.

System suitability solution—Expose 10 mL of *Standard solution 1* to daylight for 15 minutes before injection.

Test solution—Dissolve an accurately weighed quantity of Morantel Tartrate in *Mobile phase* to obtain a solution having a concentration of about 0.5 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 226-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 0.75 mL per minute. Chromatograph the *Tartrate solution, Standard solution 1,* and the *System suitability solution,* and record the peak areas as directed for *Procedure:* using the *System suitability solution,* the resolution, *R,* between morantel and its preceding peak (*(Z)*-isomer) is not less than 2.

▲The relative retention times are about 0.8, 1.0, and 1.2 for the morantel *(Z)*-isomer, morantel, and the morantel 4-methyl isomer (1-methyl-2-[(*E*)-2-(4-methylthiophen-2-yl)ethenyl]-1,4,5,6 tetrahydropyrimidine), respectively.▲*USP31*

Procedure—Separately inject equal volumes (about 20 µL) of the *Tartrate solution, Standard solution 1, Standard solution 2,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Disregarding the tartrate peak and any peak in the chromatogram of the *Test solution* less than the area of the principal peak in the chromatogram of *Standard solution 2,* calculate the area percentage of each impurity, relative to morantel, in the portion of Morantel Tartrate taken by the formula:

$$100(C_S/C_U)(r_i/r_S)$$

in which C_S and C_U are the concentrations of morantel tartrate, in mg per mL, of *Standard solution 1* and the *Test solution,* respectively; and r_i and r_S are the peak areas of each individual impurity and morantel obtained from the *Test solution* and *Standard solution 1,* respectively: ~~not more than 0.5% of any individual impurity is found, and not more than 1% of total impurities is found.~~

▲not more than 3% of the morantel 4-methyl isomer is found; not more than 0.5% of any other individual impurity is found; and not more than 1% of total other individual impurities is found.▲*USP31*

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BRIEFING

Norethindrone Tablets, *USP 29* page 1553. It is proposed to replace the *Disintegration* test with a *Dissolution* test for each product approved for the U.S. market. The chromatographic procedure in *Dissolution Test 1* was validated using an Ultrasphere C8 brand of L7 column. The chromatographic procedure in *Dissolution Test 2* was validated using a Pecosphere ODS brand of L1 column. An alternative L1 column for this procedure is 1B-Sil.

(BPC: M. Marques) RTS—C42151; C45907

Add the following:

▲**Labeling—**When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲*USP31*

Delete the following:

▲~~**Disintegration** ⟨701⟩: 15 minutes, the use of disks being omitted.~~▲*USP31*

Add the following:

▲**Dissolution** ⟨711⟩**—**

TEST 1—

Medium: 0.09% sodium lauryl sulfate in 0.1 N hydrochloric acid; 500 mL, deaerated.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Determine the amount of $C_{20}H_{26}O_2$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (3 : 2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Transfer about 35 mg, accurately weighed, of USP Norethindrone RS to a 500-mL volumetric flask. Add approximately 100 mL of methanol, and sonicate until completely dissolved. Cool to room temperature. Dilute with methanol to volume, and mix well. Transfer 2.0 mL of this solution to a 200-mL volumetric flask. Dilute with *Medium* to volume, and mix well.

Test solution—Pass the solution under test through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of norethindrone dissolved by the formula:

$$\frac{r_U \times C_S \times 500 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of norethindrone in the *Standard solution;* 500 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{20}H_{26}O_2$ is dissolved in 30 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.09% sodium lauryl sulfate in 0.1 N hydrochloric acid; 900 mL, deaerated.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Determine the amount of $C_{20}H_{26}O_2$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of 0.02 M phosphate buffer pH 6.0 and acetonitrile (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Standard solution—Transfer about 14 mg, accurately weighed, of USP Norethindrone RS to a 100-mL volumetric flask. Dilute with methanol to volume, and mix. Transfer 20.0 mL of this solution to a 100-mL volumetric flask. Dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a 200-mL volumetric flask. Dilute with *Medium* to volume, and mix.

Test solution—Pass the solution under test through a suitable 0.45-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 200-nm detector and a 4.6-mm × 10-cm column that contains 3-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Proceed as directed for *Test 1*. Calculate the percentage of norethindrone dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the *Test solution* and the *Standard solution,* respectively; C_S is the concentration, in mg per mL, of norethindrone in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Tablet label claim, in mg.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{20}H_{26}O_2$ is dissolved in 45 minutes.▲*USP31*

BRIEFING

Ofloxacin Tablets. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with the 3-µm Hypersil BDS C18 brand of L1 column. In the test for *Related compounds,* typical retention times for impurity A and impurity B are about 4 minutes and 28 minutes, respectively. In the *Assay,* the typical retention time for ofloxacin is about 7 minutes.

(MD-AA: B. Davani; BPC: M. Marques) RTS—C42637

Add the following:

▲Ofloxacin Tablets

» Ofloxacin Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ofloxacin ($C_{18}H_{20}FN_3O_4$).

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Ofloxacin RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩**—**[To come.]

Uniformity of dosage units ⟨905⟩**:** meet the requirements for *Content Uniformity.*

Related compounds—

Phosphate buffer—Dissolve 2.72 g of monobasic potassium phosphate in 1000 mL of water. Adjust with diluted phosphoric acid to a pH of 3.3 ± 0.1.

Solution A—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (88 : 12).

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Phosphate buffer* (60 : 40).

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Mobile phase—Use variable mixtures of *Solution A* and *Solution B,* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Ofloxacin RS in methanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 4 µg per mL.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of ofloxacin, to a 100-mL volumetric flask, add 70 mL of methanol, and sonicate for about 20 minutes. Dilute with methanol to volume, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, discarding the first 5 mL. Use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 294-nm detector and a 4.6-mm × 10-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–8	100	0	isocratic
8–25	100→40	0→60	linear gradient
25–26	40→100	60→0	linear gradient
26–40	100	0	isocratic

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(1/F)(r_U/r_S)(C_S/C_U)$$

in which F is the relative response factor for each impurity; r_U is the peak response of the impurity obtained from the *Test solution;* r_S is the peak response of ofloxacin obtained from the *Standard solution;* C_S is the concentration, in mg per mL, of USP Ofloxacin RS in the *Standard solution;* and C_U is the concentration, in mg per mL, of ofloxacin in the *Test solution,* based on the label claim. The impurity limits meet the requirements specified in *Table 1*.

Assay—

Buffer solution—Dissolve 2.72 g of monobasic potassium phosphate in 1000 mL of water, and adjust with diluted phosphoric acid to a pH of 3.3 ± 0.1.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (88 : 12). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent 1—Prepare a mixture of methanol and glacial acetic acid (75 : 25).

Diluent 2—Prepare a mixture of water and acetonitrile (90 : 10).

Standard preparation—Dissolve an accurately weighed quantity of USP Ofloxacin RS in *Diluent 1* to obtain a solution having a known concentration of about 1 mg per mL, and dilute quantitatively, and stepwise if necessary, with *Diluent 2* to obtain a solution having a known concentration of about 20 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of ofloxacin, to a 100-mL volumetric flask, add 70 mL of *Diluent 1,* and sonicate for

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Table 1

Name	Relative Retention Time	Relative Response Factor	Limit (%)
Impurity A (2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid)	0.5	1	0.3
Impurity B (9,10-difluoro-3-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid)	3.6	0.22	0.3
Any other impurity	—	1	0.2
All impurities	—	—	1.0

about 20 minutes. Dilute with *Diluent 1* to volume, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and collect the filtrate. Dilute 2.0 mL of the filtrate with *Diluent 2* to 100 mL, and mix well.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 294-nm detector and 4.6-mm × 10-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of ofloxacin ($C_{18}H_{20}FN_3O_4$) in the portion of Tablets taken by the formula:

$$5000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Ofloxacin RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Orlistat Capsules. Because there is no *USP* monograph for this dosage form, a new monograph is being proposed. The liquid chromatographic procedures in the tests for *Dissolution* and *Related compounds* and in the *Assay* are based on analyses performed with the Nova-Pak C18 brand of L1 column. The typical retention time is about 10.2 minutes for orlisat.

(MD-CCA: C. Anthony; BPC: M. Marques) RTS—C44029

Add the following:

▲Orlistat Capsules

» Orlistat Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of orlistat ($C_{29}H_{53}NO_5$).

Packaging and storage—Preserve in tight containers, and store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Orlistat RS. USP Orlistat Related Compound D RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

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Dissolution ⟨711⟩—

Medium: 3% sodium lauryl sulfate and 0.5% sodium chloride in water. To each 10 L of this solution, add 1 to 2 drops of *n*-octanol, and adjust with phosphoric acid to a pH of 6.0 ± 0.2; 900 mL.

Apparatus 2: 75 rpm, with a coil sinker.

Time: 45 minutes.

Determine the amount of $C_{29}H_{53}NO_5$ dissolved by employing the following method.

Mobile phase—Proceed as directed in the *Assay.*

Standard solution—Transfer about 13 mg of USP Orlistat RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 2 mL of acetonitrile, dilute with *Medium* to volume, and mix.

Test solution—Pass the solution under test through a suitable 0.2-µm filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to use a flow rate of about 2.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Proceed as directed for *Procedure* in the *Assay.* Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the amount of orlistat ($C_{29}H_{53}NO_5$) dissolved by the formula:

$$\frac{r_U \times C_S \times 900 \times 100}{r_S \times LC}$$

in which r_U and r_S are the peak responses for the *Test solution* and *Standard solution,* respectively; C_S is the concentration, in mg per mL, of orlistat in the *Standard solution;* 900 is the volume, in mL, of *Medium;* 100 is the conversion factor to percentage; and *LC* is the Capsule label claim, in mg.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{29}H_{53}NO_5$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Mobile phase—Proceed as directed in the *Assay.*

System suitability solution—Transfer about 5 mg of USP Orlistat Related Compound D RS to a 200-mL volumetric flask, and dissolve in and dilute with *Mobile phase* to volume. Transfer 1 mL of this solution to a 50-mL volumetric flask, and dilute with *Standard solution* to volume.

Standard solution—Proceed as directed for *Standard preparation* in the *Assay.*

Test solution—Proceed as directed for *Assay preparation* in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay,* except to chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between USP Orlistat RS and USP Orlistat Related Compound D RS is not less than 1.4; and the relative standard deviation for replicate injections calculated for the orlistat peak is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$20{,}000(C/FW)(r_i/r_S)$$

in which *C* is the concentration, in mg per mL, of USP Orlistat RS in the *Standard solution; W* is the weight, in mg, of orlistat in the powder sample used to prepare the *Test solution; F* is the relative response factor (see *Table 1* for values); r_i is the peak response obtained for the individual impurity in the *Test solution;* and r_S is the peak height for orlistat in the *Standard solution.* The limits of impurities are specified in *Table 1*.

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Table 1

Compound	Relative Retention Time	Relative Response Factor (*F*)	Limit (%, w/w)
(2*S*,3*R*,5*S*)-5-[*(S)*-2-Formylamino-4-methyl-pentanoyl-oxy]-2-hexyl-3-hydroxyhexadecanoic acid	0.45	0.92	1.5
(2*S*,3*S*,5*S*)-5-[(*N*-Formyl-L-leucyl)oxy]-2-hexyl-3-hydroxyhexadecanoic acid	0.5	0.95	0.3
N-Formyl-L-leucine (3*S*,4*R*,6*S*)-tetrahydro-3-hexyl-2-oxo-6-undecyl-2*H*-pyran-4-yl ester (USP Orlistat Related Compound D)	0.9	0.97	1.0
Orlistat	1.0	—	—
(S)-3-Hexyl-5,6-dihydro-6-undecyl-2*H*-pyran-2-one	2.0	0.78	0.2
N-Formyl-*S*-leucine *(S,E)*-1-undecyl-3-decenyl ester	4.7	0.45	0.3
Individual identified impurity	—	—	0.3
Individual unidentified impurity	—	1.0	0.2
Total impurities	—	—	3.0

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and phosphoric acid (860 : 140 : 0.05). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Orlistat RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.6 mg per mL.

Assay preparation—Transfer the contents of not fewer than 10 Capsules into a suitable container, weigh, and mix. Transfer an accurately weighed portion of the powder, equivalent to about 120 mg of orlistat into a 200-mL volumetric flask. Add 140 mL of *Mobile phase,* and sonicate for about 1 minute. Shake the resulting solution mechanically for about 15 minutes, and dilute with *Mobile phase* to volume. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, discarding the first few mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 195-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the orlistat peaks. Calculate the quantity, in mg, of orlistat ($C_{29}H_{53}NO_5$) in the portion of Capsules taken by the formula:

$$100C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Orlistat RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

In-Process Revision

BRIEFING

Oxybutynin Chloride Extended-Release Tablets, page 1652 of *PF* 31(6) [Nov.–Dec. 2005]. In the test for *Drug release,* it is proposed to revise the specifications for *Apparatus 7* to include the temperature at which the test should be run.

(BPC: M. Marques) RTS—C48590

Add the following:

▲Oxybutynin Chloride Extended-Release Tablets

» Oxybutynin Chloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$).

Packaging and storage—Preserve in tight containers. Store at ~~25°, excursions permitted between 15° and 30°~~ controlled room temperature.

USP Reference standards ⟨11⟩—*USP Oxybutynin Chloride RS. USP Oxybutynin Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197⟩—

Test specimen—Add a quantity of finely powdered Tablets, equivalent to about 15 mg of oxybutynin chloride, to 5 mL of water per Tablet. Mix for 1 minute. Adjust with 0.1 N sodium hydroxide to a pH between 7 and 8. Extract the solution twice with 10 mL of ether. Combine the extracts, evaporate the ether, and dry under vacuum over silica gel for at least 30 minutes. Redissolve the dried residue in a small amount of acetone, transfer the solution to an IR salt plate, and evaporate to cast a thin film.

Standard specimen—Dissolve 15 mg of USP Oxybutynin Chloride RS in 5 mL of water. Proceed as directed for the *Test specimen,* beginning with "Adjust with".

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Change to read:

Drug release ⟨724⟩—

Medium: simulated gastric fluid without enzymes; 50 mL.

Apparatus 7: 30 cycles per minute; 2- to 3-cm amplitude, ▲at 37.0 ± 0.5°.▲*USP31*

Times: 4, 10, and 24 hours.

Determine the amount of $C_{22}H_{31}NO_3 \cdot HCl$ dissolved by employing the following method.

0.035 M Phosphate buffer, pH 2.2—Dissolve about 4.83 g of monobasic sodium phosphate in 1000 mL of water, add 2.3 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.2 ± 0.2.

Acidified water—To 1 L of water add phosphoric acid dropwise to a pH of 3.5, and mix well.

Standard stock solutions—Dissolve accurately weighed quantities of USP Oxybutynin RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain solutions having known concentrations of about 250, 300, and 350 µg per mL.

Standard solutions—Prepare a series of dilutions of the *Standard stock solutions* in acidified water having final concentrations similar to those expected in the *Test solution.*

Test solution—Use portions of the solution under test. If the solution is cloudy, centrifuge at 2000 rpm for 10 minutes, and use the supernatant.

Mobile phase—Prepare a suitable filtered and degassed mixture of *0.035 M Phosphate buffer, pH 2.2* and acetonitrile (65 : 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Use a medium range *Standard solution* of USP Oxybutynin Chloride RS.

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Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 5-cm column that contains packing L11. The flow rate is about 1.5 mL per minute. The column temperature is maintained at about 35°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the tailing factor is greater than 0.5 and less than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Construct a calibration curve by plotting the peak response versus concentration of the *Standard solutions.* A weighing factor, $1/x$, is applied to the regression line of the calibration curve to enhance the accuracy of the low standard concentrations. Determine the amount of $C_{22}H_{31}NO_3 \cdot HCl$ dissolved in each interval from a linear regression analysis of the calibration curve.

Tolerances—The percentages of the labeled amount of $C_{22}H_{31}NO_3 \cdot HCl$ dissolved at the times specified conform to *Acceptance Table 1.*

FOR TABLETS LABELED TO CONTAIN 5 MG OR 10 MG OF OXYBUTYNIN CHLORIDE:

Time (hours)	Amount dissolved
4	not more than 20%
10	between 34.5% and 59.5%
24	not less than 75%

FOR TABLETS LABELED TO CONTAIN 15 MG OF OXYBUTYNIN CHLORIDE:

Time (hours)	Amount dissolved
4	not more than 20%
10	between 34.5% and 59.5%
24	not less than 75%

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Mobile phase, Diluent, Preparation medium, Impurity stock solution, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Impurity standard solution—Dilute the *Impurity stock solution* with *Diluent* to obtain a solution having a known concentration of about 1 µg of oxybutynin related compound A per mL. [NOTE—Oxybutynin related compound A is phenylcyclohexylglycolic acid.]

Test solution—Use the *Assay preparation*.

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains packing L11. The flow rate is about 1.5 mL per minute. Chromatograph the *Impurity standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is greater than 0.75 and not more than 2.5 for the phenylcyclohexylglycolic acid peak. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for oxybutynin and about 1.6 for phenylcyclohexylglycolic acid; the resolution, *R,* between oxybutynin and phenylcyclohexylglycolic acid is not less than 1.5; and the relative standard deviation of peak area responses for six replicate injections of *System suitability solution* is not more than 3% for each compound.~~

Procedure—Separately inject equal volumes (about 50 µL) of the *Impurity standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$C(r_U / r_S)$$

in which C is the concentration, in µg per mL, of oxybutynin related compound A in the *Impurity standard solution;* and r_U and r_S are the peak responses for each impurity obtained from the *Test solution* and the *Impurity standard solution,*

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respectively. Disregard any peak less than 0.1%: not more than 1% of oxybutynin related compound A is found, and not more than 2% of total impurities is found.

Assay—

Mobile phase—Prepare a mixture of water, acetonitrile, and triethylamine (65 : 35 : 0.15). Adjust with phosphoric acid to a pH of 3.9, degas, and filter.

Diluent—Use water adjusted with phosphoric acid to a pH of 3.5.

Preparation medium—Prepare a solution of methanol and acetonitrile (1 : 1).

Impurity stock solution—Dissolve an accurately weighed quantity of USP Oxybutynin Related Compound A RS in acetonitrile to obtain a solution having a known concentration of about 0.11 mg per mL.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Oxybutynin Chloride RS in acetonitrile to obtain a solution having a known concentration of about 0.37 mg per mL.

System suitability solution—Transfer 10 mL of the *Standard stock preparation* and 1 mL of the *Impurity stock solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard preparation—Dilute the *Standard stock preparation* with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—

FOR TABLETS THAT CONTAIN 5 MG OF OXYBUTYNIN CHLORIDE—Place 10 Tablets in a 500-mL volumetric flask, add 150 mL of *Preparation medium,* and stir ~~overnight~~ for at least 4 hours or until dissolved. Dilute with *Diluent* to volume. Mix thoroughly, centrifuge, and use the clear supernatant.

FOR TABLETS THAT CONTAIN 10 MG OF OXYBUTYNIN CHLORIDE OR MORE—Place 10 Tablets in a 1000-mL volumetric flask, add 300 mL of *Preparation medium,* and stir ~~overnight~~ for at least 4 hours or until dissolved. Dilute with *Diluent* to volume. If necessary, make a further dilution with *Diluent* to obtain a solution having a final concentration equivalent to 0.1 mg per mL of oxybutynin chloride. Mix thoroughly, centrifuge, and use the clear supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains packing L11. The flow rate is about 1.5 mL per minute. ~~Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is greater than 0.75 and not more than 2.5.~~ Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for oxybutynin and about 1.6 for oxybutynin related compound A; the resolution, *R,* between oxybutynin and oxybutynin related compound A is not less than 1.5; the tailing factor is greater than 0.75 and not more than 2.5 for each peak; and the relative standard deviation of peak area responses for six replicate injections is not more than 3% for each compound.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area responses for the major peaks. Calculate the quantity, in mg, of oxybutynin chloride ($C_{22}H_{31}NO_3 \cdot HCl$) in the portion of Tablets taken by the formula:

$$CVD(r_U / r_S)$$

in which C is the concentration, in mg per mL, of oxybutynin chloride in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation; D* is the dilution factor; and r_U and r_S are the peak area responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP30*

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BRIEFING

Oxycodone Hydrochloride Extended-Release Tablets, page 1104 of *PF* 31(4) [July–Aug. 2005]. It is proposed to add two *Dissolution* tests to this monograph. The chromatographic procedure in *Dissolution Test 1* was validated using the Microbondapak C18 brand of L1 column.

(BPC: M. Marques) RTS—C44026; C43993; C48625

Add the following:

▲Oxycodone Hydrochloride Extended-Release Tablets

» Oxycodone Hydrochloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$).

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

Labeling—When more than one *Dissolution Test* is given, the labeling states the *Dissolution Test* used only if *Test 1* is not used.

USP Reference standards ⟨11⟩—*USP Oxycodone RS. USP Oxycodone Related Compound A RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Transfer a portion of powdered Tablets, equivalent to about 5 mg of oxycodone hydrochloride, to a suitable screw-capped tube, add 5 mL of chloroform, sonicate for about 30 seconds, shake for several minutes, and centrifuge. Use the clear supernatant.

Standard solution: 0.9 mg of USP Oxycodone RS per mL of chloroform.

Application volume: 20 µL.

Developing solvent solution: a mixture of acetone, toluene, ether, and ammonium hydroxide (6 : 4 : 1 : 0.3).

Procedure—Proceed as directed in the chapter. Spray with iodoplatinate TS: the R_F value, color, and size of the principal spot obtained from the *Test solution* correspond to those obtained from the *Standard solution;* and no other spot is observed.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

~~**Drug release** ⟨724⟩ — [To come.]~~

Dissolution ⟨711⟩—

TEST 1—

Medium: Simulated gastric fluid (without enzymes); 900 mL.

Apparatus 1: 100 rpm.

Times: 1, 2, 4, 6, and 8 hours, for Tablets labeled to contain 10 mg, 20 mg, or 40 mg; 1, 2, 4, and 6 hours, for Tablets labeled to contain 80 mg.

Determine the amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved by employing the following method.

Standard stock solution—For Tablets labeled to contain 10 mg, transfer about 39.8 mg of USP Oxycodone RS, accurately weighed, into a 100-mL volumetric flask, dissolve in and dilute with *Medium* to volume. For Tablets labeled to contain 20 mg, 40 mg, or 80 mg, transfer about 39.8 mg of USP Oxycodone RS, accurately weighed, into a 50-mL volumetric flask, dissolve in and dilute with *Medium* to volume.

Working standard solution—Dilute the *Standard stock solution* with *Medium* to obtain solutions containing *L*/900 mg per mL, with *L* being the oxycodone Tablet label claim, in mg.

Procedure—Determine the amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved from UV absorption at a wavelength of about 226 nm (shoulder), using filtered portions of the solution under test, suitably diluted with *Medium,* if

necessary, in comparison with the appropriate *Working standard solution*. Use *Medium* as the blank, and a 1.0-cm cell for Tablets labeled to contain 10 mg, 20 mg, or 40 mg; and a 0.5-cm cell for Tablets labeled to contain 80 mg. For Tablets labeled to contain 10 mg, 20 mg, or 40 mg, calculate the amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved by the formula (1), in which C is the concentration, in mg per mL, of the appropriate *Working standard solution;* A_U and A_S are the absorbances of the solution under test and of the appropriate *Working standard solution,* respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_1 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 1 hour; C_2 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 2 hours; C_4 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 4 hours; C_6 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 6 hours; C_8 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 8 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

For Tablets labeled to contain 80 mg, calculate the amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved by the formula (2), in which C is the concentration, in mg per mL, of the appropriate *Working standard solution;* A_U and A_S are the absorbances of the solution under test and of the appropriate *Working standard solution,* respectively; V is the initial volume, in mL, of *Medium* in the vessel; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_1 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 1 hour; C_2 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 2 hours; C_4 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 4 hours; C_6 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 6 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved at the times specified conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 10 MG, 20 MG, OR 40 MG:

Time (hours)	Amount dissolved
1	between 20% and 40%
2	between 35% and 55%
4	between 55% and 75%
6	between 70% and 90%
8	not less than 80%

FOR TABLETS LABELED TO CONTAIN 80 MG:

Time (hours)	Amount dissolved
1	between 25% and 45%
2	between 45% and 65%
4	between 65% and 85%
6	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.

Medium: Simulated gastric fluid (without enzymes); 900 mL.

$$\frac{[C\times(A_U/A_S)\times(V-V_S)+(C_1\times V_S)+(C_2\times V_S)+(C_4\times V_S)+(C_6\times V_S)+(C_8\times V_S)]\times 100}{L} \quad (1)$$

$$\frac{[C\times(A_U/A_S)\times(V-V_S)+(C_1\times V_S)+(C_2\times V_S)+(C_4\times V_S)+(C_6\times V_S)]\times 100}{L} \quad (2)$$

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Apparatus 1: 100 rpm.

Times: 1, 4, and 12 hours.

Determine the amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved by employing the following method.

0.85% Phosphoric acid—Dilute 10 mL of phosphoric acid with water to 1 L.

Standard stock solution—Prepare a solution of USP Oxycodone RS in *0.85% Phosphoric acid* containing about 0.9 mg per mL.

Working standard solution—Dilute the *Standard stock solution,* quantitatively and stepwise, with *Medium* to obtain a solution having a concentration of about 40% of the Tablet label claim. [NOTE—This solution is stable for two weeks at room tempeature.]

Test solution—Pass the solution under test through a suitable 0.45-µm filter.

Mobile phase—Weigh 23.1 g of monobasic potassium phosphate into a 4-L flask, and dissolve with 3400 mL of water. Add 4 mL of triethylamine and adjust with *0.85% Phosphoric acid* to a pH of 3.0 ± 0.1. Add 600 mL of methanol and 20 mL of *tert*-butyl methyl ether, and mix well. Filter and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 3.9-mm × 30-cm column that contains 10-µm packing L1 and that is maintained at a temperature of 60°. The flow rate is about 1.0 mL per minute. Chromatograph the *Working standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5 and not less than 0.75; the capacity factor is not less than 0.5; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Working standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak reponses. Calculate the amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved by the formula (3), in which C is the concentration, in mg per mL, of the appropriate *Working standard solution;* r_U and r_S are the peak responses of the solution under test and of the appropriate *Working standard solution,* respectively; V is the initial volume, in mL, of *Medium* in the vessel under test; V_S is the volume, in mL, withdrawn from the vessel for previous samplings; C_1 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 1 hour; C_4 is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 4 hours; C_{12} is the concentration, in mg per mL, of oxycodone in the *Medium* determined at 12 hours; 100 is the conversion factor to percentage; and L is the Tablet label claim, in mg.

Tolerances—The percentages of the labeled amount of oxycodone ($C_{18}H_{21}NO_4$) dissolved at the times specified conform to *Acceptance Table 2*.

FOR TABLETS LABELED TO CONTAIN 10 MG:

Time (hours)	Amount dissolved
1	between 29% and 49%
4	between 58% and 78%
12	not less than 85%

FOR TABLETS LABELED TO CONTAIN 20 MG:

Time (hours)	Amount dissolved
1	between 33% and 53%
4	between 63% and 83%
12	not less than 85%

$$\frac{[C \times (r_U / r_S) \times (V - V_S) + (C_1 \times V_S) + (C_4 \times V_S) + (C_{12} \times V_S)] \times 100}{L} \quad (3)$$

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FOR TABLETS LABELED TO CONTAIN 40 MG:

Time (hours)	Amount dissolved
1	between 37% and 57%
4	between 68% and 88%
12	not less than 85%

FOR TABLETS LABELED TO CONTAIN 80 MG:

Time (hours)	Amount dissolved
1	between 31% and 51%
4	between 61% and 81%
12	not less than 85%

Uniformity of dosage units ⟨905⟩**:** meet the requirements.

Related compounds—

Buffer solution—Dissolve 1.5 g of sodium heptanesulfonate in 810 mL of water. Mix with 10 mL of glacial acetic acid, adjust with 5 N sodium hydroxide solution to a pH of 3.50 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (82 : 18). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Oxycodone RS and USP Oxycodone Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 1.8 µg per mL of USP Oxycodone RS and about 1.8 µg per mL of USP Oxycodone Related Compound A RS.

Standard solution—Dissolve an accurately weighed quantity of USP Oxycodone RS in *Mobile phase,* and dilute quantitatively and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.8 µg per mL.

Sensitivity test solution—Transfer 5 mL of the *Standard solution* into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to 40 mg of oxycodone hydrochloride, to a 100-mL volumetric flask, add about 20 mL of a solvent consisting of methanol and acetonitrile (50 : 50), sonicate for about 10 minutes, and stir for 20 minutes. Dilute with *Buffer solution* to volume, and mix. Pass a portion of this solution through a suitable filter, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The column is maintained at a temperature of 50°, and the flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*: the resolution, *R*, between oxycodone related compound A and oxycodone is not less than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Sensitivity test solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$10(C/W)(1/F)(r_i/r_S)$$

in which C is the concentration, in µg per mL, of USP Oxycodone RS in the *Standard solution; W* is the weight, in mg, of oxycodone hydrochloride in the powdered Tablets taken to prepare the *Test solution; F* is the relative response factor (see

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Table 1 for values); r_i is the peak response obtained for each individual impurity in the *Test solution;* and r_S is the peak response for oxycodone in the *Standard solution*.

Assay—

Buffer solution—Dissolve 1.5 g of sodium heptanesulfonate in 740 mL of water. Mix with 10 mL of glacial acetic acid, adjust with 5 N sodium hydroxide solution to a pH of 3.50 ± 0.05, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (75 : 25). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Oxycodone RS in *Mobile phase,* and dilute quantitatively and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.036 mg per mL.

Assay stock preparation—Transfer 10 Tablets into an appropriate volumetric flask, add a volume of a mixture of methanol and acetonitrile (50 : 50) equivalent to 50% of the volumetric flask volume, sonicate for about 10 minutes, and stir for about 20 minutes. Dilute with *Buffer solution* to volume, and mix.

Assay preparation—Transfer a volume of the *Assay stock preparation,* equivalent to 4 mg of oxycodone hydrochloride, into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of the solution through a suitable filter, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 4000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the oxycodone peak. Calculate the quantity, in mg, of oxycodone hydrochloride ($C_{18}H_{21}NO_4 \cdot HCl$) in the portion of Tablets taken by the formula:

$$(351.82/315.37)CD(r_U / r_S)$$

Table 1

Name	Relative Retention Time	Relative Response Factor	Limit (w/w, %)
Oxycodone	1.00	—	—
7,8 Dihydro-14-hydroxycodeine (DHC)	about 0.6	0.64	0.5
14-Hydroxycodeine (HC) (Oxycodone related compound A)	about 1.2	0.78	0.5
Individual unknown impurity	—	—	0.5
Total impurities	—	—	2.0

in which 351.82 and 315.37 are the molecular weights of oxycodone hydrochloride and oxycodone base, respectively; *C* is the concentration, in mg per mL, of USP Oxycodone RS in the *Standard preparation; D* is the dilution factor, in mL, for the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Oxytocin Injection, *USP 29* page 1623. It is proposed to make several revisions in the monograph to facillitate the use of this product in countries throughout the world. In the Definition, the *Assay* limits are changed to not less than 80.0 percent and not more than 120.0 percent. The *Packaging and storage* conditions are changed to allow for plastic containers and the explicit temperature requirements for storage are removed from the section.

(BB PP: L. Callahan) RTS—C46027

Change to read:

» Oxytocin Injection is a sterile solution of Oxytocin in a suitable diluent. Each mL of Oxytocin Injection possesses an oxytocic activity of not less than ~~90.0~~

▲80.0▲*USP31*
percent and not more than ~~110.0~~

▲120.0▲*USP31*
percent of that stated on the label in USP Oxytocin Units.

Change to read:

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass

▲or in suitable plastic containers.▲*USP31*
~~Store between 2° and 8°.~~

▲▲*USP31*

BRIEFING

Phenoxybenzamine Hydrochloride Capsules, *USP 29* page 1704. The current *USP* test methods for Phenoxybenzamine Hydrochloride Capsules are nonstability-indicating and do not include a test for related compounds suitable for quantitating the impurities (degradants) in the finished products. It is therefore proposed to incorporate validated test methods in the tests for *Uniformity of dosage units* and *Related compounds* and in the *Assay,* as approved by FDA. These tests employ an HPLC method using the Waters YMC brand of column that contains 5-µm packing L7. The typical retention time for phenoxybenzamine hydrochloride is about 8 minutes.

(MD-CV: S. Ramakrishna) RTS—C42617

Change to read:

Uniformity of dosage units ⟨905⟩: meet the requirements.

▲PROCEDURE FOR CONTENT UNIFORMITY—

Buffer solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Proceed as directed for *Standard preparation* in the *Assay.*

Test solution—Carefully open 10 Capsules and transfer each immediately into separate 50-mL volumetric flasks, including the capsule shells. Dissolve the capsule fill powder in approximately 30 mL of acetonitrile, and sonicate for 15 minutes with occasional stirring [NOTE—The capsule shell does not dissolve.]. Cool, dilute with acetonitrile to volume, mix, and pass through a 0.45-µm membrane filter, discarding the first 1.5 mL of the filtrate. Use the subsequent filtrate as the *Test solution*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of phenoxybenzamine hydrochloride in the Capsules taken by the formula:

$$(TC/D)(r_U/r_S)$$

in which *T* is the labeled quantity, in mg, of phenoxybenzamine hydrochloride in the Capsules taken; *C* is the concentration, in mg per mL, of USP Phenoxybenzamine

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Hydrochloride RS in the *Standard solution; D* is the concentration, in mg per mL, of phenoxybenzamine hydrochloride in the *Test solution,* based on the labeled quantity per Capsule and the extent of dilution; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.▲*USP31*

Add the following:

▲Related compounds—

Buffer solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Proceed as directed for *Standard preparation* in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure—Proceed as directed in the *Assay.* Calculate the percentage of each individual impurity by the formula:

$$(100 / F)(C_S / C_T)(r_U / r_S)$$

in which F is the relative response factor, which is 1.1 for the known degradant phenoxybenzamine tertiary amine and 1 for all other individual impurities; C_S is the concentration, in µg per mL, of USP Phenoxybenzamine Hydrochloride RS in the *Standard solution;* C_T is the concentration, in mg per mL, of phenoxybenzamine in the *Test solution;* r_U is the peak response for the individual impurity obtained from the *Test solution;* and r_S is the peak response for phenoxybenzamine obtained from the *Standard solution*. Not more than 0.5% of phenoxybenzamine tertiary amine is found; not more than 0.1% of any other specified or unspecified individual impurity (degradant) is found; and not more than 0.5% total of all the specified and unspecified impurities is found.▲*USP31*

Change to read:

~~**Assay**— Remove, as completely as possible, the contents of not fewer than 20 Capsules, and weigh. Transfer an accurately weighed portion of the mixed powder, equivalent to about 50 mg of phenoxybenzamine hydrochloride, to a 50-mL volumetric flask, add about 25 mL of a 1 in 1000 solution of hydrochloric acid in alcohol, and shake. Add the alcoholic hydrochloric acid to volume, mix, and filter, discarding the first 10 mL of the filtrate. Transfer 15.0 mL of the subsequent filtrate to a 100-mL volumetric flask, dilute with the alcoholic hydrochloric acid to volume, and mix. Concomitantly determine the absorbances of this solution and of a Standard solution of USP Phenoxybenzamine Hydrochloride RS in the same medium having a known concentration of about 150 µg per mL in 1-cm cells at the wavelength of maximum absorbance at about 275 nm, with a suitable spectrophotometer, using a 1 in 1000 solution of hydrochloric acid in alcohol as the blank. Calculate the quantity, in mg, of $C_{18}H_{22}ClNO \cdot HCl$ in the portion of Capsules taken by the formula:~~

~~$$0.333C(A_U / A_S),$$~~

~~in which C is the concentration, in µg per mL, of USP Phenoxybenzamine Hydrochloride RS in the Standard solution, and A_U and A_S are the absorbances of the solution from the Capsules and the Standard solution, respectively.~~

▲*Buffer solution*—Dissolve 1.1 g of anhydrous monobasic sodium phosphate in 500 mL of water. Adjust with concentrated phosphoric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (55 : 45).

Standard preparation—Prepare a solution of USP Phenoxybenzamine Hydrochloride RS in acetonitrile having a known concentration of 0.02 mg per mL. Sonicate for 5 minutes to mix well.

System suitability solution—Prepare a solution of 0.5 mL of 0.1 N sodium hydroxide and 10 mL of the *Standard preparation* taken in a vial. [NOTE—Basic solutions of phenoxybenzamine hydrochloride will produce the known degradant tertiary amine phenoxybenzamine and an unknown related substance. Severe degradation of the drug substance will be observed if the solution is allowed to stand for more than 1 hour.]

Assay preparation—Remove, as completely as possible, the contents of not fewer than 20 Capsules, and weigh. Transfer an accurately weighed portion of the mixed powder, equivalent to about 10 mg of phenoxybenzamine hydrochloride, to a 50-mL volumetric flask. Add about 40 mL of acetonitrile, and sonicate for 15 minutes with occasional swirling. Cool, and dilute with acetonitrile to volume. Allow the sample to stand undisturbed for 30 minutes such that the undissolved material settles to the bottom. Transfer the top clear solution into HPLC vials, and use as the *Assay preparation*.

Chromatographic system—The liquid chromatograph is equipped with a 268-nm detector and a 4.6-mm × 150-cm column that contains packing L7. The flow rate is about 1.0

mL per minute. The column is maintained at ambient temperatures. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution *R,* between the phenoxybenzamine hydrochloride and the nearest peak is not less than 4. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for an average of five injections determined from the phenoxybenzamine hydrochloride peak is not more than 2%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of phenoxybenzamine hydrochloride ($C_{18}H_{22}ClNO \cdot HCl$) in the portion of Capsules taken by the formula:

$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Phenoxybenzamine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Racepinephrine Hydrochloride, *USP 29* page 1889. It is proposed to revise the current tests for *Identification,* which consist of two similar UV tests, to provide the correct tests for UV absorption and chloride, as published in *USP 22*.

(MD-PS: D. Bempong) RTS—C46958

Change to read:

Identification—

A: ~~The UV absorption spectrum of a 1 in 20,000 solution exhibits maxima and minima at the same wavelengths as that of a similar solution of USP Epinephrine Bitartrate RS, concomitantly measured.~~

▲*Ultraviolet Absorption* ⟨197U⟩—

Solution: 50 µg per mL. [NOTE—Use USP Epinephrine Bitartrate RS in the preparation of the Standard solution.]

Medium: water.▲*USP31*

B: ~~*Ultraviolet Absorption* ⟨197U⟩—~~
~~*Solution:* 50 µg per mL.~~
~~*Medium:* water.~~

▲A solution (1 in 100) meets the requirements of the tests for *Chloride* ⟨191⟩.▲*USP31*

BRIEFING

Ranitidine Hydrochloride, *USP 29* page 1891 and page 3742 of the *Second Supplement*. It is proposed to revise the *Table* in the test for *Chromatographic purity* to add the chemical names of the impurities. It is also proposed to clarify numeric coefficients in the formulas in the test for *Chromatographic purity* and in the *Assay.*

(MD-GRE: E. Gonikberg) RTS—C48771

Change to read:

Chromatographic purity—

■*Diluent, Mobile phase, Resolution solution,* and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Prepare as directed for *Standard preparation* in the *Assay.*

Test solution—Prepare as directed for *Assay preparation* in the *Assay.*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and identify the ranitidine peak and the peaks due to impurities and degradation products listed in the table below. Measure the responses for the major peaks, and calculate the percentage of each impurity in the portion of Ranitidine Hydrochloride taken by the formula:

~~$20{,}000C/W(r_i/r_S)$~~

▲$100CV/W(r_i / r_S)$▲*USP31*

in which C is the concentration, in mg per mL, of ranitidine hydrochloride in the *Standard solution;*

▲V is the volume, in mL, of the *Test solution;*▲*USP31*
W is the weight, in mg, of Ranitidine Hydrochloride taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the ranitidine peak response obtained from the *Standard solution:* not more than 0.3% of ranitidine *bis-*

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compound is found, not more than 0.1% of any other single impurity is found, and not more than 0.5% of total impurities is found.■2S *(USP29)*

Name	Relative Retention Time
Ranitidine simple nitroacetamide	0.14
▲[1]▲*USP31* Ranitidine oxime	0.21
▲[2]▲*USP31* Ranitidine amino alcohol ~~hemifumarate~~	0.45
▲[3]▲*USP31* Ranitidine diamine ~~hemifumarate~~[4]	0.57
▲[4]▲*USP31* Ranitidine *S*-oxide[5]	0.64
▲[5]▲*USP31* Ranitidine *N*-oxide	0.72
▲[6]▲*USP31* Ranitidine complex nitroacetamide	0.84
▲[7]▲*USP31* Ranitidine formaldehyde adduct	1.36
▲[8]▲*USP31* Ranitidine *bis*-compound[9]	1.75
▲[9]▲*USP31*	

[1] ~~Ranitidine related compound A~~
▲*N*-methyl-2-nitroacetamide▲*USP31*

[2] ~~Ranitidine related compound C~~
▲3-(methylamino)-5,6-dihydro-2*H*-1,4-thiazin-2-one oxime▲*USP31*

[3] ~~Ranitidine related compound B~~
▲{5-[(dimethylamino)methyl]furan-2-yl}methanol▲*USP31*

[4] ▲5-{[(2-aminoethyl)thio]methyl}-*N,N*-dimethyl-2-furanmethanamine (Ranitidine related compound A)▲*USP31*

[5] ▲*N*-{2-[({5-[(dimethylamino)methyl]-2-furanyl}methyl)sulfinyl]ethyl}-*N′*-methyl-2-nitro-1,1-ethenediamine (Ranitidine related compound C)▲*USP31*

[6] ▲*N,N*-dimethyl(5-{[(2-{[1-(methylamino)-2-nitroethenyl]amino}ethyl)sulphanyl]methyl}furan-2-yl)methanamine *N*-oxide▲*USP31*

[7] ▲*N*-{2-[({5-[(dimethylamino)methyl]furan-2-yl}methyl)sulphanyl]ethyl}-2-nitroacetamide▲*USP31*

[8] ▲2,2′-methylenebis(*N*-{2-[({5-[(dimethylamino)methyl]furan-2-yl}methyl)sulphanyl]ethyl}-*N′*-methyl-2-nitroethene-1,1-diamine)▲*USP31*

[9] ▲*N,N′*-bis{2-[({5-[(dimethylamino)methyl]-2-furanyl}-methyl)thio]ethyl}-2-nitro-1,1-ethenediamine (Ranitidine related compound B)▲*USP31*

Change to read:

Assay—

■*Phosphate buffer*—Place approximately 1900 mL of water in a 2.0-L volumetric flask, accurately add 6.8 mL of phosphoric acid, and mix. Accurately add 8.6 mL of 50% sodium hydroxide solution, and dilute with water to volume. If necessary, adjust with 50% sodium hydroxide solution or phosphoric acid to a pH of 7.1, and filter.

Solution A—Prepare a mixture of *Phosphate buffer* and acetonitrile (98 : 2).

Solution B—Prepare a mixture of *Phosphate buffer* and acetonitrile (78 : 22).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Use *Solution A*.

Standard preparation—Dissolve an accurately weighed quantity of USP Ranitidine Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 0.125 mg of ranitidine hydrochloride per mL.

Resolution solution—Transfer about 1.3 mg of USP Ranitidine Resolution Mixture RS to a 10-mL volumetric flask, and dissolve in and dilute with *Diluent* to volume. [NOTE—USP Ranitidine Resolution Mixture RS contains ranitidine hydrochloride and four related impurities: ranitidine amino alcohol hemifumarate, ranitidine diamine hemifumarate, ranitidine *N*-oxide, and ranitidine complex nitroacetamide.]

Assay preparation—Transfer about 25 mg of Ranitidine Hydrochloride, accurately weighed, to a 200-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 10-cm column containing 3.5-µm packing L1 that is stable from pH 1 to 12. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	100→0	0→100	linear gradient
10–15	0	100	isocratic
15–16	0→100	100→0	linear gradient
16–20	100	0	re-equilibration

Chromatograph the *Resolution solution,* and identify the peaks using the table of impurities and degradation products (found above): the resolution, *R,* between the peaks for ranitidine *N*-oxide and ranitidine complex nitroacetamide is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the ~~quantity, in mg,~~

▲percentage▲*USP31* of $C_{13}H_{22}N_4O_3S \cdot HCl$ in the portion of Ranitidine Hydrochloride taken by the formula:

~~$200C(r_U/r_S)$~~

$$\blacktriangle 100(C_S/C_U)(r_U/r_S)\blacktriangle_{USP31}$$

in which ~~*C* is the concentration, in mg per mL, of USP Ranitidine Hydrochloride RS in the *Standard preparation;*~~

▲C_S and C_U are the concentrations, in mg per mL, of ranitidine hydrochloride in the *Standard preparation* and the *Assay preparation,* respectively;▲*USP31* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S *(USP29)*

BRIEFING

Succinylcholine Chloride, *USP 29* page 2011 and page 3746 of the *Second Supplement.* On the basis of comments received, it is proposed to clarify that in *Test 2 (Limit of choline)* in the *Chromatographic purity* section, water is used as the regenerant in the chemical suppression device.

(MD-PS: D. Bempong) RTS—C46974

Change to read:

Chromatographic purity—

TEST 1—

Buffer solution—Prepare a solution in water containing 3.85 g per L of 1-pentanesulfonic acid, 2.9 g per L of sodium chloride, and 1% (v/v) of 1 N sulfuric acid.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (95 : 5).

System suitability solution—Dissolve accurately weighed quantities of citric acid and succinic acid in *Mobile phase* to obtain a solution containing about 0.5 mg of each per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Succinylmonocholine Chloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Test solution—Transfer about 100 mg of Succinylcholine Chloride, accurately weighed, to a 10-mL volumetric flask, and dissolve in and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Samples are maintained at a temperature of about 4° during the analysis. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ■the resolution, *R,* between citric acid and succinic acid is not less than 2.9. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 3.0%.■2S *(USP29)*

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Begin integration after the edetate disodium peak, if present (retention time is about 3.5 minutes). ■The relative retention times are about 0.22 for succinic acid, 0.32 for the doublet of peaks quantitated as a single component, 0.49 for succinylmonocholine chloride, and 1.0 for succinylcholine chloride.■2S *(USP29)* Calculate the percentage of each impurity in the portion of Succinylcholine Chloride taken by the formula:

$$10C(r_i/r_S)F$$

in which C is the concentration, in mg per mL, of USP Succinylmonocholine Chloride RS in the *Standard solution;* r_i is the peak area for each impurity obtained from the *Test solution;* r_S is the succinylmonocholine chloride peak area obtained from the *Standard solution;* and F is the response factor (0.63 for succinic acid): not more than 0.1% of succinic acid is found; not more than 0.4% of the doublet of peaks quantitated as a single component is found; not more than 0.4% of succinylmonocholine chloride is found; and not more than 0.2% of any other individual impurity is found.

TEST 2 (LIMIT OF CHOLINE)—

Solution A—Prepare a solution in water containing 5% (v/v) of acetonitrile and 5% (w/v) of 0.1 M 1-hexanesulfonic acid.

Solution B—Prepare a solution of acetonitrile and water (1 : 1).

Mobile phase—Use variable amounts of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve an accurately weighed quantity of USP Choline Chloride RS and sodium chloride in water; and dilute quantitatively, and stepwise if necessary, with water to obtain a solution containing 0.05 mg per mL and ▲0.01▲*USP29* mg per mL, respectively.

Standard stock solution—Dissolve an accurately weighed quantity of USP Choline Chloride RS in water; and dilute quantitatively, and stepwise if necessary, with water to obtain a solution containing 0.5 mg per mL.

Standard solution—Dilute 1 mL of the *Standard stock solution* with water to 50 mL.

Test solution—Transfer about 50 mg of Succinylcholine Chloride, accurately weighed, to a 25-mL flask, and dissolve in and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The ion chromatograph is equipped with a suitable device for chemical suppression, a conductivity detector at 30 µS, and a 4.6-mm × 25-cm column that contains 5-µm packing L1. ~~The eluant flow is about 1 mL per minute, and uses a suitable regenerant flow rate at 50 mA output.~~

▲The eluent flow rate is about 1 mL per minute, and uses deionized water at a flow rate of 5–10 mL per minute as the regenerant for the chemical suppressor and a suppressor current setting of 50 mA.▲*USP31*

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–15	100	0	isocratic
15–16	100→0	0→100	linear gradient
16–25	0	100	isocratic
25–27	0→100	100→0	linear gradient
27–40	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between sodium and choline is not less than 2.0; and the relative standard deviation for replicate injections is not more than 3.0%.

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Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of choline in the portion of Succinylcholine Chloride taken by the formula:

$$37.5C(r_C / r_S)$$

in which C is the concentration, in mg per mL, of USP Choline Chloride RS in the *Standard solution;* and r_C and r_S are the choline peak areas obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.3% of choline is found; ▲and ▲*USP29* not more than 1.5% of total impurities is found, the results for *Test 1* and *Test 2* being added.

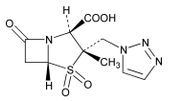
BRIEFING

Tazobactam, page 1116 of *PF* 31(4) [July–Aug. 2005]. On the basis of comments received, it is proposed to (1) add the specifications for the test for *Bacterial endotoxins,* (2) correct the limits in the test for *Specific rotation,* (3) include a limit for unspecified impurities in the test for *Related compounds,* and (4) clarify the sample treatment in the test for *Related compounds* and in the *Assay.*

(MD-ANT: B. Gilbert) RTS—C44171

Add the following:

▲Tazobactam



$C_{10}H_{12}N_4O_5S$ 300.29

4-Thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 3-methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-, 4,4-dioxide, [2*S*-(2α,3β,5α)]-.

(2*S*,3*S*,5*R*)-3-Methyl-7-oxo-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide [*89786-04-9*].

» Tazobactam contains not less than 98.0 percent and not more than 102.0 percent of $C_{10}H_{12}N_4O_5S$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Tazobactam RS. USP Tazobactam Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩, on an undried specimen.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩**—**The level of Bacterial Endotoxins are such that the requirements under the relevant dosage form monograph(s) in which Tazobactam is used can be met.

Specific rotation ⟨781S⟩**:** ~~between +60° and +167° (t = 20°).~~ between 160° and 167° (t = 20°).

Test solution: 10 mg per mL, in dimethylformamide.

Microbial limits ⟨61⟩**—**The total aerobic microbial count does not exceed 1000 cfu per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

pH ⟨791⟩**:** between 1.8 and 2.8, in a solution containing 2.5 mg per mL.

Water, *Method I* ⟨921⟩**:** not more than 0.6%.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩**:** 0.002%.

Related compounds—

Mobile phase, L-Phenylalanine solution, System suitability solution, and *Chromatographic system*—Prepare as directed in the *Assay.*

Blank—Use water.

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

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Procedure—Cool and maintain the *Standard solution,* the *System suitability solution,* the *Blank,* and the *Test solution* at 3° until injection. [NOTE—If an autosampler is used, replace the plastic tubing connected to the injection needle with a stainless steel assembly, and maintain at 3°. If a chilled autosampler is not used, then these solutions should be injected immediately after preparation.] Separately inject equal volumes (about 20 µL) of the *Standard solution*, the *System suitability solution,* the *Blank,* and the *Test solution* into the chromatograph; record the chromatograms; and measure the area responses for the peaks. Calculate the percentage of each related substance in the portion of Tazobactam taken by the formula:

$$100(r_i / r_s)$$

in which r_i is the response for each related compound in the chromatogram obtained from the *Test solution,* and r_s is the sum of the peak responses of all the peaks in the chromatogram obtained from the *Test solution:* not more than 1.0% of tazobactam related compound A is found; not more than 0.1% of any other individual impurity is found; and the sum of all impurities found, other than tazobactam related compound A, is not greater than 0.3%. [NOTE—Ignore any peaks in the chromatogram of the *Test solution* that correspond to any peaks in the chromatogram of the *Blank*.]

Organic volatile impurities, *Method IV* ⟨467⟩**:** meets the requirements.

Assay—

Mobile phase—Dissolve 1.32 g of dibasic ammonium phosphate in 750 mL of water. Adjust with 5% (v/v) phosphoric acid to a pH of 2.5, dilute with water to 1000 mL, and mix. Add 30 mL of acetonitrile, mix, and pass through a filter having a 0.2-µm porosity. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve accurately weighed quantities of USP Tazobactam RS and USP Tazobactam Related Compound A RS in water to obtain a solution having known concentrations of about 0.5 mg per mL and 0.08 mg per mL, respectively.

L-Phenylalanine solution—Prepare an aqueous solution of L-phenylalanine containing 0.8 mg per mL.

System suitability solution—Pipet 1.0 mL of *L-Phenylalanine solution* and 5.0 mL of the *Standard preparation* into a 50-mL volumetric flask. Dilute with water to volume, and mix. [NOTE—Maintain this solution at 3° until injection. Prepare fresh daily.]

Assay preparation—Transfer about 25 mg of Tazobactam, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph 20 µL of the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between tazobactam and L-phenylalanine is not less than 6.0; the tailing factor is not more than 1.8; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Cool and maintain the *Standard preparation*, the *System suitability solution*, and the *Assay preparation* at 3° until injection. [NOTE—If an autosampler is used, replace the plastic tubing connected to the injection needle with a stainless steel assembly, and maintain at 3°. If a chilled autosampler is not used, then these solutions should be injected immediately after preparation.] Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{10}H_{12}N_4O_5S$ in the portion of Tazobactam taken by the formula:

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$$50C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Tazobactam RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Tizanidine Hydrochloride, *USP 29* page 2157 and page 746 of the *Third Interim Revision Announcement* pertaining to *USP 29–NF 24.* The following changes are proposed

1. Eliminate the redundant *Content of chloride* test because the purity range required for this test is wider than the criteria in the HPLC assay.
2. Include an identification test for chloride counter ion per *Indentification Tests–General* ⟨191⟩.
3. Revise the relative response factors under the test for *Related compounds* to implement a uniform and consistent approach, as proposed in the Stimuli article, *The Use of Relative Response Factors to Determine Impurities,* published on page 960 of *PF* 31(3) [May–June 2005]. The calculations are also revised in both the *Assay* and in the *Related compounds* tests.
4. Revise the system suitability criteria in the *Assay* on the basis of the data obtained during the collaborative laboratory work performed for Reference Standard Development.

(MD-PP: R. Ravichandran) RTS—C48935

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

▲**C:** A solution of 10 mg per mL in water meets the requirements of the test for *Chloride* ⟨191⟩.▲*USP31*

Change to read:

Related compounds—

Phosphoric acid solution—Transfer 6.0 mL of phosphoric acid to a 50-mL volumetric flask, and dilute with water to volume.

Buffer solution—Dissolve about 3.5 g of sodium 1-pentanesulfonate in 1000 mL of water, and adjust with *Phosphoric acid solution* or 1 N sodium hydroxide to a pH of 3.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (80 : 20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Tizanidine related compound A solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound B solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Tizanidine related compound C solution—Dissolve an accurately weighed quantity of USP Tizanidine Related Compound C RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg per mL.

Resolution solution—Transfer about 23 mg of USP Tizanidine Hydrochloride RS to a 100-mL volumetric flask, add 20 mL of *Mobile phase* and 10 mL each of *Tizanidine related compound A solution, Tizanidine related compound B solution,* and *Tizanidine related compound C solution.* Sonicate to dissolve the USP Tizanidine Hydrochloride RS, and dilute with *Mobile phase* to volume.

Standard solution—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.046 mg per mL.

Test solution—Transfer about 57 mg of Tizanidine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 50°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are given in *Table 1;* the resolution, *R,* between tizanidine and tizanidine related compound C is not less than 4.0; and the resolution, *R,* between tizanidine and tizanidine related compound B is not less than 4.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 5000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major analyte peaks, disregarding the peaks due to the solvent. Calculate the percentage of each impurity in the portion of Tizanidine Hydrochloride taken by the formula:

~~$(253.71/290.17)5000(C/W)F(r_i/r_s)$~~

~~in which 253.71 and 290.17 are the molecular weights of tizanidine and tizanidine hydrochloride, respectively; *C* is the concentration, in mg per mL, of USP Tizanidine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of sample taken to prepare the *Test solution; F* is the relative response factor and is given in *Table 1; r_i* is the peak area for each impurity obtained from the *Test solution;*~~

▲$(253.71/290.17)100(C_S / C_T)(1/F)(r_I / r_S)$

in which 253.71 and 290.17 are the molecular weights of tizanidine and tizanidine hydrochloride, respectively; C_S and C_T are the concentration, in mg per mL, of tizanidine hydrochloride in the *Standard solution* and the *Test solution;*

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F is the relative response factor for each impurity relative to tizanidine and is given in *Table 1;* r_I is the peak area for each impurity obtained from the *Test solution;* ▲*USP31*
and r_S is the peak area of tizanidine obtained from the *Standard solution.* The limits for the impurities are specified in *Table 1.*

Table 1

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
Tizanidine related compound C	about 0.8	1.0	0.1
Tizanidine	1.0	—	—
Tizanidine related compound B	about 1.4	~~0.9~~ ▲1.1 ▲*USP31*	0.1
Tizanidine related compound A	about 10.2	~~0.9~~ ▲1.1 ▲*USP31*	0.1
Individual unknown	—	1.0	0.1
Total	—	—	0.3

Delete the following:

▲~~**Organic volatile impurities** ⟨467⟩**:** meets the requirements.~~ ▲*USP31*

Delete the following:

▲~~**Content of chloride**—Dissolve about 500 mg, accurately weighed, in 50 mL of water. Titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of chloride. Not less than 11.9% and not more than 12.5%, calculated on the dried basis, is found.~~ ▲*USP31*

Delete the following:

▲~~**Residual solvents** ⟨467⟩**:** meets the requirements.~~
~~(Official January 1, 2007)~~ ▲*USP31*

Change to read:

Assay—

Buffer solution—Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water, and adjust with 5.3 N potassium hydroxide to a pH of 7.5 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile •(80 : 20).•₃ Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve suitable quantities of USP Tizanidine Hydrochloride RS and USP Tizanidine Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* ~~to obtain a solution containing about 0.00012 mg per mL and 0.046 mg per mL, respectively.~~

▲to obtain a solution containing about 46 µg per mL and 0.12 µg per mL, respectively.▲*USP31*

Standard preparation—Dissolve an accurately weighed quantity of USP Tizanidine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.046 mg per mL.

Assay preparation—Transfer about 23 mg of Tizanidine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 35°. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for tizanidine related compound C and 1.0 for tizanidine; the resolution, R, between tizanidine and tizanidine related compound C is not less than ~~13.0; and the tailing factor for the tizanidine peak is not more than 1.6~~

▲9; and the tailing factor for the tizanidine peak is not more than 2.0.▲*USP31*

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. ~~Calculate the quantity, in mg, of $C_9H_8ClN_5S \cdot HCl$ in the portion of Tizanidine Hydrochloride taken by the formula:~~

~~$500C(r_U/r_S)$~~

~~in which C is the concentration, in mg per mL, of USP Tizanidine Hydrochloride RS in the *Standard preparation;*~~

▲Calculate the percentage of $C_9H_8ClN_5S \cdot HCl$ in the portion of Tizanidine Hydrochloride taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S and C_U are the concentrations of tizanidine hydrochloride, in mg per mL, in the *Standard preparation* and the *Assay preparation,* respectively; ▲*USP31*
and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

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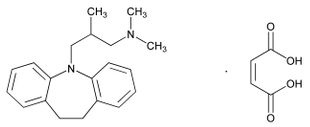
BRIEFING

Trimipramine Maleate. Because there is no existing *USP* monograph for this active drug substance, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed using the Phenomenex Luna C8 brand of L7 column. The typical retention time for trimipramine is about 15.5 minutes.

(MD-PP: R. Ravichandran) RTS—C44141

Add the following:

▲Trimipramine Maleate



$C_{20}H_{26}N_2 \cdot C_4H_4O_4$ 410.51

5*H*-Dibenz[*b,f*]azepine-5-propanamine, 10,11-dihydro-*N,N,β*-trimethyl-, *(Z)*-2-butenedioate (1 : 1).

5-[3-(Dimethylamino)-2-methylpropyl]-10,11-dihydro-5*H*-dibenz[*b,f*]azepine maleate (1 : 1) [*521-78-8*].

» Trimipramine Maleate contains not less than 98.0 percent and not more than 102.0 percent of $C_{20}H_{26}N_2 \cdot C_4H_4O_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers, and store at room temperature.

USP Reference standards ⟨11⟩—*USP Iminodibenzyl RS. USP Imipramine Hydrochloride RS. USP Trimipramine Maleate RS. USP Trimipramine Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Loss on drying ⟨731⟩**—**Dry it at 105° to constant weight: it loses not more than 0.50% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.10%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Related compounds—

Mobile phase and *Standard stock preparation*—Prepare as directed in the *Assay.*

Impurity stock solution—Dissolve accurately weighed quantities of USP Imipramine Hydrochloride RS and USP Iminodibenzyl RS in a suitable volume of *Mobile phase* to obtain a solution having a known concentration of about 50 µg per mL of iminodibenzyl and 56.5 µg per mL of imipramine hydrochloride.

Trimipramine related compound A solution—Dissolve a suitable quantity of USP Trimipramine Related Compound A RS in *Mobile phase* to obtain a solution having a concentration of about 50 µg per mL.

Trimipramine stock solution—Quantitatively dilute the *Standard stock preparation* with *Mobile phase* to obtain a solution having a known concentration of about 70 µg per mL of trimipramine maleate.

System suitability solution—Transfer about 7 mg of USP Trimipramine Maleate RS to a 10-mL volumetric flask, dissolve in a small amount of *Mobile phase,* add 0.1 mL each of the *Impurity stock solution* and the *Trimipramine related compound A solution,* and dilute with *Mobile phase* to volume.

Standard solution—Transfer 5.0 mL each of the *Impurity stock solution* and the *Trimipramine stock solution* with *Mobile phase* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume. Dilute the resulting solution quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a final solution having a known concentration of about 0.5 µg per mL each of iminodibenzyl, imipramine (free

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base), and trimipramine (free base). [NOTE—This solution is stable for one day at room temperature. The concentration of imipramine (free base), in µg per mL, can be calculated using the molecular weights of imipramine (282.41) and imipramine hydrochloride (318.88). The concentration of trimipramine (free base), in µg per mL, can be calculated using the molecular weights of trimipramine (294.43) and trimipramine maleate (410.51).]

Test solution—Use the *Assay stock preparation*.

Chromatographic system—Prepare as directed in the *Assay*. Chromatograph about 10 µL of the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between imipramine and trimipramine related compound A is not less than 1.5. [NOTE—For identification purposes, the approximate relative retention times of the specified impurities are given in *Table 1*.]

Procedure—Separately inject about 10 µL of the *Standard solution* and the *Test solution* into the chromatograph, and record the chromatogram for three times the retention time for trimipramine. Identify the components based on their relative retention times in *Table 1*. Measure the peak areas of all the peaks in the *Test solution*. Calculate the percentage of imipramine and iminodibenzyl in the portion of Trimipramine Maleate taken by the formula:

$$100(C_S / C_T)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of any given impurity (free base) in the *Standard solution;* C_T is the concentration of Trimipramine Maleate, in mg per mL, in the *Test solution;* r_U is the individual peak response of the given impurity obtained from the *Test solution;* and r_S is the corresponding response for the same impurity obtained from the *Standard solution*. Calculate the percentage of trimipramine related compound A in the portion of Trimipramine Maleate taken by the formula:

$$100(1/3.6)(C_S / C_T)(r_U / r_S)$$

in which 3.6 is the relative response factor for trimipramine related compound A; C_S is the concentration, in mg per mL, of trimipramine (free base) in the *Standard solution;* C_T is the concentration of Trimipramine Maleate, in mg per mL, in the *Test solution;* r_U is the peak response for trimipramine related compound A obtained from the *Test solution;* and r_S is the peak response of trimipramine obtained from the *Standard solution*. Calculate the percentage of each unknown impurity in the portion of Trimipramine Maleate taken by the formula:

$$100(C_S / C_T)(r_i / r_S)$$

in which C_S is the concentration, in mg per mL, of trimipramine (free base) in the *Standard solution;* C_T is the concentration of Trimipramine Maleate, in mg per mL, in the *Test solution;* r_i is the individual peak response of the given impurity obtained from the *Test solution;* and r_S is the response for trimipramine obtained from the *Standard solution:* the limits of the related compounds are given in *Table 1*. [NOTE—Disregard any peak due to the maleate counterion eluting at a relative retention time of about 0.13.]

Table 1

Peak Identification	Approximate Relative Retention Time (RRT)	Limit % (w/w)
Iminodibenzyl	0.49	NMT 0.20
Imipramine	0.72	NMT 0.20
Trimipramine related compound A	0.80	NMT 0.10
Any other individual impurity	—	NMT 0.10
Total impurites	—	NMT 0.50

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Assay—

Buffer solution—Dissolve about 1.4 g of anhydrous dibasic sodium phosphate in 1 L of water. Adjust with phosphoric acid to a pH of 7.7.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, methanol, and *Buffer solution* (18 : 12 : 10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Trimipramine Maleate RS in a suitable volume of *Mobile phase* to obtain a solution having a known concentration of about 0.7 mg per mL.

Standard preparation—Transfer 3 mL of the *Standard stock preparation* to a 10-mL volumetric flask, and dilute with *Mobile phase* to volume to obtain a final solution having a known concentration of about 0.21 mg per mL of trimipramine maleate.

Assay stock preparation—Dissolve an accurately weighed quantity of Trimipramine Maleate in a suitable volume of *Mobile phase* to obtain a solution having a known concentration of about 0.7 mg per mL.

Assay preparation—Transfer 3 mL of the *Assay stock preparation* to a 10-mL volumetric flask, and dilute with *Mobile phase* to volume to obtain a final solution having a known concentration of about 0.21 mg per mL of trimipramine maleate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 30°. Chromatograph about 20 µL of the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor for the trimipramine maleate peak is not more than 2.0; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms for up to 1.5 times the retention time of trimipramine maleate, and measure the responses for the trimipramine maleate peak. Calculate the percentage of $C_{20}H_{26}N_2 \cdot C_4H_4O_4$, in the portion of Trimipramine Maleate taken by the formula:

$$100(C_S / C_U)(r_U / r_S)$$

in which C_S is the concentration, in mg per mL, of USP Trimipramine Maleate RS in the *Standard preparation;* C_U is the concentration, in mg per mL, of Trimipramine Maleate in the *Assay preparation;* and r_U and r_S are the trimipramine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP31*

BRIEFING

Tyrosine, *USP 29* page 2228. Comments were received indicating that dissolution of the sample cannot be achieved under current conditions described in the test for *Sulfate*. On the basis of supporting data received, it is proposed to change the *Note* to indicate that diluted hydrochloric acid may be required to dissolve the test specimen.

(DSN: L. Evans) RTS—C36717

Change to read:

Sulfate ⟨221⟩—A solution containing 1.2 g shows no more sulfate than corresponds to 0.50 mL of 0.020 N sulfuric acid (0.04%). [NOTE—If necessary, dissolve the test specimen by ~~heating to near boiling and adding 1 mL of 3 *N*~~

▲adding 6 mL of diluted▲*USP31*
hydrochloric acid.]

In-Process Revision

BRIEFING

Verapamil Hydrochloride Injection, *USP 29* page 2245 and page 154 of *PF* 32(1) [Jan.–Feb. 2006]; **Verapamil Hydrochloride Tablets,** *USP 29* page 2246 and page 158 of *PF* 32(1) [Jan.–Feb. 2006]. The current official test for *Related compounds* refers to the Verapamil Hydrochloride drug substance monograph for the preparation of the *Aqueous solvent mixture, Mobile phase, System suitability solution,* and *Chromatographic system*. This revision incorporates the following changes because the drug substance monograph has been proposed for revision (see page 389 of *PF* 32(2) [Mar.–Apr. 2006]).

1. The test for *Related compounds* is revised to include methods for the preparation of *Aqueous solvent mixture, Mobile phase, System suitability solution,* and *Chromatographic system*.
2. The *Procedure* in the test for *Related compounds* is revised to specify the impurities under the term *C* in the equation.
3. The *USP Reference standards* section is also revised to include USP Verapamil Related Compound B RS.

(MD-CV: S. Ramakrishna) RTS—C48962

Change to read:

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Verapamil Hydrochloride RS. USP Verapamil Related Compound A RS.*

▲*USP Verapamil Related Compound B RS.*▲*USP31*

■*USP Verapamil Related Compound E RS. USP Verapamil Related Compound F RS.*■1S *(USP30)*

Change to read:

Related compounds—

Aqueous solvent mixture, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed ~~*for Chromatographic purity*~~ under ~~*Verapamil Hydrochloride*~~

▲in the *Assay.*▲*USP31*

Standard solution—Dissolve accurately weighed quantities of USP Verapamil Hydrochloride RS, USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

■USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS■1S *(USP30)*
in *Mobile phase* to obtain a solution having known concentrations of about 2.5 mg of USP Verapamil Hydrochloride RS per mL and 0.0075 mg each of USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

■USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS■1S *(USP30)*
per mL.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than four times the retention time for verapamil hydrochloride. Record the chromatograms, and measure all of the peak responses. The retention times are about 0.4 for ~~3,4-dimethoxybenzyl alcohol~~

■verapamil related compound F,■1S *(USP30)*
0.5 for verapamil related compound A, 0.7 for ~~3,4-dimethoxybenzaldehyde~~

■verapamil related compound E,■1S *(USP30)*
and 1.0 for verapamil. Calculate the quantity, in mg, of each individual impurity in each mL of the Injection taken by the formula:

$$C(L/D)(r_U/r_S)$$

in which C is the concentration, in mg per mL, of ~~the appropriate impurity~~

▲verapamil related compound A, verapamil related compound E, or verapamil related compound F▲*USP31*
in the *Standard solution*

▲[NOTE—For calculating any other unspecified impurity, C is the concentration, in mg per mL, of USP Verapamil Hydrochloride RS in the *Standard solution*.];▲*USP31*
L is the labeled quantity, in mg per mL, of verapamil hydrochloride in the Injection taken; D is the concentration, in mg per mL, of verapamil hydrochloride in the *Test solution,* on the basis of the labeled quantity in each mL and the extent of dilution; and r_U and r_S are the peak responses of the appropriate impurity in the *Test solution* and the *Standard solution,* respectively: not more than 0.3% of any specified impurity is found, and the sum of all impurities is not greater than 1.0%.

Change to read:

Assay—

~~*Aqueous solvent mixture, Mobile phase, System suitability solution,* and *Chromatographic system*—Proceed as directed for *Chromatographic purity* under *Verapamil Hydrochloride.*~~

▲*Aqueous solvent mixture*—Prepare a 0.015 N sodium acetate solution containing about 33 mL of glacial acetic acid per L.

Mobile phase—Prepare a filtered and degassed mixture of *Aqueous solvent mixture,* acetonitrile, and 2-aminoheptane (70 : 30 : 0.5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).▲*USP31*

Standard preparation—Dissolve an accurately weighed ~~quantities~~ ▲quantity▲*USP31*
of USP Verapamil Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 2.5 mg per mL.

Assay preparation—Dilute the Injection quantitatively, if necessary, with *Mobile phase* to obtain a solution having a concentration of not more than 2.5 mg of verapamil hydrochloride per mL.

▲*System suitability solution*—Dissolve suitable quantities of USP Verapamil Hydrochloride RS and USP Verapamil Related Compound B RS in *Mobile phase* to obtain a solution having known concentrations of about 1.9 mg per mL and 1.5 mg per mL, respectively.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 12.5- to 15-cm column that contains

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packing L1. The flow rate is about 0.9 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.88 for verapamil related compound B and 1.0 for verapamil; the resolution, *R,* between the verapamil related compound B and verapamil peaks is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.▲*USP31*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and allow the *Assay preparation* to elute for not less than four times the retention time for verapamil. Record the chromatograms, and measure the responses for all of the major peaks. Calculate the quantity, in mg, of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in each mL of the Injection taken by the formula:

$$C(L/D)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Verapamil Hydrochloride RS in the *Standard preparation; L* is the labeled quantity, in mg per mL, of verapamil hydrochloride in the Injection; *D* is the concentration, in mg per mL, of verapamil hydrochloride in the *Assay preparation,* on the basis of the labeled quantity in each mL and the extent of dilution; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Verapamil Hydrochloride Tablets, *USP 29* page 2246 and page 158 of *PF* 32(1) [Jan.–Feb. 2006]—See briefing under *Verapamil Hydrochloride Injection*.

(MD-CV: S. Ramakrishna) RTS—C48972

Change to read:

USP Reference standards ⟨11⟩—*USP Verapamil Hydrochloride RS. USP Verapamil Related Compound A RS.*

▲*USP Verapamil Related Compound B RS.*▲*USP31*

■*USP Verapamil Related Compound E RS. USP Verapamil Related Compound F RS.*■1S *(USP30)*

Change to read:

Related compounds—

Aqueous solvent mixture, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed ~~*for Chromatographic purity* under *Verapamil Hydrochloride*~~

▲in the *Assay.*▲*USP31*

Standard solution—Dissolve accurately weighed quantities of USP Verapamil Hydrochloride RS, USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

■USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS■1S *(USP30)* in *Mobile phase* to obtain a solution having known concentrations of about 1.6 mg of USP Verapamil Hydrochloride RS per mL and 0.0048 mg each of USP Verapamil Related Compound A RS, ~~3,4-dimethoxybenzaldehyde, and 3,4-dimethoxybenzyl alcohol~~

■USP Verapamil Related Compound E RS, and USP Verapamil Related Compound F RS■1S *(USP30)* per mL.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and allow the *Test solution* to elute for not less than four times the retention time for verapamil. Record the chromatograms, and measure all of the peak responses. [NOTE—The retention times are about 0.4 for ~~3,4-dimethoxybenzyl alcohol~~

■verapamil related compound F,■1S *(USP30)* 0.5 for verapamil related compound A, 0.7 for ~~3,4-dimethoxybenzaldehyde~~

■verapamil related compound E,■1S *(USP30)* and 1.0 for verapamil.] Calculate the quantity, in mg, of each individual impurity in each mL of the portion of Tablets taken by the formula:

$$25C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of ~~the appropriate impurity~~

▲verapamil related compound A, verapamil related compound E, or verapamil related compound F▲*USP31* in the *Standard solution*

▲[NOTE—For calculating any other unspecified impurity, C is the concentration, in mg per mL, of USP Verapamil Hydrochloride RS in the *Standard solution*.];▲*USP31* and r_U and r_S are the peak responses of the appropriate impurity obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.3% of any specified impurity is found; and the sum of all impurities is not more than 1.0%.

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Assay—

~~*Aqueous solvent mixture, Mobile phase, System suitability solution,* and *Chromatographic system*~~ ~~Proceed as directed for *Chromatographic purity* under *Verapamil Hydrochloride.*~~

▲*Aqueous solvent mixture*—Prepare a 0.015 N sodium acetate solution containing about 33 mL of glacial acetic acid per L.

Mobile phase—Prepare a filtered and degassed mixture of *Aqueous solvent mixture,* acetonitrile, and 2-aminoheptane (70 : 30 : 0.5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).▲*USP31*

Standard preparation—Dissolve an accurately weighed quantity of USP Verapamil Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 1.6 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg of verapamil hydrochloride, to a stoppered centrifuge tube, and add 25 mL of *Mobile phase.* Shake by mechanical means for 15 minutes, centrifuge, and if necessary filter the supernatant.

▲*System suitability solution*—Dissolve suitable quantities of USP Verapamil Hydrochloride RS and USP Verapamil Related Compound B RS in *Mobile phase* to obtain a solution having known concentrations of about 1.9 mg per mL and 1.5 mg per mL, respectively.

Chromatographic system (see*Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 12.5- to 15-cm column that contains packing L1. The flow rate is about 0.9 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.88 for verapamil related compound B and 1.0 for verapamil; the resolution, *R,* between the verapamil related compound B and verapamil peaks is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.▲*USP31*

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and allow the *Assay preparation* to elute for not less than four times the retention time for verapamil. Record the chromatograms, and measure the responses for all of the major peaks. Calculate the quantity, in mg, of verapamil hydrochloride ($C_{27}H_{38}N_2O_4 \cdot HCl$) in the portion of Tablets taken by the formula:

$$25C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Verapamil Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

DIETARY SUPPLEMENTS—MONOGRAPHS

BRIEFING

Alpha Lipoic Acid Capsules. *USP 29* page 2352. On the basis of comments received, the solvent composition used in the *Standard solution, Test solution 1,* and *Test solution 2* in the test for the *Content of alpha lipoic acid* is being revised. A binary solvent system composed of equal amounts of acetonitrile and water will be used as the diluent throughout the preparation of each of the mentioned solutions.

(DSN: L. Evans) RTS—C48869

Change to read:

Content of alpha lipoic acid—

Mobile phase—Prepare a filtered and degassed mixture of 0.025 M phosphoric acid and acetonitrile (62 : 38).

Standard solution—Dissolve an accurately weighed quantity of USP Alpha Lipoic Acid RS in acetonitrile

▲and water (1 : 1),▲*USP31*
and dilute quantitatively, and stepwise if necessary, with acetonitrile

▲and water (1 : 1)▲*USP31*
to obtain a solution having a known concentration of 0.05 mg per mL.

Test solution 1 (for hard gelatin capsules)—Empty and mix thoroughly the contents of not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of alpha lipoic acid, to a suitable container, add about 70 mL of a mixture of acetonitrile and water (1 : 1), and shake for 45 minutes by mechanical means. Transfer to a 100-mL volumetric flask, dilute with the mixture of acetonitrile and water (1 : 1) to volume, mix, and filter a portion of this preparation, discarding the first 5 mL of the filtrate. Transfer 5.0 mL of the remaining filtrate to a 100-mL volumetric flask, dilute with ~~water~~

▲acetonitrile and water (1 : 1)▲*USP31*
to volume, and mix.

Test solution 2 (for soft gelatin capsules)—Using a suitable cutting instrument, open an accurately counted number of Capsules equivalent to about 500 mg of alpha lipoic acid. Transfer the contents and the shells to a suitable container with stopper, add 500.0 mL of a mixture of acetonitrile and water (1 : 1), and shake for 45 minutes by mechanical means. Filter a portion of this preparation, discarding the first 5 mL of the filtrate. Transfer 5.0 mL of the remaining filtrate to a 100-mL volumetric flask, dilute with ~~water~~

▲acetonitrile and water (1 : 1)▲*USP31*
to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the tailing factor for alpha lipoic acid is not more than 1.2; the efficiency of the column is not less than 1300 theoretical plates; and the relative standard deviation for replicate injections is not more than 1.0%.

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Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the appropriate *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of alpha lipoic acid in the portion of hard gel Capsules taken by the formula:

$$2000C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Alpha Lipoic Acid RS in the *Standard solution;* and r_U and r_S are the peak responses of alpha lipoic acid obtained from *Test solution 1* and the *Standard solution,* respectively. Calculate the quantity, in mg, of alpha lipoic acid in each soft gel Capsule taken by the formula:

$$10{,}000(C/N)(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Alpha Lipoic Acid RS in the *Standard solution; N* is the number of capsules taken; and r_U and r_S are the peak responses of alpha lipoic acid obtained from *Test solution 2* and the *Standard solution*, respectively.

BRIEFING

Calcium Glycerophosphate. Because there is no existing *USP* monograph for this dietary supplement, a new monograph, based on validated procedures, is being proposed.

(DSN: L. Evans) RTS—C46401

Add the following:

▲Calcium Glycerophosphate

$C_3H_7CaO_6P$ 210.14

1,2,3-Propanetriol, mono(dihydrogen phosphate) calcium salt (1 : 1).

Calcium glycerophosphate. [*27214-00-2*].

» Calcium Glycerophosphate is a mixture, in variable proportions, of calcium *(RS)*-2,3-dihydroxypropyl phosphate and calcium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate, which may be hydrated. Calcium Glycerophosphate contains not less than 18.6 percent and not more than 19.4 percent of calcium (Ca), calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Appearance of solution—

Opalescent suspension—Dissolve 1 g of hydrazine sulfate in sufficient water to produce 100 mL, and allow to stand for 4 to 6 hours. Add 25 mL of this solution to a solution containing 2.5 g of methenamine in 25 mL of water, mix well, and allow to stand for 24 hours.

Primary reference suspension—Dilute 15.0 mL of the *Opalescent suspension* with water to 1000.0 mL. [NOTE—This suspension is freshly prepared, and may be stored for at most 24 hours.]

Reference suspension—To 30 mL of the *Opalescent suspension,* add 70 mL of water, and mix. [NOTE—Shake before using.]

Test solution—Dissolve 1.5 g at room temperature in carbon dioxide-free water, and dilute with the same solvent to 150 mL.

Procedure—Compare the opalescence of equal volumes of the *Test solution* and the *Reference suspension*. The *Test solution* is not more opalescent than the *Reference suspension*.

Identification—

A: Ignite 0.1 g in a crucible. Take up the residue with 5 mL of nitric acid, heat on a water bath for 1 minute, and filter. Mix 1 mL of the filtrate with 2 mL of ammonium molybdate TS: a yellow color develops.

B: Dissolve about 20 mg of the substance being examined in 5 mL of 5 M acetic acid, and add 0.5 mL of potassium ferrocyanide solution (53 g in 1000 mL). The resulting solution remains clear. To the clear solution, add about 50 mg of ammonium chloride: a white crystalline precipitate is produced.

Acidity or alkalinity—Dissolve 1 g in water, and dilute with the same solvent to 100 mL. Add 0.1 mL of 1.0% (w/v) phenolphthalein solution. Not more than 0.5 mL of 0.1 M sodium hydroxide or 0.1 M hydrochloric acid is required to change the color of the indicator.

Citric acid—

Mercury (II) sulfate solution—Dissolve 1 g of mercuric oxide in a mixture of water and sulfuric acid (5 : 1).

Procedure—Mix 5 g with 20 mL of carbon dioxide-free water, and filter. To the filtrate, add 0.15 mL of sulfuric acid, and filter. To the filtrate, add 5 mL of *Mercury (II) sulfate solution,* and heat to boiling. Add 0.5 mL of 0.2 M potassium permanganate, and heat to boiling. No precipitate is formed.

Loss on drying ⟨731⟩**—**Dry it at 150° for 4 hours: it loses not more than 12.0% of its weight.

Glycerol and alcohol-soluble substances—Mix 1 g with 25 mL of alcohol, and shake for 1 minute. Filter, evaporate the filtrate to dryness on a water bath, and dry the residue at 70° for 1 hour. The residue weighs not more than 5 mg (0.5%).

Lead ⟨251⟩**:** not more than 4 µg per g.

Iron ⟨241⟩**—**

Standard solution—Dilute 1 volume of *Standard Iron Solution,* prepared as directed under *Iron* ⟨241⟩, with water to 10 volumes (1 ppm).

Procedure—Dissolve 0.20 g in 10 mL of water. Add 2 mL of a 20% (w/v) solution of citric acid to 0.1 mL of thioglycolic acid, mix, make alkaline with 10 M ammonia, dilute with water to 20 mL, and allow to stand for 5 minutes. Any pink color produced is not more intense than that obtained by treating 4 mL of the *Standard solution* in the same manner.

Heavy metals, *Method I* ⟨231⟩**:** 20 µg per g.

Limit of chloride—

Chloride standard solution—Dissolve an accurately weighed quantity of sodium chloride in water to obtain a solution having a concentration of about 0.824 mg per mL. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Dissolve 0.125 g in a 10-mL mixture of water and 5 M acetic acid (8 : 2), and dilute with water to 15 mL.

Procedure—To the *Test solution,* add 1 mL of 2 M nitric acid, then add the resulting solution to 1 mL of a silver nitrate solution (17 g in 1000 mL), and allow to stand for 5 minutes protected from light. To 10 mL of the *Chloride standard solution,* add 5 mL of water and 1 mL of 2 M nitric acid. To this solution, add 1 mL of silver nitrate solution (17 g in 1000 mL), and allow to stand for 5 minutes protected from light. When viewed against a dark background, the *Test solution* is not more turbid than the *Chloride standard solution:* not more than 400 ppm.

Limit of sulfate—

Sulfate standard solution—Dissolve an accurately weighed quantity of potassium sulfate in water to obtain a solution having a concentration of about 1.81 mg per mL. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Use the *Test solution* prepared as directed in the test for *Appearance of solution*.

Procedure—To 15 mL of the *Sulfate standard solution,* add 0.5 mL of 5 M acetic acid and 1 mL of barium chloride solution (250 g in 1000 mL). Repeat, using 15 mL of the *Test solution*. Allow the solutions to stand for 5 minutes protected from light. When viewed against a dark background, the *Test solution* is not more turbid than the *Sulfate standard solution:* not more than 0.2%.

Limit of arsenic—

Arsenic trioxide stock solution—In a 250-mL volumetric flask, dissolve 330 mg of arsenic trioxide in 5 mL of 2 N sodium hydroxide, and dilute with water to volume. Transfer 1 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Arsenic standard solution—Transfer 1 mL of the *Arsenic trioxide stock solution* to a 10-mL volumetric flask, dilute with water to volume, and mix.

Tin (II) chloride solution—Transfer 1 mL of the *Arsenic trioxide stock solution* to a 10-mL volumetric flask, dilute with water to volume, and mix.

Test solution—In a 25-mL volumetric flask, dissolve 330 mg of Calcium Glycerophosphate in water, dilute with water to volume, and mix.

Apparatus—Prepare a 100-mL side-arm conical flask containing a magnetic stirring bar. Attach to the conical flask a ground–glass stopper through which passes a 20-cm long glass tube with an internal diameter of 5 mm. The lower end of the tube is inside the conical flask and has been drawn to a tip with an internal diameter of 1 mm. About 15 mm from the tip, and at least 3 mm below the lower surface of the stopper, is an orifice about 3 mm in diameter. The upper end of the tube has a flat ground surface at a right angle to the axis of the tube. A second glass tube of the same internal diameter and 30 mm long, with a similar flat ground surface, is placed in contact with the ground surface of the first tube and is held in position by a clamp and springs. Into the lower tube insert about 55 mg of loosely packed lead acetate cotton. Between the flat surfaces of the tubes place a disk of mercuric bromide paper.

Procedure—Before placing the tube assembly into the flask transfer the *Test solution* to the flask, and add 15.0 mL of hydrochloric acid, 0.1 mL of *Tin (II) chloride solution,* and 5 mL of potassium iodide TS. Allow to stand for 15 minutes, and add 5 g of activated zinc. Assemble the apparatus immediately, and immerse the flask in a water bath at a temperature such that a uniform evolution of gas is maintained. After not less than 2 hours examine the stain produced on the mercuric bromide paper. Perform the same procedure using the *Arsenic standard solution*. The stain produced on the mercuric bromide paper by the *Test solution* is not more intense than that produced by the *Arsenic standard solution* (1 ppm).

Limit of phosphates—

Sulfomolybdic solution—Dissolve with heating 2.5 g of ammonium molybdate in 20 mL of water. Dilute 28 mL of sulfuric acid in 50 mL of water, and cool. Mix the two solutions, and dilute with water to 100 mL.

Tin (II) chloride solution—Heat 20 g of tin with 85 mL of hydrochloric acid until no more hydrogen is released. Allow to cool. Dilute 1 volume of this solution with 10 volumes of dilute hydrochloric acid (20 g of hydrochloric acid in 100 mL of water).

Phosphate standard stock solution—Dissolve an accurately weighed quantity of monobasic potassium phosphate in water to obtain a solution having a concentration of about 1.43 mg per mL. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix.

Phosphate standard solution—Transfer 50.0 mL of the *Phosphate standard stock solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer 2.5 mL of the *Test solution* from the test for *Appearance of solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Procedure—To 100 mL of the *Test solution,* add 4 mL of *Sulfomolybdic solution,* mix, and add 0.1 mL of *Tin (II) chloride solution*. To 100 mL of the *Phosphate standard solution,* add 4 mL of *Sulfomolybdic solution,* mix, and add 0.1 mL of *Tin (II) chloride solution*. Allow the preparations to stand for 10 minutes, then examine 20 mL of each preparation. Any color produced by the *Test solution* is not more intense than that produced by the *Phosphate standard solution* (400 ppm).

Assay—Dissolve about 200 mg of Calcium Glycerophosphate, accurately weighed, in 300 mL of water. Add 6 mL of 10 M sodium hydroxide and about 15 mg of calconecarboxylic acid triturate, and titrate with 0.1 M edetate disodium VS until the solution is a distinct blue color. Each mL of 0.1 M edetate disodium is equivalent to 4.008 mg of calcium (Ca). ▲*USP31*

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 24* page 3257, page 3816 of the *Second Supplement,* and page 1478 of *PF* 32(5) [Sept.–Oct. 2006]. It is proposed to add *Fully Hydrogenated Rapeseed Oil* to the *Coating Agent* and *Stiffening Agent* categories and *Superglycerinated Fully Hydrogenated Rapeseed Oil* to the *Coating Agent, Emulsifying and/or Solubilizing Agent,* and *Stiffening Agent* categories to complement the proposed new monographs for *Fully Hydrogenated Rapeseed Oil* and *Superglycerinated Fully Hydrogenated Rapeseed Oil,* respectively, which appear elsewhere in this issue of *PF.*

(EM2) RTS—C44784; C44797

Change to read:

Bulking Agent for Freeze-Drying
Creatinine
Mannitol

■Polydextrose ■2S *(NF25)*

Change to read:

Coating Agent

■Amino Methacrylate Copolymer ■1S *(NF25)*
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Carboxymethylcellulose, Sodium
Cellaburate
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate
Cellulose Acetate Phthalate (see Cellacefate)

■Coconut Oil ■1S *(NF25)*
Copovidone

■Corn Syrup Solids ■1S *(NF25)*

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion ■1S *(NF25)*
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Maltodextrin
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose

■Palm Kernel Oil ■2S *(NF25)*
Polyethylene Glycol

■Polyvinyl Acetate ■1S *(NF25)*
Polyvinyl Acetate Phthalate

▲Fully Hydrogenated Rapeseed Oil ▲*NF26*

▲Superglycerinated Fully Hydrogenated Rapeseed Oil ▲*NF26*
Shellac
Starch, Pregelatinized Modified
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Desiccant
Calcium Chloride
Calcium Sulfate

■Polyvinyl Acetate ■1S *(NF25)*
Silicon Dioxide

Change to read:

Emollient
Alkyl (C12-15) Benzoate
Hydrogenated Soybean Oil

■Oleyl Oleate ■1S *(NF25)*

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Carbomer Copolymer
Carbomer Interpolymer
Cholesterol

■Coconut Oil ■1S *(NF25)*
Diethanolamine (Adjunct)
Diethylene Glycol Stearates
Ethylene Glycol Stearates
Glyceryl Distearate
Glyceryl Monolinoleate
Glyceryl Monooleate
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)

■Oleyl Oleate ■1S *(NF25)*

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■Palm Kernel Oil■2S (*NF25*)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
Polyoxyl 40 Stearate
Polyoxyl Lauryl Ether
Polyoxyl Stearyl Ether
Polysorbate 20
Polysorbate 40
Polysorbate 60

Polysorbate 80
Propylene Glycol Monostearate

▲Superglycerinated Fully Hydrogenated Rapeseed Oil▲*NF26*
Sodium Cetostearyl Sulfate
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Sorbitan Sesquioleate
Sorbitan Trioleate
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:

Humectant

■Corn Syrup Solids■1S (*NF25*)

■Erythritol■1S (*NF25*)
Glycerin
Hexylene Glycol
■Maltitol■2S (*NF24*)

■Polydextrose■2S (*NF25*)
Propylene Glycol
Sorbitol
Sorbitol Sorbitan Solution
■Tagatose■1S (*NF24*)

Change to read:

Polymer Membrane

■Amino Methacrylate Copolymer■1S (*NF25*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
Cellaburate
Cellulose Acetate

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■1S (*NF25*)

Change to read:

Sequestering Agent
Beta Cyclodextrin (see Betadex)
Betadex (formerly Beta Cyclodextrin)
■Gamma Cyclodextrin■1S (*NF25*)

■Hydroxypropyl Betadex■2S (*NF25*)
Sodium Tartrate

Change to read:

Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol

▲Canola Oil▲*NF25*
Caprylocaproyl Polyoxylglycerides
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol
▲Lauroyl Polyoxylglycerides▲*NF24*
Linoleoyl Polyoxylglycerides
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil
Oleoyl Polyoxylglycerides
Peanut Oil
Polyethylene Glycol
Polyethylene Glycol Monomethyl Ether
Propylene Glycol
Sesame Oil
Stearoyl Polyoxylglycerides
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:

Stiffening Agent
Castor Oil, Hydrogenated
Cetostearyl Alcohol
Cetyl Alcohol
Cetyl Esters Wax
Cetyl Palmitate
Hard Fat
Paraffin
Synthetic Paraffin

▲Fully Hydrogenated Rapeseed Oil▲*NF26*

▲Superglycerinated Fully Hydrogenated Rapeseed Oil▲*NF26*
Stearyl Alcohol
Wax, Emulsifying
Wax, White
Wax, Yellow

Change to read:

Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
Alamic Acid

Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carbomer Copolymer
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

■Corn Syrup Solids■1S (*NF25*)
Dextrin
Gelatin
Gellan Gum
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Magnesium Aluminum Silicate
Maltodextrin
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate
Starch, Corn
Starch, Potato
Starch, Tapioca
Starch, Wheat
Tragacanth
Xanthan Gum

Change to read:

Sweetening Agent
Acesulfame Potassium
Aspartame
Aspartame Acesulfame

■Corn Syrup Solids■1S (*NF25*)
Dextrates
Dextrose
Dextrose Excipient

■Erythritol■1S (*NF25*)
Fructose
Galactose
■Maltitol■2S (*NF24*)
Maltose
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

■Tagatose■1S (*NF24*)

Change to read:

Tablet Binder
Acacia
Alginic Acid

■Amino Methacrylate Copolymer■1S (*NF25*)
Ammonio Methacrylate Copolymer
Ammonio Methacrylate Copolymer Dispersion
▲Carbomer Homopolymer▲*NF24*
Carbomer Interpolymer
Carboxymethylcellulose Sodium
Cellulose, Microcrystalline
Copovidone

■Corn Syrup Solids■1S (*NF25*)
Dextrin

■Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion■1S (*NF25*)
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum
Low-Substituted Hydroxypropyl Cellulose
Hydroxypropyl Methylcellulose (see Hypromellose)
Hypromellose (formerly Hydroxypropyl Methylcellulose)
Hypromellose Acetate Succinate
Maltodextrin
Maltose
Methylcellulose
Polyethylene Oxide

■Polyvinyl Acetate■1S (*NF25*)
Povidone
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Syrup

Change to read:

Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered

■Corn Syrup Solids■1S (*NF25*)
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose, Anhydrous
Lactose, Monohydrate
■Maltitol■2S (*NF24*)
Maltodextrin
Maltose

In-Process Revision

Mannitol
Sorbitol
Starch
Starch, Corn
Starch, Potato
Starch, Pregelatinized
Starch, Pregelatinized Modified
Starch, Tapioca
Starch, Wheat
Sucrose
Sugar, Compressible
Sugar, Confectioner's

Change to read:

Tonicity Agent

■Corn Syrup Solids■1S (*NF25*)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:

Vehicle

FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

■Corn Syrup Solids■1S (*NF25*)
Dextrose
Peppermint Water
Sorbitol Solution
Syrup

OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil

▲Canola Oil▲*NF25*
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane

SOLID CARRIER
Sugar Spheres

STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

MONOGRAPHS (NF)

BRIEFING

Oleic Acid, *NF 24* page 3382. It is proposed to add a spectrophotometric *Identification* test employing *Infrared Absorption* ⟨197F⟩. It is also proposed to add a *USP Reference standards* section to include USP Oleic Acid RS, to be used to perform the IR absorption test.

(EM1: C. Sheehan) RTS—C49130

Add the following:

▲**USP Reference standards** ⟨11⟩—*USP Oleic Acid RS.*▲*NF26*

Add the following:

▲**Identification—**

Infrared Absorption ⟨197F⟩, on undried specimen.▲*NF26*

BRIEFING

Fully Hydrogenated Rapeseed Oil. Because there is no existing *NF* monograph for this excipient, it is proposed to add a new monograph, based on the monograph *Rapeseed Oil, Fully Hydrogenated,* in the *Food Chemicals Codex, Fifth Edition,* page 382, and on the monograph *Hydrogenated Cottonseed Oil, NF 24* page 3318.

(EM2: H. Wang; NOM: W. Paul) RTS—C44784

Add the following:

▲Fully Hydrogenated Rapeseed Oil

Fully hydrogenated rapeseed oil [*84681-71-0*].

» Fully Hydrogenated Rapeseed Oil is the product obtained by refining and hydrogenating oil obtained from the seeds of *Brassica napus* and *Brassica campestris* (Fam. Cruciferae). The product is a mixture of triglycerides in which the fatty acid composition is a mixture of saturated fatty acids.

Packaging and storage—Preserve in tight, light-resistant containers. No storage requirements specified.

Identification—It meets the requirements of the test for *Fatty acid composition*.

Acid value ⟨401⟩**:** not more than 6.0.

Iodine value ⟨401⟩**:** not more than 4.

Peroxide value ⟨401⟩**:** not more than 2.0.

Unsaponifiable matter ⟨401⟩**:** not more than 1.5%.

Fatty acid composition—Fully Hydrogenated Rapeseed Oil exhibits the following fatty acid composition profile, as determined in the section *Fatty Acid Composition* under *Fats and Fixed Oils* ⟨401⟩:

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
14	0	< 1.0
16	0	3–5
18	0	38–42
20	0	8–10
22	0	42–50
24	0	1.0–2.0
18	1	≤ 1.0
18	2	< 1.0
20	1	< 1.0
22*	1	≤ 1.0

* Erucic acid.

Residue on ignition ⟨281⟩**:** when a 5-g sample of Fully Hydrogenated Rapeseed Oil is ignited at an ignition temperature of 800 ± 25°, not more than 0.5%.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Limit of erucic acid: not more than 1.0%, as determined in the test for *Fatty acid composition*.

Alkaline impurities—Prepare a mixture of 2.0 g of Fully Hydrogenated Rapeseed Oil, 1.5 mL of alcohol, and 3.0 mL of toluene. Dissolve by gentle heating. Add 0.05 mL of bromophenol blue TS, and titrate with 0.01 N hydrochloric acid to a yellow endpoint: not more than 0.4 mL of 0.01 N hydrochloric acid is required.

Limit of nickel—

Test solution—Weigh 5.0 g of Fully Hydrogenated Rapeseed Oil into a previously tared platinum or silica crucible. Cautiously heat the substance, and introduce into it a wick formed from twisted ashless filter paper. Ignite the wick. When the substance ignites, stop heating. After combustion, ignite in a muffle furnace at about 600°. Continue the incineration until white ash is obtained. After cooling, transfer the residue, with the aid of two 2-mL portions of diluted hydrochloric acid, to a 25-mL volumetric flask, add 0.3 mL of nitric acid, and dilute with water to volume.

Nickel standard solution—Immediately before use, dilute 10 mL of nickel standard solution TS with water to 500 mL. This solution contains the equivalent of 0.2 µg of nickel per mL.

In-Process Revision

Standard solutions—Into three identical 10-mL volumetric flasks, introduce respectively 1.0, 2.0, and 4.0 mL of *Nickel standard solution*. To each flask, add a 2.0-mL portion of the *Test solution,* and dilute with water to volume.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at least three times each, at the wavelength of maximum absorbance at 232.0 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a graphite furnace and a nickel hollow-cathode lamp. Record the average of the steady readings for each of the *Standard solutions* and the *Test solution.* Plot the absorbances of the *Standard solutions* and the *Test solution* versus the added quantity of nickel. [NOTE—The *Test solution* should be plotted as if it had a content of added nickel equivalent to 0 µg.] Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel, *C,* in µg per mL, in the *Test solution.* Calculate the content of nickel in the portion of Fully Hydrogenated Rapeseed Oil taken by the formula:

$$25C / W$$

in which *W* is the weight, in g, of Fully Hydrogenated Rapeseed Oil taken to prepare the *Test solution*: not more than 1 µg per g is found.▲*NF26*

BRIEFING

Superglycerinated Fully Hydrogenated Rapeseed Oil. Because there is no existing *NF* monograph for this excipient, it is proposed to add a new monograph, based on the monograph *Rapeseed Oil, Superglycerinated,* in the *Food Chemicals Codex, Fifth Edition,* page 382, and on the monograph *Hydrogenated Cottonseed Oil, NF 24* page 3318.

(EM2: H. Wang; NOM: W. Paul) RTS—C44797

Add the following:

▲Superglycerinated Fully Hydrogenated Rapeseed Oil

Superglycerinated fully hydrogenated rapeseed oil.

» Superglycerinated Fully Hydrogenated Rapeseed Oil is the product obtained by refining, hydrogenating, and glycerinating oil obtained from the seeds of *Brassica napus* and *Brassica campestris* (Fam. Cruciferae). The product is a mixture of mono-, di-, and triglycerides, with triglycerides as a minor component.

Packaging and storage—Preserve in tight, light-resistant containers. No storage requirements specified.

Labeling—Label it to indicate the *Hydroxyl value* and the *Content of 1-monoglycerides.*

Identification—It meets the requirements of the test for *Fatty acid composition*.

Acid value ⟨401⟩**:** not more than 6.0.

Iodine value ⟨401⟩**:** not more than 4.

Hydroxyl value ⟨401⟩**:** not less than 90.0% and not more than 110.0% of that indicated on the label.

Peroxide value ⟨401⟩**:** not more than 2.0.

Unsaponifiable matter ⟨401⟩**:** not more than 1.5%.

Fatty acid composition—Superglycerinated Fully Hydrogenated Rapeseed Oil exhibits the following fatty acid composition profile, as determined in the section *Fatty Acid Composition* under *Fats and Fixed Oils* ⟨401⟩:

Carbon-Chain Length	Number of Double Bonds	Percentage (%)
14	0	<1.0
16	0	3–5
18	0	38–42
20	0	8–10
22	0	42–50
24	0	1.0–2.0
18	1	≤ 1.0
18	2	<1.0
20	1	<1.0
22*	1	≤ 1.0

* Erucic acid.

Residue on ignition ⟨281⟩**:** when a 5-g sample of Superglycerinated Fully Hydrogenated Rapeseed Oil is ignited at an ignition temperature of $800 \pm 25^{\circ}$, not more than 0.5%.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Limit of erucic acid: not more than 1.0%, as determined in the test for *Fatty acid composition*.

Content of 1-monoglycerides—

Periodic acid solution—Dissolve 5.4 g of periodic acid in 100 mL of water, add 1900 mL of glacial acetic acid, and mix. Preserve in a light-resistant, glass-stoppered bottle.

Chloroform—Use chloroform that meets the following test. Add 50.0 mL of *Periodic acid solution* to each of three 500-mL flasks. Add 50 mL of chloroform and 10 mL of water to two of the flasks, and add 50 mL of water to the third flask. Add 20 mL of potassium iodide TS to each flask, mix gently, and continue as directed in the *Procedure,* beginning with "and allow to stand at least 1 minute, but no longer than 5 minutes, before titrating". The difference between the volume of 0.1 N sodium thiosulfate VS required in the titrations with and without the chloroform is not greater than 0.5 mL.

Test solution—Melt Superglycerinated Fully Hydrogenated Rapeseed Oil at a temperature not higher than 10° above its melting point, and mix thoroughly. Transfer an accurately weighed quantity of it, equivalent to about 150 mg of 1-monoglycerides, to a 100-mL beaker, dissolve in 25 mL of *Chloroform,* and mix.

In-Process Revision

Procedure—Transfer the *Test solution,* with the aid of an additional 25 mL of *Chloroform,* to a separator. Wash the beaker with 25 mL of water, and add the washing to the separator. Close the separator tightly with a stopper, shake vigorously for 30 to 60 seconds, and allow the layers to separate. [NOTE—Add 1 to 2 mL of glacial acetic acid to break emulsions due to the presence of soap.] Collect the aqueous layer in a 500-mL glass-stoppered Erlenmeyer flask, and again extract the chloroform solution in the separator with two 25-mL portions of water. Retain the combined aqueous extracts, which will be used in the test for *Limit of free glycerin.* Transfer the chloroform layer to a 500-mL glass-stoppered Erlenmeyer flask, and add 50.0 mL of *Periodic acid solution* to this flask and to each of two blank flasks containing a mixture of 50 mL of *Chloroform* and 10 mL of water. Swirl the flasks during the addition of *Periodic acid solution,* and allow to stand for at least 30 minutes, but no longer than 90 minutes. To each flask, add 20 mL of potassium iodide TS, and allow to stand at least 1 minute, but no longer than 5 minutes, before titrating. Add 100 mL of water, and titrate with 0.1 N sodium thiosulfate VS, using a magnetic stirrer to keep the solution thoroughly mixed, to the disappearance of the brown iodine color. Add 2 mL of starch TS, and continue the titration to the disappearance of the blue color. Calculate the percentage of 1-monoglycerides in the Superglycerinated Fully Hydrogenated Rapeseed Oil taken by the formula:

$$17.9(V_B - V_S)N/W$$

in which 17.9 is the molecular weight of glyceryl monostearate divided by 20; V_B is the volume, in mL, of sodium thiosulfate VS consumed in the blank determination; V_S is the volume, in mL, of sodium thiosulfate VS required in the titration of the Superglycerinated Fully Hydrogenated Rapeseed Oil; N is the normality, in mol per L, of the sodium thiosulfate VS; and W is the weight, in g, of the Superglycerinated Fully Hydrogenated Rapeseed Oil taken to prepare the *Test solution*: not less than 90.0% and not more than 110.0% of that indicated on the label is found.

Limit of free glycerin—

Periodic acid solution and *Chloroform*—Prepare as directed in the test for *Content of 1-monoglycerides.*

Test solution—Use the combined aqueous extracts obtained as directed in the test for *Content of 1-monoglycerides.*

Procedure—Transfer 50.0 mL of *Periodic acid solution* each to two flasks: a 500-mL glass-stoppered Erlenmeyer flask containing the *Test solution* and a 500-mL glass-stoppered Erlenmeyer blank flask containing 75 mL of water. Continue as directed for *Procedure* in the test for *Content of 1-monoglycerides,* beginning with "Swirl the flasks during the addition of *Periodic acid solution,* and allow to stand for at least 30 minutes, but no longer than 90 minutes". Calculate the percentage of free glycerin in the Superglycerinated Fully Hydrogenated Rapeseed Oil taken by the formula:

$$2.3(V_B - V_S)N/W$$

in which 2.3 is the molecular weight of glycerin divided by 40; V_B is the volume, in mL, of sodium thiosulfate VS consumed in the blank determination; V_S is the volume, in mL, of sodium thiosulfate VS required in the titration of the Superglycerinated Fully Hydrogenated Rapeseed Oil; N is the normality, in mol per L, of the sodium thiosulfate VS; and W is the weight, in g, of the Superglycerinated Fully Hydrogenated Rapeseed Oil taken to prepare the *Test solution* as directed in the test for *Content of 1-monoglycerides:* not more than 1% is found.

Limit of nickel—

Test solution—Weigh 5.0 g of Superglycerinated Fully Hydrogenated Rapeseed Oil into a previously tared platinum or silica crucible. Cautiously heat the substance, and introduce into it a wick formed from twisted ashless filter paper. Ignite the wick. When the substance ignites, stop heating. After combustion, ignite in a muffle furnace at about 600°. Continue the incineration until white ash is obtained. After cooling, transfer the residue, with the aid of two 2-mL portions of diluted hydrochloric acid, to a 25-mL volumetric flask, add 0.3 mL of nitric acid, and dilute with water to volume.

Nickel standard solution—Immediately before use, dilute 10 mL of nickel standard solution TS with water to 500 mL. This solution contains the equivalent of 0.2 µg of nickel per mL.

Standard solutions—Into three identical 10-mL volumetric flasks, introduce respectively 1.0, 2.0, and 4.0 mL of *Nickel standard solution*. To each flask, add a 2.0-mL portion of the *Test solution,* and dilute with water to volume.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at least three times each, at the wavelength of maximum absorbance at 232.0 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a graphite furnace and a nickel hollow-cathode lamp. Record the average of the steady readings for each of the *Standard solutions* and the *Test solution.* Plot the absorbances of the *Test solution* and the *Standard solutions* versus the added quantity of nickel. [NOTE—The *Test solution* should be plotted as if it had a content of added nickel equivalent to 0 µg.] Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel, C, in µg per mL, in the *Test solution*. Calculate the content of nickel in the portion of Superglycerinated Fully Hydrogenated Rapeseed Oil taken by the formula:

$$25C / W$$

in which W is the weight, in g, of Superglycerinated Fully Hydrogenated Rapeseed Oil taken to prepare the *Test solution*: not more than 1 µg per g is found. ▲*NF26*

BRIEFING

Sodium Tartrate, *NF 24* page 3429. On the basis of comments received, it is proposed to delete the test for *Limit of oxalate*.

(EM1: C. Sheehan) RTS—C49010

Delete the following:

▲~~**Limit of oxalate**—Dissolve 1.0 g of Sodium Tartrate in 10 mL of water, then add 5 drops of diluted acetic acid and 2 mL of calcium chloride TS: no turbidity develops within 1 hour. Not more than 0.1% is found.~~ ▲*NF26*

In-Process Revision

BRIEFING

Stearyl Alcohol, *NF 24* page 3441. On the basis of comments received, it is proposed to revise the system suitability requirements for determining %RSD for the *Chromatographic system* in the *Assay.*

(EM1: C. Sheehan) RTS—C49015

Change to read:

Assay—

System suitability solution—Dissolve accurately weighed quantities of USP Stearyl Alcohol RS and USP Cetyl Alcohol RS in dehydrated alcohol to obtain a solution containing about 9 mg per mL and 1 mg per mL, respectively.

Assay preparation—Dissolve 100 mg of Stearyl Alcohol in 10.0 mL of dehydrated alcohol, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 2-m column packed with 10% liquid phase G2 on support S1A. The carrier gas is helium. The temperature of the column is maintained at about 205°, the injection port temperature is maintained at about 275°, and the detector temperature is maintained at about 250°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between cetyl alcohol and stearyl alcohol is not less than 4.0; and the relative standard deviation for replicate injections,

▲calculated with the area ratio of stearyl alcohol to cetyl alcohol,▲*NF26*
is not more than 1.5%.

Procedure—Inject about 2 µL of the *Assay preparation* into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of $C_{18}H_{38}O$ in the portion of Stearyl Alcohol taken by the formula:

$$100(r_U / r_s)$$

in which r_U is the peak area for stearyl alcohol obtained from the *Assay preparation;* and r_s is the sum of the areas of all the peaks except the solvent peak.

BRIEFING

Succinic Acid, *NF 24* page 3442. Because of problems reported with the use of hexane in the *Identification* test, it is proposed to replace the solvent with ethyl ether.

(EM1: C. Sheehan) RTS—C49105

Change to read:

Identification—Place a drop of a saturated solution of the sample in a micro-test tube, and add a drop of ammonium chloride solution (0.5 in 100) and several mg of zinc powder. Cover the mouth of the tube with a disk of filter paper moistened with a solution in ~~hexane~~

▲ethyl ether▲*NF26*
containing *p*-dimethylaminobenzaldehyde (5 in 100) and trichloroacetic acid (20 in 100). Heat with a small flame for about 1 minute: a pink to red-violet stain appears on the paper.

BRIEFING

Sugar Spheres, *NF 24* page 3445 and page 3633 of the *First Supplement.* It is proposed to delete the reference to *Method I* of the general chapter *Particle Size Distribution Estimation by Analytical Sieving* ⟨786⟩. *Method I,* a dry sieving method, and *Method II,* a wet sieving method, were removed from the harmonized chapter. The chapter now directs that particle size distribution be estimated as described under *Dry Sieving Method* unless otherwise specified in the individual monograph.

(EM1: C. Sheehan) RTS—C49109

Change to read:

Particle size ~~*Method I*~~

▲▲*NF26*
⟨786⟩: not less than 90% of it passes the coarser sieve size stated in the labeling; all of it passes the next coarser sieve size listed in *Table 1* of the general chapter. Not more than 10% passes the finer sieve size stated in the labeling.

In-Process Revision

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**11**⟩ **USP Reference Standards,** *USP 29* page 2458, page 3754 of the *Second Supplement,* page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 840 of *PF* 28(3) [May–June 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 710 of *PF* 29(3) [May–June 2003], page 2022 of *PF* 29(6) [Nov.–Dec. 2003], page 613 of *PF* 30(2) [Mar.–Apr. 2004], page 1338 of *PF* 30(4) [July–Aug. 2004], page 1674 of *PF* 30(5) [Sept.–Oct. 2004], page 2092 of *PF* 30(6) [Nov.–Dec. 2004], page 99 of *PF* 31(1) [Jan.–Feb. 2005], page 507 of *PF* 31(2) [Mar.–Apr. 2005], page 822 of *PF* 31(3) [May–June 2005], page 1154 of *PF* 31(4) [July–Aug. 2005], page 1433 of *PF* 31(5) [Sept.–Oct. 2005], page 1680 of *PF* 31(6) [Nov.–Dec. 2005], page 181 of *PF* 32(1) [Jan.–Feb. 2006], page 407 of *PF* 32(2) [Mar.–Apr. 2006], page 829 of *PF* 32(3) [May–June 2006], page 1161 of *PF* 32(4) [July–Aug. 2006], and page 1491 of *PF* 32(5) [Sept.–Oct. 2006].

(HDQ) RTS—C44141; C44282; C46802; C48880; C49076; C49130

Add the following:

▲**USP Carboprost Tromethamine RS.**▲*USP31*

Add the following:

▲**USP Carprofen RS.**▲*USP31*

Add the following:

▲**USP Carprofen Related Compound A RS** [carbazole] ($C_{12}H_9N$ ✧ 167.21).▲*USP31*

Add the following:

▲**USP Fosinopril Related Compound A RS** [(4*S*)-4-cyclohexyl-(4-phenylbutyl)phosphinyl]acetyl-L-proline] ($C_{23}H_{34}NO_5P$ ✧ 435.49).▲*USP31*

Add the following:

▲**USP Fosinopril Related Compound B RS** [(4*S*)-4-cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-D-proline propionate (ester), hemibarium salt, sesquihydrate] ($C_{30}H_{46}NO_7P \cdot ½Ba \cdot 1½H_2O$ ✧ 659.35).▲*USP31*

Add the following:

▲**USP Fosinopril Related Compound C RS** [(4*S*)-4-cyclohexyl-1-[[(*RS*)-[(*RS*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt] ($C_{30}H_{45}NNaO_7P$ ✧ 585.64).▲*USP31*

Add the following:

▲**USP Fosinopril Related Compound D RS** [(4*R*)-4-cyclohexyl-1-[[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt] ($C_{30}H_{45}NNaO_7P$ ✧ 585.64).▲*USP31*

Add the following:

▲**USP Fosinopril Related Compound E RS** [(4*S*)-4-phenyl-1-[[(*R*)-[(*S*)-1-hydroxy-2-methylpropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt] ($C_{30}H_{39}NNaO_7P$ ✧ 579.60).▲*USP31*

Add the following:

▲**USP Fosinopril Related Compound F RS** [(4*S*)-4-cyclohexyl-1-[*(R)*-[*(S)*-1-hydroxypropoxy](4-phenylbutyl)phosphinyl]acetyl-L-proline propionate (ester), sodium salt] ($C_{29}H_{43}NNaO_7P$ ✧ 571.62).▲*USP31*

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Add the following:

▲USP Fosinopril Related Compound G RS [(4-phenylbutyl)phosphinylacetic acid**]** ($C_{12}H_{17}O_4P$ ✧ 256.23).▲*USP31*

Add the following:

▲USP Fosinopril Related Compound H RS [4-phenylbutyl phosphonic acid**]** ($C_{10}H_{15}O_3P$ ✧ 214.20).▲*USP31*

Change to read:

USP

▲Diluted▲*USP31*

Isosorbide Mononitrate RS.

Change to read:

USP

▲Diluted▲*USP31*

Isosorbide Mononitrate Related Compound A RS [1,4 : 3,5-dianhydro-D-glucitol 2-nitrate**]** ($C_6H_9NO_6$ ✧ 191.14).

Add the following:

▲USP Orlistat RS.▲*USP31*

Add the following:

▲USP Orlistat Related Compound D RS [*N*-formyl-L-leucine (3*S,*4*R,*6*S*)-tetrahydro-3-hexyl-2-oxo-6-undecyl-2*H*-pyran-4-yl ester**]**.▲*USP31*

Add the following:

▲USP Trimipramine Maleate RS.▲*USP31*

Add the following:

▲USP Trimipramine Related Compound A RS [5-[3-(dimethylamino)-2-methylpropyl]-5*H*-dibenz[*b,f*]azepine**]** ($C_{20}H_{24}N_2$ ✧ 292.42).▲*USP31*

Apparatus for Tests and Assays

BRIEFING

〈**31**〉 **Volumetric Apparatus,** *USP 29* page 2497. It is proposed to align the capacity tolerances for volumetric flasks with the most recent ASTM standards. Accordingly, it is also proposed to update the references in footnote 1. In addition, corrections are made to values in the *Burets* table.

(GC: H. Pappa) RTS—48636

Change to read:

Standards of Accuracy—The capacity tolerances for volumetric flasks, transfer pipets, and burets are those accepted by the National Institute of Standards and Technology (Class A),[1] as indicated in the accompanying tables. Use Class A volumetric apparatus unless otherwise specified in the individual monograph. For plastic volumetric apparatus, the accepted capacity tolerances are Class B.[2]

The capacity tolerances for measuring (i.e., "graduated") pipets of up to and including 10-mL capacity are somewhat larger than those for the corresponding sizes of transfer pipets, namely 10, 20, and 30 µL for the 2-, 5-, and 10-mL sizes, respectively.

Transfer and measuring pipets calibrated "to deliver" should be drained in a vertical position and then touched against the wall of the receiving vessel to drain the tips. Volume readings on burets should be estimated to the nearest 0.01 mL for 25- and 50-mL burets, and to the nearest 0.005 mL for 5- and 10-mL burets. Pipets calibrated "to contain" are called for in special cases, generally for measuring viscous fluids like syrups; however, a volumetric flask may be substituted for a "to contain" pipet. In such cases, the pipet or flask should be washed clean, after draining, and the washings added to the measured portion.

[1] See ~~"Testing of Glass Volumetric Apparatus," N.B.S. Circ. 602, April 1, 1959, and NTIS COM 73-10504, National Technical Information Service.~~ ▲ASTM 288-06, ASTM E287-02, ASTM E1189-00, and ASTM E969-02.▲*USP31*

[2] See ASTM E 288, Fed. Spec. NNN-F-289, and ISO Standard 384.

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Volumetric Flasks

Designated volume, mL	10	25	50	100	250	500	1000
Limit of error, mL	0.02	0.03	0.05	0.08	0.12	~~0.15~~	0.30
Limit of error, %	0.20	0.12	0.10	0.08	0.05	▲0.20▲*USP31* ~~0.03~~ ▲0.04▲*USP31*	0.03

Transfer Pipets

Designated volume, mL	1	2	5	10	25	50	100
Limit of error, mL	0.006	0.006	0.01	0.02	0.03	0.05	0.08
Limit of error, %	0.60	0.30	0.20	0.20	0.12	0.10	0.08

Burets

Designated volume, mL	10 (“micro” type)	25	50
Subdivisions, mL	0.02	~~0.10~~	~~0.10~~
Limit of error, mL	0.02	▲0.1▲*USP31* 0.03	▲0.1▲*USP31* 0.05

BRIEFING

〈**41**〉 **Weights and Balances,** *USP 29* page 2499 and page 514 of *PF* 32(2) [Mar.–Apr. 2006]. On the basis of comments received, it is proposed to revise the chapter to further discuss the three requirements for assessing control of the analytical balance. It is also proposed, in the *Repeatability* section, to modify the formula for estimating *s* when its value is zero, as recommended in NISTIR 6919. In addition, editorial changes have been made.

(GC: H. Pappa) RTS—C46517; C47507; C50641

Change to read:

▲INTRODUCTION▲*USP31*

~~The intent of this section is to bring the requirements for weights into conformity with American National Standard ANSI/ASTM E617, “Laboratory Weights and Precision Mass Standards.” This standard is incorporated by reference and should be consulted for full descriptions and information on the tolerances and construction of weights.[+]~~

▲▲*USP31*

Pharmacopeial tests and assays require balances that vary in capacity, sensitivity, and reproducibility.

▲Measurement uncertainty from the balance is only one contributor to overall weighing errors. Other contributors to weighing errors include changes in water content of samples during weighing and errors due to a static charge on the sample. This chapter addresses the control of the analytical balance for routine operation.▲*USP31*

Unless otherwise specified, when substances are to be “accurately weighed” for *Assay,* the weighing is to be performed with a weighing device whose measurement uncertainty ~~(random plus systematic error) does not exceed 0.1% of the reading. Measurement uncertainty is satisfactory if three times the standard deviation of not less than ten replicate weighings divided by the amount weighed, does not exceed 0.001. Unless otherwise specified, for titrimetric limits tests, the weighing shall be performed to provide the number of significant figures in the weight of the analyte that corresponds to the number of significant figures in the concentration of the titrant.~~

~~Assessment of measurement uncertainty is typically done prior to the balance being placed in operation (e.g., during IQ/OQ/PQ) and periodically thereafter. Two steps are performed in measuring uncertainty: (1) measurement of repeatability and (2) verification of accuracy against certified weights.~~

~~The class designations below are in order of increasing tolerances.~~

~~Class 1.1 weights are used for calibration of low-capacity, high-sensitivity balances. They are available in various denominations from 1 to 500 mg. The tolerance for any denomination in this class is 5 µg. They are recommended for calibration of balances using optical or electrical methods for accurately weighing quantities below 20 mg.~~

~~Class 1 weights are designated as high-precision standards for calibration. They may be used for weighing accurately quantities below 20 mg. (For weights of 10 g or less, the requirements of class 1 are met by *USP XXI* class M.)~~

~~[+] Copies of ASTM Standard E 617-81 (Reapproved 1985) may be obtained from the American Society for Testing and Materials, 1916 Race Street, Philadelphia, PA 19103.~~

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~~Class 2 weights are used as working standards for calibration, built-in weights for analytical balances, and laboratory weights for routine analytical work. (The requirements of class 2 are met by *USP XXI* class S.)[2]~~

~~Class 3 and class 4 weights are used with moderate precision laboratory balances. (Class 3 requirements are met by *USP XXI* class S 1; class 4 requirements are met by *USP XXI* class P.)[2]~~

~~A weight class is chosen so that the tolerance of the weights used does not exceed 0.1% of the amount weighed. Generally, class 2 may be used for quantities greater than 20 mg, class 3 for quantities of greater than 50 mg, and class 4 for quantities of greater than 100 mg. Weights should be calibrated periodically, preferably against an absolute standard weight.~~

▲does not exceed 0.1% of the reading. There are three requirements for control of the analytical balance: assessment of measurement uncertainty (represented mainly by the repeatability of the measurement), verification of accuracy, and a calibration check. The first two requirements are typically performed prior to placing the balance in operation (e.g., during IQ/OQ/PQ) and periodically thereafter. The calibration check is typically performed each day or prior to each series of weighings.▲*USP31*

Add the following:

▲REPEATABILITY

Assessment of repeatability may be performed using either *Method A* or *Method B*.

Method A—In this method, repeatability is determined at the lower end of the desired operating range (i.e., the range of weights for which the balance has been qualified to meet the requirements of this chapter). The measurement of repeatability using this method is satisfactory if two times the standard deviation of not less than 10 replicate weighings divided by the amount weighed does not exceed 0.001, as shown in the formula:

$$2s/w \leq 0.001$$

in which s is the standard deviation of not less than 10 replicate weighings; and w is the nominal mass, in mg, of the weight used.

Method B—This method may be used to determine the low end of the operating range (e.g., minimum weight). Minimum weight can be derived from the following formula:*

$$(2/U_{rel})s$$

in which U_{rel} represents the uncertainty factor of 0.001; and s is the standard deviation, in mg, of not less than 10 replicate measurements of a mass near the low end of the operating range. Because of scale resolution, it is possible to make measurements in which every one results in the same value. A true scale standard deviation of zero is not statistically possible, although the standard deviation may be less than one display increment d. In this situation, the standard deviation of the scale can be estimated as

~~$$s = \frac{d}{\sqrt{3}} = 0.577d$$~~

$$s = \frac{d}{2\sqrt{3}} = 0.29d$$ ▲*USP 31*

Add the following:

▲VERIFICATION OF ACCURACY

Using multiple weights of suitable accuracy as described in the table *Weights Used for Calibration Check of Balances,* the measured weight is within 0.1% of the certified value over the operating range of the balance. The operating range refers to the range used for performing the assay, and not necessarily to the operating range for other weighing operations.

~~[2] Note that the designations S and P no longer designate weight classes but rather weight grades, that is, design limitations such as range of density of materials, surface area, surface finish, corrosion resistance, and hardness.~~

* Derived from the expanded uncertainty equation in NISTIR 6919, *Recommended Guide for Determining and Reporting Uncertainties for Balances and Scales,* January 2002.

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Weights Used for Calibration Check of Balances

Application	Appropriate Class of Weight	Lowest Weight With a Tolerance Within 0.1%*
Calibration of the weights used for other applications or other specialized applications	OIML Classes E1, E2, and ASTM Class 0 [NOTE—Special control of humidity and temperature is needed.]	OIML E1, 5 mg OIML E2, 10 mg ASTM Class 0, 5 mg
Routine analytical work using microbalances	ASTM Classes 1, 2	ASTM Class 1, 10 mg ASTM Class 2, 20 mg
Routine analytical work using 4–5 place analytical balances	ASTM Classes 3, 4 OIML Classes F1, F2	ASTM Class 3, 50 mg ASTM Class 4, 100 mg OIML Class F1, 50 mg OIML Class F2, 200 mg

* ASTM standard E617 may be obtained from ASTM, 100 Barr Harbor Drive, West Conshohocken, PA 19428. OIML R111 may be obtained from OIML (International Organization of Legal Metrology), 11 Rue Turgot, F-75009, Paris, France.

▲*USP31*

Add the following:

▲CALIBRATION CHECK

Analytical balances vary greatly in the features they offer to ensure that the balance is maintained in a calibrated state. A calibration check to ensure that the balance is in a calibrated state is performed each day or before each series of weighings. Typically, the calibration check uses internal or external weights to verify that the balance is still in a calibrated state.▲*USP31*

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GENERAL CHAPTERS

General Information

BRIEFING

⟨**1058**⟩ **Analytical Instrument Qualification,** page 595 of *PF* 32(2) [Mar.–Apr. 2006]. On the basis of comments received, it is proposed to revise this general information chapter. Extensive changes were introduced under *AIQ Documentation;* modifications were also introduced under *Instrument Categories.* Other minor changes were introduced throughout the document.

(GC: H. Pappa) RTS—C45470; C46136; C47505; C47424; C47654; C48451

Add the following:

▲⟨1058⟩ ANALYTICAL INSTRUMENT QUALIFICATION

INTRODUCTION

A large variety of laboratory instruments and ~~tools~~ equipment, ranging from simple nitrogen evaporators to complex multiple-function technologies (see *Instrument Categories*), are used in the pharmaceutical industry to acquire data to help ensure that products are suitable for their intended use. ~~and that they do not pose high safety risks. The~~ An analyst's objective is to consistently obtain reliable and valid data suitable for the intended purpose. Depending on the applications, users validate their procedures, ~~and perform system suitability tests and in process quality control checks check samples~~ calibrate their instruments, and perform additional instrument checks, such as system suitability tests and analysis of in-process quality control check samples to help ensure that the acquired data are reliable. ~~These activities help enhance the quality of data, and there are specific guidances and procedures for performing these activities.~~ With the increasing sophistication and automation of analytical instruments, an increasing demand has been placed on users to qualify their instruments.

Unlike method validation and system suitability activities, analytical instrument qualification (AIQ) currently has no specific guidance or procedures. Competing opinions ~~abound~~ exist regarding instrument qualification and validation procedures and the roles and responsibilities of those who perform them. Consequently, various approaches have been used for instrument qualification, approaches that require varying amounts of resources and generate widely differing amounts of documentation. This chapter provides a scientific approach to AIQ and considers AIQ as one of the major components required for generating reliable and consistent data. ~~Note that a risk-based approach may be used to provide flexibility in the qualification process, depending on the complexity and intended use of the instrumentation.~~ Note that the amount of rigor applied to the qualification process will depend on the complexity and intended use of the instrumentation. ~~This chapter provides an efficient science- and risk-based process for AIQ.~~ This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments. ~~The approach provided in this chapter focuses on scientific value rather than on producing documents.~~

Validation versus Qualification

~~Because there is ambiguity in the use of the terms "validation" and "qualification", in this chapter the term "validation" will be is used for processes, and software, including~~

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~~analytical procedures and software procedures, and the term "qualification" will be is used for instruments.~~ In this chapter, the term validation is used for manufacturing processes, analytical procedures, and software procedures and the term qualification is used for instruments. Thus, the phrase "analytical instrument qualification" (AIQ) is used for the process of ensuring that an instrument is suitable for its intended application. ~~The term "validation" is reserved for processes including analytical procedures and software procedures.~~

COMPONENTS OF DATA QUALITY

There are four critical components involved in the generation of reliable and consistent data (quality data). *Figure 1* shows these components as layered activities within a quality triangle. Each layer adds to the overall quality. Analytical instrument qualification forms the ~~base~~ basis for generating quality data. The other components essential for generating quality data are analytical method validation, system suitability tests, and quality control ~~checks~~ check samples. These quality components are described below.

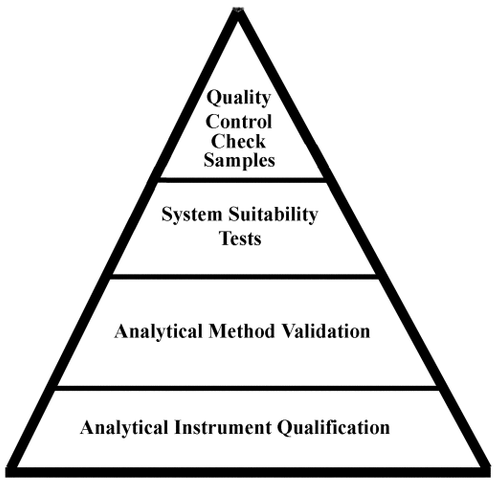

Figure 1. Components of data quality.

Analytical Instrument Qualification

AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose. ~~and that it is properly maintained and calibrated.~~ Use of a qualified instrument in analyses contributes to confidence in the ~~veracity~~ validity of generated data.

Analytical Method Validation

Analytical method validation is the collection of documented evidence that an analytical procedure ~~does what it purports to do and addresses the required attributes of the procedure~~ is suitable for its intended use. Use of a validated procedure with qualified analytical instruments provides confidence that the procedure will generate test data of acceptable quality. ~~Users of compendial procedures perform validation using the criteria provided in general information chapter *Validation of Compendial Methods* ⟨1225⟩.~~ Additional guidance on validation of compendial procedures may be found in the general information chapter *Validation of Compendial Procedures* ⟨1225⟩.

System Suitability Tests

System suitability tests verify that the system will perform ~~according to~~ in accordance with ~~the analyst's expectations and according to~~ the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test. USP general chapter *Chromatography* ⟨621⟩ presents a more detailed discussion of system suitability tests as related to chromatographic systems.

Quality Control ~~Checks~~ Check Samples

Most analyses are performed on instruments ~~calibrated or~~ standardized using reference materials ~~or~~ and/or calibration standards. ~~The calibration or standardization process uses a single- or multiple-point calibration, depending on the instru-~~

~~ment and the intended application. The calibration or standardization of an instrument during analysis ensures that the instrument response correlates with the known quantity or quality of the calibration standard or reference material. In addition to calibration or standardization, some~~ Some analyses also require the inclusion of quality control check samples to provide an in-process or ongoing assurance of the test's suitable performance.

~~The extent of system suitability tests and/or quality control checks check samples varies for different analyses, depending on their intended use.~~ The extent of system suitability and/or quality control check sample testing needed to demonstrate a continuing state of control may vary depending on the complexity or difficulty of the analysis. ~~Chemical analyses, which are largely subject to Good Manufacturing Practices (GMP) regulations and require tighter precision and accuracy, may require more system suitability tests than bioanalytical work, which is largely subject to Good Laboratory Practice (GLP) regulations. Bioanalytical work requires sensitive, specific, broad range analysis and therefore is generally performed with more quality control checks during sample analysis.~~ Generally, chemical analyses exhibit tighter precision and accuracy than bioanalytical work, and for these analyses system suitability tests are often more appropriate. Due to the inherent variability, bioanalytical analyses are generally performed with more quality control checks during sample analysis. Control check samples are also appropriate when high-variability tests or instruments ~~(i.e., those with a relative standard deviation [RSD] higher than 5%)~~ are considered. Other use-specific considerations may also determine the extent of system suitability tests or quality-control-check sample analysis. Whatever the case, the sum total of such controls provides an important step in delivering quality data for the intended purpose.

In summary, analytical instrument qualification and analytical method validation ensure the quality of analysis *before* conducting the tests. System suitability tests and quality control checks ensure the quality of analytical results *immediately before* or *during* sample analysis.

ANALYTICAL INSTRUMENT QUALIFICATION PROCESS

The following sections address in detail the AIQ process. The other three components of building quality into analytical-data—analytical method validation, system suitability tests, and quality control ~~checks~~ check samples—are not within the scope of this chapter.

Qualification Phases

Instrument qualification is not a single continuous process, but instead results from several discrete activities. For convenience, these activities can be grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

~~Some of these qualification terms have their roots in manufacturing process validation. Note, however, that adoption of process validation terms does not imply that all process validation activities are necessary for AIQ. Also, some AIQ activities cover more than one qualification phase and could arguably be performed within any of the phases. It is important that the required AIQ activities be performed; however, within which qualification phase an activity is performed or reported is not as important. *Table 1* accommodates these overlapping activities by letting users perform them under one or another phase as necessary. The user should describe where the activity is performed and reported.~~ Some AIQ activities cover more than one qualification phase and could potentially be performed during any of the phases (see *Table 1*). However, in many instances there is need for specific order to the AIQ activities; for example, installation qualification must occur first in order to initiate other qualification activities. The AIQ activities will be defined and documented.

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Table 1. Timing, Applicability, and Activities for Each Phase of Analytical Instrument Qualification*

Design Qualification	Installation Qualification		Operational Qualification		Performance Qualification
		Timing and applicability			
Prior to purchase of a new ~~type~~ model of instrument	At installation of each instrument (new, old, or existing unqualified)		After installation or major repair of each instrument		Periodically at specified intervals for each instrument
		Activities			
Assurance of ~~vendor's~~ manufacturer's DQ	System description	⇆	Fixed parameters		Preventive maintenance and repairs
Assurance of adequate support availability from manufacturer	Instrument delivery				~~SOPs for~~ Establish practices to address operation, calibration, maintenance, and change control
Instrument's fitness for use in laboratory	Utilities/facility	⇆	Environment		
	Network and data storage	⇆	Secure data storage, backup, and archive		
	Assembly and installation				
	Installation verification	⇆	Instrument function tests	⇆	Performance checks

* Activities under each phase are usually performed as given in the table. However, in some cases, it may be more appropriate to perform or combine a given activity with another phase. Such activities spanning more than one qualification phase are shown as connected by double arrows. If an activity listed under a given phase is performed under another phase, it is not necessary to repeat the activity under the phase where the activity is listed. Performing the activity is far more important than the phase under which the activity is performed.

DESIGN QUALIFICATION

Design qualification (DQ) is the documented collection of activities that define the functional and operational specifications of the instrument, based on the intended purpose. Design qualification (DQ) may not only be performed by the instrument developer or manufacturer ~~Because the instrument design is already in place for commercial off-the-shelf (COTS) systems, users do not need to repeat all aspects of DQ. However, users should ensure that COTS instruments are suitable for their intended applications meet all necessary user requirements and that the manufacturer has adopted a quality system for developing, manufacturing, and testing. Users should also establish that manufacturers and vendors adequately support installation, service, and training. Methods for ascertaining the manufacturer's design qualification and an instrument's suitability for its intended use depend on the nature of the instrument, the complexity of the proposed application, and the extent of the user's previous interaction with the manufacturer. Vendor audits or required vendor supplied documentation may satisfy part of the DQ requirements. The required scope~~

~~and comprehensiveness of the audits and documentation vary with users' familiarity with the instrument and their previous interactions with the vendor should be based on the risk the instrument will impose on operations.~~

~~Informal processes also form an important part of DQ. Informal personal communications and networking with peers at technical or user group meetings significantly inform users about the suitability of instrument design for various applications and the quality of vendor support services. Informal site visits to other users' and vendors' facilities to obtain data on representative samples that used the specified instrument are another good source of information about suitability for intended use. In many instances an assessment of the quality of vendor support, gleaned from informal discussions with peer users, significantly influences instrument selection~~ but also may be performed by the user. The manufacturer is responsible for robust design and maintaining information describing how the analytical instrument is manufactured (design specifications, functional requirements, etc.) and tested before shipment to users. The user should ensure that commercial off-the-shelf (COTS) instruments are suitable for their intended application and that the manufacturer has adopted a quality system that provides for reliable equipment. Users should also determine the manufacturer's capability for support installation, services, and training. This determination might be aided by the user's previous interaction with the manufacturer.

INSTALLATION QUALIFICATION

~~Installation qualification (IQ) is the documented collection of activities necessary for installing an instrument in the user's environment.~~ Installation qualification (IQ) is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, and is properly installed in the selected environment, and that this environment is suitable for the ~~intended purpose~~ instrument. IQ applies to an instrument that is new or was pre-owned, or to any instrument that exists on site but has not been previously qualified. Relevant parts of IQ would also apply to a qualified instrument that has been ~~packed and~~ transported to another location or is being reinstalled for other reasons, such as prolonged storage. The activities and documentation typically associated with IQ are as follows.

System Description—Provide a description of the instrument or the collection of instrument components, including its manufacturer, model, serial number, software version, and location. Use drawings and flow charts where appropriate.

Instrument Delivery—Ensure that the instrument, software, manuals, supplies, and any other accessories arrive as specified with the instrument as the purchase order specifies and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Utilities/Facility/Environment—Verify that the installation site satisfactorily meets ~~vendor specified~~ manufacturer-specified environmental requirements. ~~A commonsense judgment for the environment suffices: one need not measure the exact voltage for a standard voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.~~

Network and Data Storage—Some analytical systems require users to provide network connections and data storage capabilities at the installation site. When required, connect the instrument to the network, and check its functionality.

Assembly and Installation—Assemble and install the instrument, and perform any preliminary diagnostics and testing. Assembly and installation ~~of complex instruments are best~~ may be done by the manufacturer, vendor, specialized engineers, or qualified in-house personnel. ~~whereas users can assemble and install simple ones. For complex instruments, vendor established~~ Manufacturer-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance. Any abnormal event observed during assembly and installation merits documenting. ~~If the pre-owned, unqualified existing instrument or transported instrument requires assembly and installation, perform the tasks as~~

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~~specified above, then perform the installation verification procedure, described below.~~ Installation packages purchased from the manufacturer or the vendor may, however, need to be supplemented with user-specific criteria.

Installation Verification—Perform the initial diagnostics and testing of the instrument after installation. ~~On obtaining acceptable results, the user and, when present, the installing engineer should confirm that the installation was successful before proceeding with the next qualification phase.~~ Before proceeding to the next qualification phase, confirm that the IQ has been successfully completed.

OPERATIONAL QUALIFICATION

After a successful IQ, the instrument is ready for OQ testing. Operational qualification (OQ) is the documented collection of activities necessary to demonstrate that an instrument will function according to its operational specification in the selected environment. The OQ phase may consist of these test parameters.

Fixed Parameters—These tests measure the instrument's nonchanging parameters such as length, height, weight, voltage inputs, acceptable pressures, and loads. If the ~~vendor supplied~~ manufacturer-supplied specifications for these parameters satisfy the user, the test requirements may be waived. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument, and therefore never need redetermination. [NOTE—These tests could also be performed during the IQ phase (see *Table 1*); if so, fixed parameters need not be redetermined as part of OQ testing.]

Secure Data Storage, Backup, and Archiving—When ~~required~~ applicable, test secure data handling such as storage, backup, and archiving at the user's site according to written procedures.

Instrument Function Tests—~~Important instrument~~ Instrument functions should be tested to verify that the instrument operates as intended by the manufacturer. ~~and required by the user. The user should select~~ The user may select additional ~~important~~ instrument parameters for testing according to the instrument's intended use. ~~Vendor supplied~~ Manufacturer-supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets ~~vendor~~ manufacturer ~~and user specifications~~ specifications in the user's environment.

The extent of OQ testing that an instrument undergoes depends on its intended applications. Therefore, no specific OQ tests for any instrument or application are offered in this chapter. ~~Nevertheless, as a guide to the types of tests possible during OQ, consider the following, which apply to an HPLC unit:~~

- ~~pump flow rate~~
- ~~gradient linearity~~
- ~~detector wavelength accuracy~~
- ~~detector linearity~~
- ~~column oven temperature~~
- ~~injector precision and accuracy~~
- ~~peak retention time precision~~

Routine analytical tests do not constitute OQ testing. OQ tests are specifically designed to verify the instrument's operation according to specifications in the user's environment, and repeating the testing at regular intervals may not be required. However, when the instrument undergoes major repairs or modifications, relevant OQ and/or PQ tests should be repeated to verify whether the instrument continues to operate satisfactorily. ~~Relevant OQ tests should also be repeated for an instrument that has been transported to another location, although a move within the laboratory, or from one room to another, that does not disturb instrument operation may not require requalification.~~ If an instrument is moved to another location an assessment should be made of what if any OQ test should be repeated.

OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate interchanging of such components without requalification. ~~and should be performed whenever possible.~~ Holistic tests, which involve the entire system, are also acceptable. ~~in lieu of modular testing. Having successfully completed OQ testing, the instrument is qualified for use in regulated samples analysis.~~

Operational Verification—Before proceeding to the next qualification phase, confirm that OQ has been successfully completed.

PERFORMANCE QUALIFICATION

Performance qualification (PQ) is the documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use. After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through performance qualification. The PQ phase may include the following parameters.

Performance Checks—Set up a test or series of tests to verify the acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications ~~Some~~ and may consist of analyzing known components or standards. The tests should be based on good science and reflect the general intended use of the instrument. ~~These~~ Some system suitability tests or quality control checks that are performed concurrently with the test samples can be used to demonstrate that the instrument is performing suitably. PQ tests may resemble those performed during OQ, but the specifications for their results can be set differently if required. ~~PQ tests should be performed routinely on a working instrument, not only on a new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications.~~ Nevertheless, user specifications for PQ tests should ~~evince~~ demonstrate trouble-free instrument operation for the intended applications. ~~PQ tests should be performed independently of the routine analytical testing performed on the instrument.~~ As is the case with OQ testing, PQ tests can be modular or holistic. However, because many modules within a system interact, holistic tests generally prove to be more effective because they evaluate the entire system, not simply the system's individual modules.

Testing frequency depends on the ruggedness of the instrument and the criticality of the tests performed. Testing may be unscheduled—for example, each time the instrument is used. It may also be scheduled for regular intervals, such as weekly or monthly. Experience with the instrument can influence this decision. ~~Generally, the same PQ tests are repeated~~ It may be useful to repeat the same PQ tests each time the instrument is used so that a history of the instrument's performance can be compiled. Alternatively, the instrument may be incorporated into an integrated support system to assure that it remains continually qualified. Some system suitability tests or quality control checks that are performed concurrently with the test samples also imply that the instrument is performing suitably. ~~However, although system suitability tests can supplement periodic PQ tests, they cannot replace them.~~

Preventive Maintenance and Repairs—When an instrument fails to meet PQ test specifications, it requires maintenance or repair. A periodic preventive maintenance may also be recommended for many instruments. The relevant PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

~~**Standard Operating Procedure[s]**~~ **Practices for Operation, Calibration, ~~and~~ Maintenance, and Change Control**—Establish ~~standard operating procedures~~ practices to maintain and calibrate the instrument. ~~Use a logbook, binder, or electronic record to document each~~ Each maintenance and calibration activity should be documented.

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ROLES AND RESPONSIBILITIES

Users

Users are ultimately responsible for instrument operations and data quality. The user's group encompasses analysts, their supervisors, and organization management. Users should be adequately trained in the instrument's use, and their training records should be maintained as required by the regulations.

Users should also be responsible for qualifying their instruments because their training and expertise in the use of instruments make them the best-qualified group to design the instrument test(s) and specification(s) necessary for successful AIQ. Consultants, equipment manufacturer or vendors, validation specialists, and quality assurance (QA) personnel can advise and assist as needed, but the final responsibility for qualifying instruments lies with the users. The users must also maintain the instrument in a qualified state by routinely performing PQ.

Quality ~~Assurance~~ Unit

The ~~QA role~~ role of the Quality Unit in AIQ remains the same as for any other regulated ~~study~~ activity. ~~QA~~ Quality personnel should understand the instrument qualification process, and they should learn about the instrument's application by working with the users. Finally, they should review the AIQ process to determine whether it meets regulatory requirements and ~~they should make certain that the users attest to the scientific validity of the process~~ the intended use of the equipment supported by scientifically valid and documented data.

Manufacturers

Manufacturers and developers are responsible for DQ when designing the instrument. They are also responsible for validation of relevant processes used in manufacturing and assembly of the hardware and for software associated with the instrument (see also *Software Validation*). Manufacturers and developers are also responsible for writing stand-alone software for analytical work in a documented quality manner and for the validation of this software. Manufacturers should test the assembled instruments before shipping them to users.

Manufacturers and vendors should make available to users a summary of their validation efforts and the results of final instrument and software tests, and they should provide the critical functional test scripts that can be used to qualify the instrument and software at the user site. For instance, manufacturers and vendors can provide a large database and scripts for functional testing of the network's bandwidth for laboratory information management system (LIMS) software.

Finally, it is desirable that manufacturers and vendors should notify all known users about hardware or software defects discovered after a product's release; offer user training, service, repair, and installation support; and invite user audits as necessary.

SOFTWARE VALIDATION

Software used for analytical work can be classified into three categories: firmware; instrument control, data acquisition, and processing software; and stand-alone software. Although software validation is not the primary focus of this chapter, the following sections describe in which cases this activity is under the scope of the analytical instrument qualification.

Firmware

Computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and users generally cannot alter firmware design or function. Firmware is therefore considered a component of the instrument itself. Indeed, the qualification of hardware is not possible without operating it via its firmware. Thus, when the hardware (that is, the analytical instrument) is qualified at the user's site,

the integrated firmware is also essentially qualified. No separate on-site qualification of the firmware is needed. Any changes made to firmware versions should be tracked through change control of the instrument (see *Change Control,* below).

Instrument Control, Data Acquisition, and Processing Software

Software for instrument control, data acquisition, and processing for many of today's computerized instruments is loaded on a computer connected to the instrument. Operation of the instrument is then controlled via the software, leaving fewer operating controls on the instrument. Also, the software is needed for data acquisition and postacquisition calculations. Thus, both hardware and software, their functions inextricably intertwined, are critical to providing analytical results.

The manufacturer should perform DQ, validate this software, and provide users with a summary of validation. At the user site, holistic qualification, which involves the entire instrument and software system, is more efficient than modular validation of the software alone. Thus, the user qualifies the instrument control, data acquisition, and processing software by qualifying the instrument according to the AIQ process.

Stand-Alone Software

An authoritative guide for validating stand-alone software, such as LIMS, is available.[1] The validation process is administered by the software developer, who also specifies the development model appropriate for the software. Validation takes place in a series of activities planned and executed through various stages of the development cycle.

The software validation guide cited in the previous paragraphs indicates that user-site testing is an essential part of the software development cycle. Note, however, that user-site testing, though essential, is only part of the validation process for stand-alone software and does not constitute complete validation. Refer to the software validation guide for activities that must be performed at the user site for testing stand-alone software used in analytical work.

CHANGE CONTROL

Changes to ~~the instrument and~~ instruments, including software, become inevitable as manufacturers add new features and correct known defects. However, implementing all such changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary and should also assess the effects of changes to determine what, if any, requalification is required. The change control process enables them to do this.

Change control follows the DQ/IQ/OQ/PQ classification process. For DQ, evaluate the changed parameters, and determine whether need for the change warrants implementing it. If implementation of the change is needed, install the changes to the system during IQ. Evaluate which of the existing OQ and PQ tests need revision, deletion, or addition as a result of the installed change. Where the change calls for additions, deletions, or revisions to the OQ or PQ tests, follow the procedure outlined below.

Operational Qualification—Revise OQ tests as necessitated by the change. Perform ~~the revised OQ testing. If the OQ did not need revision, repeat only~~ the relevant tests affected by the change. This ensures the instrument's effective operation after the change is installed.

Performance Qualification—Revise PQ tests as necessitated by the change. Perform the PQ testing after installation of the change if similar testing is not already performed during OQ. In the future, perform the revised PQ testing.

[1] *General Principles of Software Validation: Final Guidance for Industry and FDA Staff,* U.S. Department of Health and Human Services, Food and Drug Administration, Rockville, MD, January 11, 2002. http://www.fda.gov/cdrh/comp/guidance/938.html (accessed September 2004).

For changes to firmware and to software for instrument control, data acquisition, and processing, change control is performed through DQ/IQ/OQ/PQ of the affected instrument. Change control for stand-alone software requires user-site testing of changed functionality.

AIQ DOCUMENTATION

~~Two types of documents result from AIQ: static and dynamic.~~

~~Static Documents~~

~~Static documents are obtained during the DQ, IQ, and OQ phases and should be kept in a "Qualification" binder retained in an accessible manner.~~ Documents obtained during instrument qualification should be retained in an accessible manner. Where multiple instruments of one kind exist, documents common to all instruments ~~should go into one binder or section,~~ and documents specific to an instrument ~~should go into that instrument's binder or section~~ may be stored separately. During change control, additional documents ~~can be placed with~~ may supplement ~~the static ones~~ those obtained during the qualification process, and both sets of documents should ~~be removed~~ be retained. When necessary, such documents may be archived.

~~Dynamic Documents~~

~~Dynamic documents are generated during the OQ and PQ phases when the instrument is maintained or tested for performance. Arranged in a binder or logbook, they provide a running record for the instruments and should be kept with them. These documents ay should also be archived as necessary.~~ These documents provide a running record for the instruments and should be stored and maintained in a suitable manner which allows for appropriate protection and access.

INSTRUMENT CATEGORIES

Modern laboratories typically include a suite of ~~tools~~ instruments and equipment varying from simple nitrogen evaporators to complex automated instruments. Therefore, applying a single set of principles to qualifying such dissimilar instruments would be scientifically inappropriate. Users are most capable of establishing the level of qualification needed for an instrument. On the basis of the level needed, it is convenient to categorize instruments into three groups: A, B, and C, as defined below. Examples of instruments in each group are provided. Note that the list of instruments provided here is for illustration only and is not meant to be exhaustive. It does not provide the exact category for an instrument at a user site. That category should be determined by users for their specific instruments or applications.

The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.

Group A

Conformance of Group A ~~instruments to user requirements is determined by visual observation. Since requirements are often straightforward, documentation of requirements may not be required. No independent qualification process is required.~~ equipment may not require formal qualification. ~~Examples of instruments in this group are nitrogen evaporators, magnetic stirrers, vortex mixers, mortar and pestle sets, water baths, and glass pipets.~~ Examples of equipment in this group are nitrogen evaporators, magnetic stirrers, vortex mixers, and pipets.

Group B

Conformance of Group B instruments to user requirements is determined according to an instrument's standard operating procedures. ~~Conformity assessments are generally unambiguous.~~ Installation of Group B instruments is relatively simple, and ~~causes of their failure are readily discernible by simple observation~~ conformity assessments are generally unambiguous. Examples of instruments in this group are balances, incubators, ~~IR spectrometers,~~ melting point apparatus, muffle furnaces, light microscopes, pH meters, variable pipets, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, ovens, water baths, and viscosimeters.

Group C

Conformance of Group C instruments to user requirements is complex and highly method-specific; conformity bounds are determined by the application. Installing these instruments can be a complicated undertaking and may require the assistance of specialists. A full qualification process, as outlined in this document, should apply to these instruments. Examples of instruments in this group include the following:

- atomic absorption spectrometers
- differential scanning calorimeters
- dissolution apparatus
- electron microscopes
- flame absorption spectrometers
- high-pressure liquid chromatographs
- mass spectrometers
- microplate readers
- thermal gravimetric analyzers
- X-ray fluorescence spectrometers
- X-ray powder diffractometers
- densitometers
- diode-array detectors
- elemental analyzers
- gas chromatographs
- IR spectrometers
- near IR spectrometers
- Raman spectrometers
- UV/Vis spectrometers
- inductively coupled argon–plasma emission spectrometers

~~Again, it must be emphasized that the placement of these instruments in the given three groups is for illustrative purposes only. The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.~~

~~CONCLUSION~~

~~The purpose of the use of analytical instruments is to generate reliable data. Analytical instrument qualification helps fulfill this purpose. No authoritative guide existed that considered the risk of instrument nonperformance and combined that risk with users' scientific knowledge and ability to use the instrument to deliver reliable and consistent data. In the absence of such a guide, the qualification of analytical instruments became a subjective and often fruitless document-generating exercise.~~

~~This chapter is based on the outcome of a user workshop-conference on the subject and provides an efficient science- and risk-based process for AIQ. This approach emphasizes AIQ's place in the overall process of obtaining reliable data from analytical instruments. The process provided in this chapter focuses on scientific value rather than on producing documents. Implementing such a process should increase efficiency and remove ambiguous or varying interpretations by different groups.~~▲*USP31*

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DIETARY SUPPLEMENTS

General Chapters—General Information

BRIEFING

⟨2040⟩ Disintegration and Dissolution of Dietary Supplements, *USP 29* page 3089 and page 184 of *PF* 32(1) [Jan.–Feb. 2006]. On the basis of comments received, it is proposed to revise this general information chapter to include dietary supplements other than vitamin–mineral dosage forms and botanicals, which currently are not covered. A brief introduction is provided to explain the purpose of the chapter and define categories of dietary supplements. In the *Disintegration* section, *Apparatus B* specifications are revised, a general procedure for disintegration is provided, and testing times are made consistent for the same dietary supplement dosage forms, regardless of their categories. Sections relating to capsules are now referred to as *Hard Shell Capsules* or *Soft Shell Capsules,* encompassing capsules made from gelatin and nongelatin materials. In the *Dissolution* section, the provision of general chapter *Disintegration* ⟨701⟩ allowing the use of enzymes for hard or soft gelatin capsules and gelatin-coated tablets is adopted. *Notes* are added to explain dissolution conditions for articles containing folic acid and for index vitamins and index minerals. Procedures for dissolution testing of dietary supplements other than vitamin–mineral and botanical dosage forms are now provided. The DS-BA Expert Committee decided to present this proposal in *In-Process Revision* and encourages interested parties to submit their comments and pertinent data.

(DS-BA: D. Cairatti; G. Giancaspro) RTS—C47711

Add the following:

▲INTRODUCTION

This general chapter is provided to determine compliance with the disintegration and dissolution standards for dietary supplements where stated in the individual monographs.

For the purposes of this chapter, dietary supplement dosage forms have been divided into three categories: *Vitamin–Mineral, Botanical,* and *Dietary Supplements Other Than Vitamin–Mineral and Botanical.Vitamin–Mineral Dosage Forms* include articles prepared with vitamins, minerals, or combinations of these dietary ingredients (e.g., USP dietary supplements *Classes I* to *VI* described below); *Botanical Dosage Forms* comprise formulations containing ingredients of botanical origin, including plant materials and extracts; and *Dietary Supplements Other Than Vitamin–Mineral and Botanical Dosage Forms* encompass dietary supplements formulated with lawfully recognized dietary ingredients which are different from those pertaining to the two foregoing categories (e.g., amino acids, chondroitin, and glucosamine.)

Where a dietary supplement represents a combination of the categories mentioned above, and there is a difference between the requirements for the individual categories, the more stringent requirement applies.

Dissolution testing as described in this chapter is a quality-control tool to enable the performance of dietary supplements to be routinely assessed.▲*USP31*

Change to read:

DISINTEGRATION

~~This test is provided to determine compliance with the limits on *Disintegration* stated below or in the individual class monographs on dietary supplements, including botanical dosage forms. This test applies to uncoated and plain coated tablets and to hard gelatin and soft gelatin capsules. It does not apply to tablets or capsules designed to liberate vitamin or mineral content over an extended period or where the label states that the dosage form is to be chewed. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.~~

~~For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell remaining on the screen of the test apparatus, is a soft mass having no palpably firm core.~~

▲This test is provided to determine whether dietary supplement tablets or capsules disintegrate within the prescribed time when placed in a liquid medium at the experimental conditions presented below. Compliance with the limits on *Disintegration* stated in the individual monographs for dietary supplements is required except where the label states that the products are intended for use as troches, are to be chewed, or are designed as extended-release dosage forms. Dietary

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supplements claiming to be extended-release dosage forms must comply with standards other than disintegration to verify that the release of the dietary ingredients from the dosage form is for a defined period of time. Dietary supplements claiming to be extended-release dosage forms shall not be labeled as in compliance with USP unless a USP monograph exists for such product. Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more units.

For purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus or adhering to the lower surface of the disk, if used, is a soft mass having no palpably firm core.▲*USP31*

Apparatus

Apparatus A—Use the *Apparatus* described under *Disintegration* ⟨701⟩ for tablets or capsules that are not greater than 18-mm long. For larger tablets or capsules, use *Apparatus B.*

Apparatus B—The apparatus[1] consists of a basket-rack assembly, a 1000-mL, low-form beaker for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than ~~5.3 cm~~

▲53 mm▲*USP31*
and not more than ~~5.7 cm~~

▲57 mm.▲*USP31*
The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least ~~2.5 cm~~

▲15 mm▲*USP31*
below the surface of the fluid and descends to not less than ~~2.5 cm~~

▲25 mm▲*USP31*
from the bottom of the vessel on the downward stroke.

▲At no time should the top of the basket-rack assembly become submerged.▲*USP31*
The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-Rack Assembly—The basket-rack assembly consists of three open-ended transparent tubes, each ~~7.95 ± 0.05 cm~~

▲77.5 ± 2.5 mm▲*USP31*
long and having an inside diameter of ~~approximately 33.3mm~~

▲32.0 to 34.6 mm▲*USP31*
and a wall ~~approximately 2.4 mm~~

▲2.0 to 3.0 mm▲*USP31*
thick; the tubes are held in a vertical position by two plastic plates, each about ~~9.7 cm~~

▲97 mm▲*USP31*
in diameter and ~~9.5 mm~~

▲7.5 to 10.5 mm▲*USP31*
in thickness, with three holes, each about ~~39 mm~~

▲33 to 34 mm▲*USP31*
in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is 10-mesh No. 23 (0.025-inch) W. and M. gauge woven stainless-steel wire cloth having a plain square weave. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks—Each tube is provided with a perforated cylindrical disk 15.3- ± 0.15-mm thick and 31.4 ± 0.13 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Seven ~~3.2 mm~~

▲3.15- ± 0.1-mm▲*USP31*
holes extend between the ends of the cylinder, one of the holes being through the cylinder axis and the others parallel with it equally spaced on a ~~6 mm~~

▲4.2- ± 0.1-mm▲*USP31*
radius from it. All surfaces of the disk are smooth.

▲[2]▲*USP31*

~~Procedure~~

~~VITAMIN–MINERAL DOSAGE FORMS~~

~~**Uncoated Tablets and Film-Coated Tablets**—Place 1 tablet in each of the tubes of the basket, add a disk to each tube, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid. At the end of 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Plain-Coated Tablets (Other Than Film-Coated Tablets)**—Place 1 tablet in each of the tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then add a disk to each tube, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid. After 45 minutes of operation in water, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Hard Gelatin Capsules**—Apply the test for *Uncoated Tablets,* using 0.05 M acetate buffer, prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain~~

[1] An apparatus and disks meeting these specifications are available from ~~Van-Kel Technology Group~~ ▲Varian Inc.,▲*USP31* 13000 Weston Parkway, Cary, NC 27513, or from laboratory supply houses.

[2] The use of automatic detection employing modified disks is permitted where the use of disks is specified or allowed. Such disks must comply with the requirements for density and dimensions given in this chapter.

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~~1000 mL of solution having a pH of 4.50 ± 0.05, maintained at 37 ± 2° as the immersion fluid. At the end of 45 minutes, lift the basket from the fluid, and observe the capsules: all of the capsules disintegrate except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.~~

~~**Soft Gelatin Capsules**—Proceed as directed under *Hard Gelatin Capsules*.~~

~~★*Rupture Test for Soft Gelatin Capsules* ▲USP30~~

~~BOTANICAL DOSAGE FORMS~~

~~**Uncoated Tablets and Film-Coated Tablets**—[NOTE—Omit the use of disks unless otherwise specified in the individual monograph.] Place 1 tablet in each of the tubes of the basket, and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid. At the end of 20 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Plain-Coated Tablets (other than Film-Coated Tablets)**—[NOTE—Omit the use of disks, unless otherwise specified in the individual monograph.] Place 1 tablet in each of the tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Operate the apparatus using water maintained at 37 ± 2° as the immersion fluid. After 20 minutes of operation in water, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 of the tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Delayed-Release (Enteric-Coated) Tablets**—Place 1 tablet in each of the six tubes of the basket, and if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS, maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.~~

~~**Hard Gelatin Capsules**—Apply the test for *Uncoated Tablets*, using 0.05 M acetate buffer, prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain 1000 mL of solution having a pH of 4.50 ± 0.05, maintained at 37 ± 2° as the immersion fluid. At the end of 20 minutes, lift the basket from the fluid, and observe the capsules: all of the capsules disintegrate except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.~~

~~**Soft Gelatin Capsules**—Proceed as directed under *Hard Gelatin Capsules*.~~

~~★*Rupture Test for Soft Gelatin Capsules* ▲USP30~~

▲Procedure

Uncoated Tablets—Place 1 tablet in each of the tubes of the basket and, if prescribed, add a disk to each tube. Operate the apparatus, using water or the specified medium as the immersion fluid, maintained at 37 ± 2°. At the end of 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Place 1 tablet in each of the tubes of the basket and, if the tablet has a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes. Then, if prescribed, add a disk to each tube, and operate the apparatus, using water or the specified medium as the immersion fluid, maintained at 37 ± 2°. At the end of 30 minutes, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Delayed-Release (Enteric-Coated) Tablets—Place 1 tablet in each of the six tubes of the basket, and if the tablet has a soluble external sugar coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS, maintained at 37 ± 2°, as the immersion fluid for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*. At the end of the time limit specified in the individual monograph, all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not fewer than 16 of the total of 18 tablets tested disintegrate completely.

Hard Shell Capsules—Apply the test for *Uncoated Tablets,* using as the immersion fluid, maintained at 37 ± 2°, a 0.05 M acetate buffer prepared by mixing 2.99 g of sodium acetate trihydrate and 1.66 mL of glacial acetic acid with water to obtain a 1000-mL solution having a pH of 4.50 ± 0.05. Attach a removable wire cloth, as described under *Basket-Rack Assembly,* to the surface of the upper plate of the basket-rack assembly. At the end of 30 minutes, lift the basket from the fluid, and observe the capsules: all of the capsules disintegrate except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not fewer than 16 of the total of 18 capsules tested disintegrate completely.

Soft Shell Capsules—Proceed as directed under *Rupture Test for Soft Shell Capsules.*

Use of Disks—

VITAMIN–MINERAL DOSAGE FORMS—Add a disk to each tube unless otherwise specified in the individual monograph.

BOTANICAL DOSAGE FORMS—Omit the use of disks unless otherwise specified in the individual monograph.

DIETARY SUPPLEMENTS OTHER THAN VITAMIN–MINERAL AND BOTANICAL DOSAGE FORMS—Omit the use of disks unless otherwise specified in the individual monograph.

NOTE—The use of disks for enteric-coated tablets is not permitted.▲*USP31*

Change to read:

▲~~RUPTURE TEST FOR SOFT GELATIN CAPSULES~~

▲RUPTURE TEST FOR SOFT SHELL CAPSULES▲*USP31*

Medium: water; 500 mL.

Apparatus—Use *Apparatus 2* as described under *Dissolution* ⟨711⟩, operating at 50 rpm.

Time: 15 minutes.

Procedure—Place 1 capsule in each vessel, and allow the capsule to sink to the bottom of the vessel before starting rotation of the blade. Observe the capsules, and record the time taken for each capsule shell to rupture.

Tolerances—The requirements are met if all of the capsules tested rupture in not more than 15 minutes. If 1 or 2 of the capsules rupture in more than 15 but not more than 30 minutes, repeat the test on 12 additional capsules: not more than 2 of the total of 18 capsules tested rupture in more than 15 but not more than 30 minutes.▲*USP30*

Change to read:

DISSOLUTION

▲This test is provided to determine compliance with the *Dissolution* requirements where stated in the individual monograph for dietary supplements, except where the label states that tablets are to be chewed.

See *Dissolution* ⟨711⟩ for description of apparatus used, *Apparatus Suitability Test,* and other related information. Of the types of apparatus described in ⟨711⟩, use the one specified in the individual monograph.

For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the dissolution specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual mono-

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graph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

This nonspecific dissolution is intended to be diagnostic of known technological problems that may arise as a result of coatings, lubricants, disintegrants, and other substances inherent in the manufacturing process. For dosage forms containing botanical extracts, this dissolution measurement allows an assessment of the extent of decomposition of the extract to polymeric or other nondissoluble compounds that may have been produced by excessive drying or other manipulations involved in the manufacture of botanical extracts. The operative assumption inherent in this procedure is that if the index or marker compound(s) or the extract is demonstrated to have dissolved within the time frame and under conditions specified, the dosage form does not suffer from any of the above formulation or manufacturing related problems.▲*USP31*

Vitamin–Mineral Dosage Forms

~~This test is provided to determine compliance with the dissolution requirements where stated in the individual class monographs for a tablet or capsule dosage form, except where the label states that the tablets are to be chewed. It does not apply to tablets or capsules designed to release vitamin or mineral content over a delayed or extended period of time. Soft gelatin capsule preparations of dietary supplements meet the requirements for *Disintegration.*~~

All dietary supplements belonging to USP *Classes II* to *VI,* prepared as tablets or capsules, are subject to the dissolution test and criteria described in this chapter for folic acid (if present) and for index vitamins and index minerals. This test is ~~also required if the product labeling includes a health claim concerning~~

▲required because of the importance of▲*USP31*
the relationship between folate deficiency and the risk of neural tube defects. The accompanying table lists the dissolution requirements for the individual USP classes of dietary supplements. *Class I* dietary supplements are combinations of oil-soluble vitamins ~~which are exempt from dissolution requirements;~~

▲for which dissolution standards are not established; ▲*USP31*
hence, dissolution requirements do not apply to the oil-soluble vitamins contained in formulations belonging to *Class IV* or *Class V.*

▲Vitamin–mineral combinations that may not be strictly covered by USP *Classes I* to *VI* are subject to the dissolution test and criteria specified in the individual monographs.▲*USP31*

Dietary Supplements—Vitamin–Mineral Dosage Forms

USP Class	Combination of Vitamins or Minerals Present	Dissolution Requirement
I	Oil-Soluble Vitamins	not applicable
II	Water-Soluble Vitamins	one index vitamin; folic acid (if present)
III	Water-Soluble Vitamins with Minerals	one index vitamin and one index element; folic acid (if present)
IV	Oil- and Water-Soluble Vitamins	one index water-soluble vitamin; folic acid (if present)
V	Oil- and Water-Soluble Vitamins with Minerals	one index water-soluble vitamin and one index element; folic acid (if present)
VI	Minerals	one index element

Unless otherwise stated in the individual monograph, test 6 dosage units for dissolution as directed under *Dissolution* ⟨711⟩.

DISSOLUTION CONDITIONS FOR FOLIC ACID

NOTE—Perform this test under ~~subdued light~~

▲light conditions that minimize photo degradation.▲*USP31*

Medium: water; 900 mL. If the units tested do not meet the requirements for dissolution in water, test 6 additional dosage units for dissolution in a medium of 900 mL of 0.05 M pH 6.0 citrate buffer solution, prepared by mixing 9.5 mL of 0.1 M citric acid monohydrate and 40.5 mL of 0.1 M sodium citrate dihydrate in a 100-mL volumetric flask, diluting with water to volume, mixing, and adjusting to a pH of 6.0 by using either 0.1 M hydrochloric acid or 0.1 M sodium hydroxide solution.
Apparatus 1: 100 rpm, for capsules.
Apparatus 2: 75 rpm, for tablets.
Time: 1 hour.

▲NOTE—Compliance with the dissolution requirements for folic acid does not exempt the product from dissolution testing of the pertinent index vitamin or the corresponding index mineral.▲*USP31*

DISSOLUTION CONDITIONS FOR INDEX VITAMINS AND INDEX MINERALS

Medium: 0.1 N hydrochloric acid; 900 mL.
Apparatus 1: 100 rpm, for capsules.
Apparatus 2: 75 rpm, for tablets.
Time: 1 hour.
For formulations containing 25 mg or more of the index vitamin, riboflavin, use the following conditions:
Medium: 0.1 N hydrochloric acid; 1800 mL.
Apparatus 1: 100 rpm, for capsules.
Apparatus 2: 75 rpm, for tablets.
Time: 1 hour.

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▲NOTE—Compliance with dissolution requirements for the pertinent index vitamin or index mineral does not exempt the product from dissolution testing of folic acid, if present.▲*USP31*

SELECTION OF INDEX VITAMINS AND INDEX ELEMENTS

Compliance with the dissolution requirements for dietary supplements representing combinations of water-soluble vitamins (*Water-Soluble Vitamins Capsules* and *Water-Soluble Vitamins Tablets*) and combinations of oil- and water-soluble vitamins (*Oil- and Water-Soluble Vitamins Capsules* and *Oil- and Water-Soluble Vitamins Tablets*) is determined by measuring the dissolution of a single index vitamin from the water-soluble vitamins present. Riboflavin is the index vitamin when present in the formulation. For formulations that do not contain riboflavin, pyridoxine is the index vitamin. If neither riboflavin nor pyridoxine is present in the formulation, the index vitamin is niacinamide (or niacin), and in the absence of niacinamide (or niacin), the index vitamin is thiamine. If none of the above four water-soluble vitamins is present in the formulation, the index vitamin is ascorbic acid.

Compliance with the dissolution requirements for dietary supplements representing combinations of minerals (*Minerals Capsules* and *Minerals Tablets*) is determined by measuring the dissolution of only one index element. Iron is the index element when present in the formulation. For formulations that do not contain iron, the index element is calcium. If neither iron nor calcium is present, the index element is zinc, and in the absence of all three of these elements, magnesium is the index element.

Compliance with dissolution requirements for dietary supplements representing combinations of water-soluble vitamins and minerals (*Water-Soluble Vitamins with Minerals Capsules* and *Water-Soluble Vitamins with Minerals Tablets*) and combinations of oil- and water-soluble vitamins and minerals (*Oil- and Water-Soluble Vitamins with Minerals Capsules* and *Oil- and Water-Soluble Vitamins with Minerals Tablets*) is determined by measuring the dissolution of one index water-soluble vitamin and one index element, designated according to the respective hierarchies described above.

PROCEDURES

In the following procedures, combine equal volumes of the filtered solutions of the 6 individual specimens withdrawn, and determine the amount of folic acid or the index vitamin or element dissolved, based on the average of 6 units tested. Make any necessary modifications including concentration of the analyte in the volume of test solution taken. Use the *Medium* for preparation of the Standard solution and dilution, if necessary, of the test solution.

Folic Acid—Determine the amount of $C_{19}H_{19}N_7O_6$ dissolved by employing the procedure set forth in the *Assay for folic acid* under *Oil- and Water-Soluble Vitamins with Minerals Tablets*, in comparison with a Standard solution having a known concentration of USP Folic Acid RS in the same *Medium*.

Niacin or Niacinamide, Pyridoxine, Riboflavin, and Thiamine—Determine the amount of the designated index vitamin dissolved by employing the procedure set forth in the *Assay for niacin or niacinamide, pyridoxine, riboflavin, and thiamine* under *Water-Soluble Vitamins Tablets.*

Ascorbic Acid—Determine the amount of $C_6H_8O_6$ dissolved by adding 10 mL of 1.0 N sulfuric acid and 3 mL of starch TS to 100.0 mL of test solution, and titrating immediately with 0.01 N iodine VS. Perform a blank determination, and make any necessary correction.

Iron, Calcium, Magnesium, and Zinc—Determine the amount of the designated index element dissolved by employing the procedure set forth in the appropriate *Assay* under *Minerals Capsules*.

TOLERANCES

The requirements are met if not less than 75% of the labeled content of folic acid and not less than 75% of the labeled content of the index vitamin or the index element from the units tested is dissolved in 1 hour.

Botanical Dosage Forms

~~This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form. See *Dissolution* ⟨711⟩ for description of apparatus used, *Apparatus Suitability Test,* and other related information. Of the types of apparatus described in ⟨711⟩, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-Release Articles* under *Drug Release* ⟨724⟩ is applied, unless otherwise specified in the individual monograph. Compliance with dissolution requirements is determined by testing 6 dosage units individually, or testing 2 or more counted number of dosage units in each vessel, and measuring the dissolution of one or more index/marker compound(s) or the extract specified in the individual monograph. This nonspecific dissolution is intended to be diagnostic of known technological problems that may arise due to coatings, lubricants, disintegrants, and other substances inherent in the manufacturing process. Further, this dissolution measurement allows an assessment of the extent of decomposition of the extract to polymeric or other nondissoluble compounds that may have been produced by excessive drying or other manipulations involved in the manufacture of botanical extracts. The operative assumption inherent in this procedure is that if the index or marker compound(s) or the extract is demonstrated to have dissolved within the time frame and under conditions specified, the dosage form does not suffer from any of the above formulation or manufacturing related problems.~~

▲Compliance with dissolution requirements necessitates the testing of 6 dosage units individually, or testing 2 or more dosage units in each of the 6 vessels of the dissolution apparatus, and measuring the dissolution of one or more index/marker compound(s) or the extract specified in the individual monograph.▲*USP31*

PROCEDURES

Combine equal volumes of the filtered solutions of the 6 or more individual specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of index or marker compound(s) or the extract dissolved in the pooled sample by the *Procedure* specified in the individual monograph. Make any necessary modifications, including concentration of the analyte in the volume of the test solution taken. Use the *Medium* for preparation of the Standard solution and dilution, if necessary, of the test solution.

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INTERPRETATION

Pooled Sample—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the index or marker compound(s) or the extract dissolved from the pooled sample conform to the accompanying acceptance table. The quantity, *Q*, is the amount of dissolved index or marker compound(s) or the extract specified in the individual monograph, expressed as a percentage of the labeled content. The 5%, 15%, and 25% values in the acceptance table are percentages of the labeled content so that these values and *Q* are in the same terms.

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q

▲Dietary Supplements Other Than Vitamin–Mineral and Botanical Dosage Forms

Unless otherwise stated in the individual monographs for dietary supplement dosage forms in this category, compliance requires the testing of 6 individual units, measuring the dissolution of the dietary ingredient as the average of the 6 units tested.

PROCEDURES

Combine equal volumes of the filtered solutions of the 6 specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of dietary ingredient dissolved in the pooled sample by the *Procedure* specified in the individual monograph. Make any necessary modifications, including concentration of the analyte in the volume of the test solution taken. Use the *Medium* for preparation of the Standard solution and for dilution, if necessary, of the test solution.

TOLERANCES

Because of the diversity of chemical characteristics and solubilities of dietary ingredients pertaining to this category, general tolerances cannot be established. See individual monographs for *Tolerances*.▲*USP31*

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REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Dicyclohexylamine, *USP 29* page 3125 and page 651 of *PF* 32(2) [Mar.–Apr. 2006]. It is proposed to update the specification of this reagent to reflect the product currently available on the market.

(HDQ: M. Marques) RTS—C47908

Change to read:

Dicyclohexylamine, $(C_6H_{11})_2NH$—**181.32**

[■*101-83-7*]■1S *(USP30)*
—Clear, strongly alkaline liquid. ▲▲*USP29* Sparingly soluble in water. Miscible with common organic solvents. ~~Density: 0.9104. Solidifies at −0.1°; melts at about 20°.~~

~~*Assay*—Accurately weigh about 400 mg in a tared, small weighing bottle equipped with a well-fitting closure. Transfer the stoppered bottle to a 250-mL beaker, add sufficient glacial acetic acid TS to cover the bottle, and open the bottle under the surface of the acid. Add crystal violet TS, and titrate with 0.1 N perchloric acid VS. Each mL of 0.1 N perchloric acid is equivalent to 18.13 mg of $(C_6H_{11})_2NH$. Not less than 98% is found.~~

~~*Specific gravity* ⟨841⟩: between 0.911 and 0.917.~~
~~*Boiling range* (Reagent test): between 255° and 257°.~~
~~*Water, Method I* ⟨921⟩: not more than 0.5%.~~

▲Use a suitable grade with a content of not less than 98%.▲*USP31*

BRIEFING

Digoxigenin. It is proposed to add this new reagent used in the *System suitability preparation* in the *Assay* in the monograph for *Digoxin*.

(HDQ: M. Marques) RTS—C47708

Add the following:

▲**Digoxigenin** *(3β,12β,14β,21-Tetrahydroxy-20(22)-norcholenic Acid Lactone; 3β,12β,14-Trihydroxy-5β,20(22)-cardenolide; 5β,20(22)-Cardenolide-3β,12β,14-triol; Lanadigenin),* $C_{23}H_{34}O_5$—**390.51** [*1672-46-4*]—Use a suitable grade.▲*USP31*

BRIEFING

Digoxigenin Bisdigitoxoside, *USP 29* page 3125. It is proposed to delete this reagent. It will be replaced by Digoxigenin.

(HDQ: M. Marques) RTS—C47707

Delete the following:

~~▲**Digoxigenin Bisdigitoxoside**—Use a suitable grade.
[NOTE—A suitable grade is available from Crescent Chemical Co., Inc., 1324 Motors Parkway, Hauppauge, NY 11788.]▲*USP31*~~

BRIEFING

Guanidine Hydrochloride, *USP 29* page 3132 and page 912 of *PF* 32(3) [May–June 2006]. It is proposed to update the information regarding this reagent to reflect the products currently available on the market.

(HDQ: M. Marques) RTS—C48554

Change to read:

Guanidine Hydrochloride

▲*(Aminoformamidine Hydrochloride; Aminomethanamidine Hydrochloride),*▲*USP31*
$CH_5N_3 \cdot HCl$—**95.53**

■[*50-01-1*]■1S *(USP30)*
—White, crystalline powder. Freely soluble in water and in alcohol.
~~*Melting range* ⟨741⟩: between 178° and 189°.~~
~~*Chloride content*—Dissolve about 400 mg, accurately weighed, in 5 mL of water. Add 5 mL of glacial acetic acid, 50 mL of methanol, and 1 drop of eosin Y TS, and titrate with 0.1 N silver nitrate VS. Each mL of 0.1 N silver nitrate is equivalent to 3.545 mg of Cl. Not less than 36.1% and not more than 37.1%, calculated on the anhydrous basis, is found.~~

▲Use a suitable grade with a content not less than 99%.▲*USP31*

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BRIEFING

Hydroxypropyl-β-cyclodextrin, page 1701 of *PF* 31(6) [Nov.–Dec. 2005]. It is proposed to clarify the text for this reagent.

(HDQ: M. Marques) RTS—C48210

Change to read:

▲**Hydroxypropyl-β-cyclodextrin,** *(Hydroxypropylbetadex),* $C_{42}H_{70}O_{35}(C_3H_6O)_x$ with x = 7 molar substitution—[*94035-02-6]*—Use a suitable grade with a ~~molar substitution not less than 0.40 and not more than 1.50.~~▲ substitution degree between 0.40 and 1.50.▲*USP31* ▲*USP30*

BRIEFING

1-Octanol. It is proposed to add this new reagent used in the preparation of the *Medium* in the *Dissolution* test in the proposed new monograph for *Orlistat Capsules,* also appearing in this issue of *PF.*

(HDQ: M. Marques) RTS—C48703

Add the following:

▲**1-Octanol** *(Alcohol C8; Capryl Alcohol; Octyl Alcohol),* $C_8H_{18}O$—**130.23**[*111-87-5*]—Use ACS reagent grade.▲*USP31*

BRIEFING

Polysaccharide Molecular Weight Standards, *USP 29* page 3146. It is proposed to update the information regarding a possible supplier of this reagent.

(HDQ: M. Marques) RTS—C48260

Change to read:

Polysaccharide Molecular Weight Standards—Polymaltotriose polymers of different weight-average molecular weight, M_w, values ranging from 5,000 to 400,000 Da.

[NOTE—A suitable set is available from ~~Showdex~~ ▲Shodex (www.shodex.com)▲*USP31* as Kit P-82.]

BRIEFING

Tetrabutylammonium Iodide, *USP 29* page 3157 and page 1275 of *PF* 32(4) [July–Aug. 2006]. It is proposed to update the specification for this reagent to reflect the products currently available on the market.

(HDQ: M. Marques) RTS—C47996

Change to read:

Tetrabutylammonium Iodide, $(C_4H_9)_4NI$—**369.37**

■[*311-28-4*]■2S (*USP30*)

—White, shiny, crystalline flakes. Soluble in alcohol and in ether; slightly soluble in water.

~~*Assay*—Dissolve 200 mg, accurately weighed, in 40 mL of boiling water with vigorous stirring, and cool to room temperature. Stir the solution by mechanical means, add 5 mL of 2 N nitric acid, and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically, using a glass-silver electrode system and adding the titrant in 0.1 mL increments as the endpoint is approached. Perform a complete blank determination, and make any necessary correction. Each mL of 0.1 N silver nitrate is equivalent to 36.94 mg of $(C_4H_9)_4NI$. not less than 99.0% is found.~~

~~*Melting range* ⟨741⟩: between 146° and 147°.~~

▲Use a suitable grade with a content of not less than 99%.▲*USP31*

Test Solutions

BRIEFING

Test Solutions, *USP 29* page 3168, page 3812 of the *Second Supplement,* and page 1538 of *PF* 32(5) [Sept.–Oct.. 2006]. It is proposed to delete one test solution, *Dicyclohexylamine Acetate,* which is not used in any *USP–NF* monograph.

(HDQ: M. Marques) RTS—C48135

Add the following:

■**Acetic Acid, Strong, TS**—Add 300.0 mL of glacial acetic acid, and dilute with water to 1000 mL. This solution contains about 30% (v/v) of CH_3COOH and has a concentration of about 5 N.■2S (*USP30*)

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Add the following:

■**Ammonium Pyrrolidinedithiocarbamate, Saturated, TS**—Add about 10 g of ammonium pyrrolidinedithiocarbamate to a 1000-mL volumetric flask, and dilute with water to volume.■2S (*USP30*)

Delete the following:

~~★**Dicyclohexylamine Acetate TS**—Dissolve 50 g of dicyclohexylamine in 150 mL of acetone, cool in an ice bath, and add, with stirring, a solution consisting of 18 mL of glacial acetic acid in 150 mL of acetone. Recrystallize the precipitate that forms, by heating the mixture to boiling and allowing it to cool in an ice bath, then collect the crystals on a filtering funnel, wash with a small volume of acetone, and air-dry. Dissolve 300 mg of the dicyclohexylamine acetate so obtained in 200 mL of a mixture of 6 volumes of chloroform and 4 volumes of water saturated ether. Use immediately.★(*USP21*)~~

Volumetric Solutions

BRIEFING

Volumetric Solutions, *USP 29* page 3175, page 3812 of the *Second Supplement,* and page 1292 of *PF* 32(4) [July–Aug. 2006]. For *Mercuric Nitrate, Tenth-Molar (0.1 M),* it is proposed to correct the formula used to calculate molarity. For *Sodium Tetraphenylboron, Fiftieth-Molar (0.02M),* it is proposed to add the formula for calculating molarity.

(HDQ: M. Marques) RTS—C47709; C47698

Add the following:

■**Bismuth Nitrate, 0.01 mol/L**

$Bi(NO_3)_3 \cdot 5H_2O$, **485.07**

1000 mL of this solution contains 4.851 g of bismuth nitrate pentahydrate

Dissolve 4.86 g of bismuth nitrate pentahydrate in 60 mL of dilute nitric acid, add water to make 1000 mL, and standardize the solution as follows.

Accurately measure 25 mL of the prepared bismuth nitrate solution, add 50 mL of water and 1 drop of xylenol orange TS, and titrate the solution with 0.01 mol/L disodium dihydrogen ethylenediamine tetraacetate VS until the red color changes to yellow. Calculate the molarity factor.■2S (*USP30*)

Add the following:

■**Magnesium Chloride, 0.01 M**

$MgCl_2 \cdot 6H_2O$, **203.30**

2.0330 g in 1000 mL

Dissolve about 2.04 g of magnesium chloride in 1000 mL of freshly boiled and cooled water, and standardize the solution as follows.

Accurately measure 25 mL of the prepared magnesium chloride solution. Add 50 mL of water, 3 mL of ammonia–ammonium chloride buffer TS and 0.04 g of eriochrome black T–sodium chloride reagent. Titrate with 0.05 M edetate disodium VS until the red-purple color of the solution changes to blue-purple.

$$M = \frac{(\text{mL edetate disodium VS}) \times (\text{M edetate disodium})}{\text{mL magnesium chloride}}$$ ■2S (*USP30*)

Change to read:

Mercuric Nitrate, Tenth-Molar (0.1 M)

$Hg(NO_3)_2$, **324.60**

32.46 g in 1000 mL

Dissolve about 35 g of mercuric nitrate in a mixture of 5 mL of nitric acid and 500 mL of water, and dilute with water to 1000 mL. Standardize the solution as follows.

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Transfer an accurately measured volume of about 20 mL of the solution to a conical flask, and add 2 mL of nitric acid and 2 mL of ferric ammonium sulfate TS. Cool to below 20°, and titrate with 0.1 N ammonium thiocyanate VS to the first appearance of a permanent brownish color.

~~$$M = \frac{\text{mL } NH_4SCN \times \text{N } NH_4SCN}{\text{mL } Hg(NO_3)_2}$$~~

▲$$M = \frac{\text{mL } NH_4SCN \times \text{N } NH_4SCN}{\text{mL } Hg(NO_3)_2 \times 2}$$ ▲*USP 31*

Change to read:

Potassium Hydroxide, Normal (1 N)

KOH, **56.11**

56.11 g in 1000 mL

Dissolve 68 g of potassium hydroxide in about 950 mL of water. Add a freshly prepared saturated solution of barium hydroxide until no more precipitate forms. Shake the mixture thoroughly, and allow it to stand overnight in a stoppered bottle. Decant the clear liquid, or filter the solution in a tight, polyolefin bottle, and standardize by the procedure set forth for *Sodium Hydroxide, Normal (1 N)*.

~~$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH}}$$~~

■$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL KOH}}$$ ■1S (*USP30*)

Change to read:

Sodium Hydroxide, Normal (1 N)

NaOH, **40.00**

40.00 g in 1000 mL

Dissolve 162 g of sodium hydroxide in 150 mL of carbon dioxide-free water, cool the solution to room temperature, and filter through hardened filter paper. Transfer 54.5 mL of the clear filtrate to a tight, polyolefin container, and dilute with carbon dioxide-free water to 1000 mL.

Accurately weigh about 5 g of potassium biphthalate, previously crushed lightly and dried at 120° for 2 hours, and dissolve in 75 mL of carbon dioxide-free water. Add 2 drops of phenolphthalein TS, and titrate with the sodium hydroxide solution to the production of a permanent pink color. Each ~~204.2 mg~~ ■204.23 mg■1S (*USP30*) of potassium biphthalate is equivalent to 1 mL of 1 N sodium hydroxide.

$$N = \frac{\text{g } KHC_8H_4O_4}{0.20423 \times \text{mL NaOH solution}}$$

NOTES—(1) Solutions of alkali hydroxides absorb carbon dioxide when exposed to air. They should be preserved in bottles having well-fitted, suitable stoppers, provided with a tube filled with a mixture of sodium hydroxide and lime (soda-lime tubes) so that air entering the container must pass through this tube, which will absorb the carbon dioxide. (2) Prepare solutions of lower concentration (e.g., 0.1 N, 0.01 N) by quantitatively diluting accurately measured volumes of the 1 N solution with sufficient carbon dioxide-free water to yield the desired concentration.

Restandardize the solution frequently.

Change to read:

Sodium Hydroxide, Alcoholic, Tenth-Normal (0.1 N)

NaOH, **40.00**

To 250 mL of alcohol add 2 mL of a 50% ~~(w/w)~~

■(w/v)■2S *(USP29)*
solution of sodium hydroxide.

Dissolve about 200 mg of benzoic acid, accurately weighed, in 10 mL of alcohol and 2 mL of water. Add 2 drops of phenolphthalein TS, and titrate with the alcoholic sodium hydroxide solution until a permanent pale pink color is produced.

$$N = \frac{\text{mg benzoic acid}}{122.1 \times \text{mL sodium hydroxide}}$$

Change to read:

Sodium Tetraphenylboron, Fiftieth-Molar (0.02 M)

$NaB(C_6H_5)_4$, **342.22**

6.845 g in 1000 mL

Dissolve an amount of sodium tetraphenylboron, equivalent to 6.845 g of $NaB(C_6H_5)_4$, in water to make 1000 mL, and standardize the solution as follows.

Pipet two 75-mL portions of the solution into separate beakers, and to each add 1 mL of acetic acid and 25 mL of water. To each beaker add, slowly and with constant stirring, 25 mL of potassium biphthalate solution (1 in 20), and allow to stand for 2 hours. Filter one of the mixtures through a filtering crucible, and wash the precipitate with cold water. Transfer the precipitate to a container, add 50 mL of water, shake intermittently for 30 minutes, filter, and use the filtrate as the saturated potassium tetraphenylborate solution in the following standardization procedure. Filter the second mixture through a tared filtering crucible, and wash the precipitate with three 5-mL portions of saturated potassium tetraphenylborate solution. Dry the precipitate at 105° for 1 hour. Each g of potassium tetraphenylborate is equivalent to 955.1 mg of sodium tetraphenylboron.

$$\text{▲}M = \frac{gKTPB \times 0.9551 \times 0.075}{342.22}\text{▲}_{USP\ 31}$$

NOTE—Prepare this solution just before use.

Change to read:

Sodium Thiosulfate, Tenth-Normal (0.1 N)

$Na_2S_2O_3 \cdot 5H_2O$, **248.19**

24.82 g in 1000 mL

Dissolve about 26 g of sodium thiosulfate and 200 mg of sodium carbonate in 1000 mL of recently boiled and cooled water. Standardize the solution as follows.

Accurately weigh about 210 mg of primary standard potassium dichromate, previously pulverized and dried ~~at 120° for 4 hours,~~
■according to the instructions on its label, if necessary,■1S *(USP30)*
and dissolve in 100 mL of water in a glass-stoppered, 500-mL flask. Swirl to dissolve the solid, remove the stopper, and quickly add 3 g of potassium iodide, 2 g of sodium bicarbonate, and 5 mL of hydrochloric acid. Insert the stopper gently in the flask, swirl to mix, and allow to stand in the dark for exactly 10 minutes. Rinse the stopper and the inner walls of the flask with water, and titrate the liberated iodine with the sodium thiosulfate solution until the solution is yellowish green in color. Add 3 mL of starch TS, and continue the titration until the blue color is discharged. Perform a blank determination.

Restandardize the solution as frequently as supported by laboratory stability data. In the absence of such data, restandardize the solution weekly.

$$N = \frac{\text{mg } K_2Cr_2O_7}{49.04 \times \text{mL } Na_2S_2O_3}$$

In-Process Revision

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 29* page 3184, page 3813 of the *Second Supplement,* and page 1539 of *PF* 32(5) [Sept.–Oct. 2006].

(HDQ) RTS—C41808; C42512; C42637; C44029; C44435; C44780

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Add the following:	
■Acetaminophen, Chlorpheniramine, and Dextromethorphan Tablets	$T_{■2S\ (USP30)}$
Add the following:	
▲Benazepril Hydrochloride Tablets	$W_{▲USP30}$
Add the following:	
■Capecitabine Tablets	$T_{■2S\ (USP30)}$
Add the following:	
▲Carprofen Tablets	$T_{▲USP31}$
Add the following:	
■Cat's Claw Capsules	$T, LR_{■2S\ (USP30)}$
Add the following:	
■Cat's Claw Tablets	$T, LR_{■2S\ (USP30)}$
Add the following:	
■Dantrolene Sodium Capsules	$T, LR_{■2S\ (USP30)}$

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	$W_{■1S\ (USP30)}$
Add the following:	
▲Diclofenac Potassium Tablets	$T, LR_{▲USP30}$
Add the following:	
■Didanosine Tablets	$T_{■1S\ (USP30)}$
Add the following:	
■Estradiol Vaginal Tablets	$T_{■1S\ (USP30)}$
Add the following:	
■Estradiol and Norethindrone Acetate Tablets	$W_{■1S\ (USP30)}$
Add the following:	
■Fexofenadine Hydrochloride Tablets	$W_{■1S\ (USP30)}$
Add the following:	
■Fosinopril Sodium Tablets	$T_{■1S\ (USP30)}$
Add the following:	
■Fosinopril Sodium and Hydrochlorothiazide Tablets	$T_{■1S\ (USP30)}$
Add the following:	
▲Gabapentin Tablets	$W_{▲USP31}$
Add the following:	
▲Ginkgo Capsules	$T, LR_{▲USP30}$
Add the following:	
▲Ginkgo Tablets	$T, LR_{▲USP30}$
Change to read:	
Asian Ginseng Capsules	$T, \sout{LR}$ ■ $_{■1S\ (USP30)}$
Add the following:	
■Glipizide and Metformin Hydrochloride Tablets	$W_{■1S\ (USP30)}$

In-Process Revision

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets	T, LR■2S *(USP30)*
Add the following:	
■Glucosamine and Methylsulfonylmethane Tablets	T, LR■2S *(USP30)*
Add the following:	
▲Hydrocodone Bitartrate and Homatropine Methylbromide Tablets	T, LR▲*USP31*
Add the following:	
■Irbesartan Tablets	W■1S *(USP30)*
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W■1S *(USP30)*
Add the following:	
■Isosorbide Mononitrate Tablets	T■1S *(USP30)*
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■2S *(USP30)*
Add the following:	
■Ketoprofen Capsules, Extended-Release	T■1S *(USP30)*
Add the following:	
▲Loratadine and Pseudoephedrine Sulfate Tablets, Extended-Release	LR▲*USP31*
Add the following:	
■Meloxicam Tablets	W■2S *(USP30)*
Add the following:	
■Metformin Hydrochloride Tablets, Extended-Release	W, LR■1S *(USP30)*

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
■Methylsulfonylmethane Tablets	T, LR■1S *(USP30)*
Add the following:	
■Modafinil Tablets	T■1S *(USP30)*
Add the following:	
▲Morphine Sulfate Capsules, Extended-Release	T, LR▲*USP30*
Add the following:	
■Nefazodone Hydrochloride Tablets	T■1S *(USP30)*
Add the following:	
■Nevirapine Tablets	W■1S *(USP30)*
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■1S *(USP30)*
Add the following:	
▲Ofloxacin Tablets	W▲*USP31*
Add the following:	
▲Orlistat Capsules	T▲*USP31*
Add the following:	
▲Oxybutynin Chloride Tablets, Extended-Release	T▲*USP30*
Add the following:	
■Oxycodone Hydrochloride Tablets, Extended-Release	T, LR■1S *(USP30)*
Add the following:	
■Pravastatin Sodium Tablets	T■1S *(USP30)*
Add the following:	
■Quinapril Tablets	W■1S *(USP30)*
Add the following:	
■Risperidone Tablets	T, LR■2S *(USP30)*

In-Process Revision

Container Specifications for Capsules and Tablets *(Continued)*

Monograph Title	*Container Specification*
Add the following:	
▲Tizanidine Tablets	T▲*USP30*
Add the following:	
■Valerian Capsules	T, LR■1S (*USP30*)
Add the following:	
■Valganciclovir Tablets	T■1S (*USP30*)
Add the following:	
▲Valsartan and Hydrochlorothiazide Tablets	~~W~~ T▲*USP30*

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 29* page 3191, page 3814 of the *Second Supplement,* page 8589 of *PF* 25(4) [July–Aug. 1999], page 1908 of *PF* 27(1) [Jan.–Feb. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 1405 of *PF* 30(4) [July–Aug. 2004], page 1822 of *PF* 30(5) [Sept.–Oct. 2004], page 2183 of *PF* 30(6) [Nov.–Dec. 2004], page 122 of *PF* 31(1) [Jan.–Feb. 2005], page 591 of *PF* 31(2) [Mar.–Apr. 2005], page 861 of *PF* 31(3) [May–June 2005], page 1193 of *PF* 31(4) [July–Aug. 2005], page 1491 of *PF* 31(5) [Sept.–Oct. 2005], page 1703 of *PF* 31(6) [Nov.–Dec. 2005], page 188 of *PF* 32(1) [Jan.–Feb. 2006], page 662 of *PF* 32(2) [Mar.–Apr. 2006], page 942 of *PF* 32(3) [May–June 2006], page 1301 of *PF* 32(4) [July–Aug. 2006], and page 1541 of *PF* 32(5) [Sept.–Oct. 2006].

(HDQ) RTS—C44141; C44282; C44784; C44797; C48957

Add the following:

▲**Carprofen:** White crystalline powder. Freely soluble in ether, in acetone, in ethyl acetate, and in sodium hydroxide TS or sodium carbonate TS; practically insoluble in water.▲*USP31*

Change to read:

Meropenem: Colorless to white crystals. Soluble in dimethylformamide and in 5% ~~monobasic~~

▲dibasic▲*USP31*
potassium phosphate solution; sparingly soluble in water

▲and in 5% monobasic potassium phosphate solution;▲*USP31*
very slightly soluble in alcohol; practically insoluble in acetone and in ether.

Add the following:

▲**Fully Hydrogenated Rapeseed Oil:** White, waxy solid. Insoluble in water and in alcohol. *NF category:* Coating agent; stiffening agent.▲*NF26*

Add the following:

▲**Superglycerinated Fully Hydrogenated Rapeseed Oil:** White solid. Insoluble in water and in alcohol. *NF category:* Coating agent; emulsifying and/or solubilizing agent; stiffening agent.▲*NF26*

Add the following:

▲**Trimipramine Maleate:** White to almost white crystalline powder. Slightly soluble in water and in alcohol.▲*USP31*

Pending Proposals

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

In order for an item to be adopted into the *USP–NF* and become officially binding, it must first be proposed and published in the *Pharmacopeial Forum (PF)* to allow the public an opportunity to review and comment upon it. When an item is adopted, it is published in the *USP–NF*, its *Supplements*, or an *IRA.* Those items that have not yet been adopted are marked as *Pending Proposals.*

The *Pending Proposals* list contains these items separated into the following categories: General Notices and Requirements; *USP* monographs; Dietary Supplements Monographs; General Chapters; Reference Tables; Excipients; and *NF* Monographs. Each entry in the *Pending Proposals* list contains the monograph title and the citation of the most recent publication of the monograph. When the appropriate USP Expert Committee is considering advancing to official status a pending proposal that is more than 2 years old, it is republished in *PF* for additional opportunity for public review and comment. Reprints of *PF* proposals may be purchased from USP by sending a written request for information to custsvc@usp.org.

To check the status of a *Pending Proposal,* please contact USP as directed below.

- The briefing accompanying the monograph or general chapter lists the names of the Scientific Liaisons responsible for the proposed revisions. The contact information (phone number and email) for the Scientific Liaison is available in the *Staff Directory* section of *How to Use PF*. For *USP–NF Online* subscribers, the name and contact information for the assigned Scientific Liaison is available in the *Auxiliary Information* portion of each monograph.
- Call USP at 301-816-8344 and ask to speak with the Scientific Liaison assigned to the monograph or general chapter of interest.
- Submit questions by email to stdsmonographs@usp.org. Please indicate the name of the monograph or general chapter in the subject line of the email.

Following these lists the reader will find the *Canceled Proposals* list. These are items that were published in *PF* and were pending, but have since been canceled. This list contains cumulative entries for the six issues per volume of *PF* [i.e., 32(1) through 32(6)]. Note that canceled proposals may be republished in *PF* to be considered for future adoption into the *USP–NF.*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
<u>*USP Monographs*</u>			
Acetaminophen Extended-Release Tablets—*Packaging and storage*	30	4	1161
Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets (new)	32	5	1434
Acetazolamide Oral Solution (new)	32	1	43
Acetazolamide Oral Suspension (new)	32	1	44
Acetylcysteine—*USP Reference standards, Assay*	31	3	726
Medical Air—*Definition, Packaging and storage*	31	4	1024
Albumin Human—*Definition, Packaging and storage, Expiration date, Labeling, USP Reference standards* (add), *Identification A, B* (add), *Bacterial endotoxins* (add), *Safety* (add), *Sterility* (add), *pH* (add), *Molecular size distribution* (add), *Heat stability* (add), *Incubation* (add) *Prekallikrein activator* (add), *Protein content* (add), *Heme content* (add), *Potassium content* (add), *Sodium content* (add)	31	5	1338
Albuterol Sulfate—*Identification, Assay*	32	5	1436
Albuterol Tablets—*Assay*	31	3	726
Allopurinol—*Definition, Packaging and storage, USP Reference standards, Chromatographic purity (delete), Related compounds,* (add), *Assay*	32	2	302
Alprazolam Oral Suspension (new)	32	1	46
Alumina, Magnesia, and Calcium Carbonate Tablets—*Title* (name change)	29	6	1835
Alumina, Magnesia, and Calcium Carbonate Chewable Tablets (new)	29	6	1836
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—*Title* (name change)	29	6	1837
Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets (new)	29	6	1837
Alumina, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1841
Alumina, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1842
Aluminum Sulfate and Calcium Acetate Powder for Topical Solution (new)	32	3	755

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Aminosalicylate Sodium Tablets—*Limit of m-aminophenol*	32	5	1437
Aminosalicylic Acid—*Assay*	32	5	1438
Amitriptyline Hydrochloride—*USP Reference standards, Identification, Chromatographic purity* (delete), *Related compounds* (add), *Assay*	31	6	1606
Amlodipine Besylate (new)	32	3	757
Anecortave Acetate (new)	30	2	445
Anecortave Acetate Injectable Suspension (new)	30	2	447
Apomorphine Hydrochloride—*Packaging and storage*	32	5	1438
Aprotinin (new)	31	3	732
Aprotinin Injection (new)	31	3	736
Atracurium Besylate—*Chromatographic purity, Assay*	32	2	305
Azathioprine Oral Suspension (new)	32	1	48
Azithromycin—*Labeling, USP Reference standards, Limit of related substances*	32	2	306
Aztreonam for Injection—*Assay*	31	3	737
Baclofen Oral Solution (new)	32	1	49
Baclofen Oral Suspension (new)	32	1	51
Bemotrizinol (new)	32	4	1044
Benazepril Hydrochloride—*Absorptivity, Related compounds, Assay*	32	5	1438
Benazepril Hydrochloride Tablets (new)	32	1	52
Benzonatate Capsules—*Dissolution* (add)	32	1	55
Bethanechol Chloride Oral Solution (new)	32	1	55
Bethanechol Chloride Oral Suspension (new)	32	1	57
Bicalutamide (new)	31	3	738
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Metal or Plastic Carriers (new)	30	1	63
Biological Indicators for Moist Heat, Dry Heat, and Gaseous Modes of Sterilization, Liquid Spore Suspensions (new)	30	1	66
Biphasic Isophane Insulin Human Suspension (new)	31	4	1033
Bismuth Subsalicylate Oral Suspension (new)	31	4	1035
Bismuth Subsalicylate Tablets (new)	32	5	1440
Bisoctrizole (new)	32	2	309
Bromocriptine Mesylate Capsules—*Dissolution*	32	1	58
Budesonide (new)	30	6	1978
Bupropion Hydrochloride Extended-Release Tablets—*Drug release, Dissolution*	32	4	1047
Buspirone Hydrochloride—*Content of chloride*	31	3	742
Butorphanol Tartrate Nasal Solution (new)	32	4	1049
Calcitonin Salmon (new)	32	3	760
Calcitonin Salmon Nasal Solution (new)	32	3	767
Calcitonin Salmon Injection (new)	30	4	1177
Calcitriol (new)	32	1	58
Calcitriol Injection (new)	32	1	61
Calcium Carbonate and Magnesia Tablets—*Title* (name change)	29	6	1852
Calcium Carbonate and Magnesia Chewable Tablets (new)	29	6	1852
Calcium Carbonate, Magnesia, and Simethicone Tablets—*Title* (name change)	29	6	1853
Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets (new)	29	6	1854
Calcium Lactate—*USP Reference standards* (add), *Identification*	31	6	1608
Calcium Lactate Tablets—*Identification*	31	6	1609
Calcium Pantothenate—*USP Reference standards, Ordinary impurities*	32	1	62
Dibasic Calcium Phosphate Dihydrate—*Harmonization*	32	4	1329
Anhydrous Dibasic Calcium Phosphate—*Harmonization*	32	4	1332
Camphor—*Water*	31	3	742
Capecitabine (new)	32	4	1052
Capecitabine Tablets (new)	32	4	1054
Captopril Oral Solution (new)	32	1	63
Captopril Oral Suspension (new)	32	1	64
Carbamazepine—*USP Reference standards, Chromatographic purity (Related compounds), Assay*	32	1	65
Carbon Dioxide—*Definition, Packaging and storage*	31	4	1045
Carboxymethylcellulose Sodium—*Heavy metals*	31	5	1349
Carboxymethylcellulose Sodium Paste—*Heavy metals*	31	5	1349
Carvedilol (new)	32	4	1057
Cefaclor Tablets (new)	32	2	314
Cefadroxil for Oral Suspension—*Dissolution* (add)	32	2	315

Pending Proposals (*continued*)

(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Cefepime Hydrochloride—*Limit of N-methylpyrrolidine, Related compounds*	32	2	316
Cefonicid for Injection—*Assay*	32	1	67
Ceftazidime—*USP Reference standards, Assay*	32	1	67
Ceftazidime Injection—*USP Reference standards*	32	1	68
Ceftazidime for Injection—*USP Reference standards*	32	1	68
Cetirizine Hydrochloride (new)	32	2	317
Chlorhexidine Gluconate Oral Rinse—*Assay*	32	3	768
Chlorhexidine Gluconate Solution—*Assay*	32	3	768
Chlorophyllin Copper Complex Sodium—*Content of total copper*	32	3	769
Chlorthalidone—*USP Reference standards, Limit of 4'-chloro-3'-sulfamoyl-2-benzophenone carboxylic acid (CCA) (Limit of chlorthalidone related compound A), Assay*	32	1	68
Cholestyramine Resin—*Dialyzable quaternary amines*	32	2	320
Cilostazol (new)	32	5	1441
Cimetidine—*Identification, Chromatographic purity*	32	3	769
Cimetidine Tablets—*Dissolution*	32	1	72
Ciprofloxacin—*Chromatographic purity, Assay*	32	2	320
Ciprofloxacin and Dexamethasone Otic Suspension (new)	32	2	321
Ciprofloxacin Hydrochloride—*Chromatographic purity, Assay*	32	2	325
Ciprofloxacin Injection—*Bacterial endotoxins, Limit of ciprofloxacin ethylenediamine analog, Assay*	32	4	1059
Citalopram Hydrobromide—*Labeling* (add), *USP Reference standards, Related compounds*	32	4	1060
Citalopram Tablets—*Identification* (add), *Related compounds, Assay*	32	3	770
Anhydrous Citric Acid *(Harmonization), Sulfate*	31	3	749
Citric Acid Monohydrate *(Harmonization), Sulfate*	31	3	750
Citric Acid, Magnesium Oxide, and Sodium Carbonate Irrigation—*USP Reference standards, Assay for citric acid (delayed implementation to January 1, 2009)*	31	2	394
Cladribine—*Specific rotation, Related compounds, Limit of residual solvents*	32	3	774
Clonazepam Oral Suspension (new)	32	1	73
Clopidogrel Bisulfate—*Related compounds, Assay*	32	1	74
Clopidogrel Tablets—*Related compounds, Assay*	32	1	76
Clotrimazole Lozenges—*Dissolution*	32	1	78
Cod Liver Oil—*Identification*	32	5	1443
Cyclopropane—*Definition, Packaging and storage*	31	4	1052
Cyclosporine Capsules—*Labeling* (add), *USP Reference standards, Identification A, B, Dissolution, Droplet size* (add), *Content of alcohol* (add), *Assay*	27	4	2721
Dalteparin Sodium (new)	30	5	1598
Dantrolene Sodium (new)	32	2	327
Dantrolene Sodium Capsules (new)	32	4	1063
Dantrolene Sodium for Injection (new)	32	3	779
Dapsone—*Assay*	31	3	750
Desmopressin Acetate (new)	31	4	1052
Desmopressin Injection (new)	31	4	1057
Desmopressin Nasal Spray Solution (new)	31	4	1059
Desogestrel (new)	28	6	1785
Desogestrel and Ethinyl Estradiol Tablets (new)	30	5	1604
Diazepam Extended-Release Capsules—*USP Reference standards, Assay*	32	2	330
Diclofenac Potassium (new)	31	5	1350
Diclofenac Potassium Tablets (new)	31	5	1352
Diclofenac Sodium Delayed-Release Tablets—*Identification*	31	3	751
Diclofenac Sodium Extended-Release Tablets (new)	30	2	476
Didanosine (new)	32	3	781
Didanosine for Oral Solution (new)	31	5	1357
Didanosine Tablets (new)	32	5	1444
Dihydroxyaluminum Sodium Carbonate Tablets—*Title* (name change)	29	6	1873
Dihydroxyaluminum Sodium Carbonate Chewable Tablets (new)	29	6	1873
Diltiazem Hydrochloride Oral Solution (new)	32	1	79
Diltiazem Hydrochloride Oral Suspension (new)	32	1	80

Pending Proposals (*continued*)
(Items from earlier numbers of *PF* that have not yet been adopted and become official)

Title and Proposal	*PF Volume, Issue, and Page Numbers of Pending Proposals* *Vol.*	*No.*	*Page(s)*
Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1612
Diphenoxylate Hydrochloride and Atropine Sulfate Tablets—*Identification, Assay for diphenoxylate hydrochloride* (delete), *Assay for atropine sulfate* (delete), *Assay* (add)	31	6	1614
Diphtheria Toxin for Schick Test (delete)	31	6	1616
Dipyridamole Oral Suspension (new)	32	1	81
Divalproex Sodium (new)	31	5	1362
Dolasetron Mesylate Oral Solution (new)	32	1	83
Dolasetron Mesylate Oral Suspension (new)	32	1	84
Doxazosin Mesylate (new)	32	4	1066
Doxazosin Tablets (new)	29	1	64
Doxepin Hydrochloride—*USP Reference standards, Identification, Melting range* (delete), *Chloride content* (delete), *Related compounds* (add)	32	2	330
Dronabinol—*USP Reference standards, Identification, Limit of* Δ^8*-tetrahydrocannabinol* (delete), *Related compounds* (add), *Assay*	32	1	86
Drospirenone (new)	32	3	787
Edetate Calcium Disodium—*Harmonization*	32	4	1335
Edetate Disodium—*Assay*	32	4	1070
Edetate Disodium Injection—*Assay*	32	4	1071
Egg Phospholipids (new)	31	3	757
Enoxaparin Sodium (new)	29	6	1876
Enoxaparin Sodium Injection (new)	31	3	761
Ensulizole—*Assay*	31	6	1617
Estradiol and Norethindrone Acetate Tablets (new)	31	5	1364
Estradiol Transdermal System (new)	31	4	1063
Estradiol Vaginal Inserts (new)	32	4	1071
Conjugated Estrogens—*Definition*	30	3	840
Conjugated Estrogens Tablets—*Dissolution*	32	4	1074
Synthetic Conjugated Estrogens (new)	31	6	1620
Ethotoin Tablets—*USP Reference standards, Assay*	32	2	332
Etidronate Disodium—*Limit of phosphite*	31	6	1625
Famotidine Injection (new)	32	2	333
Fenofibrate (new)	31	3	763
Fentanyl (new)	31	6	1626
Fexofenadine Hydrochloride (postponed indefinitely)—*Labeling* (add), *Identification, Water, Specific surface area* (delete), *Limit of fexofenadine related compound B, Related compounds*	32	5	1447
Fexofenadine Hydrochloride Capsules (postponed indefinitely)—*Water, Related compounds*	32	5	1449
Fexofenadine Hydrochloride Tablets (new)	30	6	1997
Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets (new)	31	2	403
Fluconazole—*Related compounds*	32	2	335
Flucytozine Oral Suspension (new)	32	1	92
Flumazenil—*USP Reference standards, Related compounds, Assay*	32	1	94
Fluorometholone Acetate (new)	31	5	1371
Flurazepam Hydrochloride—*Identification*	31	3	766
Fluticasone Propionate—*Definition, Bromofluoromethane content* (delete)	32	2	337
Fluticasone Propionate Nasal Spray (new)	32	2	339
Fluvastatin Sodium—*Packaging and storage, USP Reference standards, Identification, Chromatographic purity*	32	1	103
Fluvastatin Capsules—*USP Reference standards, Identification, Chromatographic purity*	32	1	105
Fluvoxamine Maleate—*Definition, Maleic acid* (delete), *Assay*	32	5	1449
Fluvoxamine Maleate Tablets (new)	30	5	1622
Formoterol Fumarate (new)	32	5	1450
Fosinopril Sodium (new)	32	3	789
Fosinopril Sodium Tablets (new)	30	6	2004
Fosinopril Sodium and Hydrochlorothiazide Tablets (new)	30	6	2006
Gabapentin (new)	31	1	50
Ganciclovir Oral Suspension (new)	32	1	113
Gemcitabine for Injection—*USP Reference standards, Chromatographic purity*	31	6	1630

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Gemcitabine Hydrochloride—*USP Reference standards*	32	1	114
Glipizide—*USP Reference standards, Related compounds, Assay*	32	5	1453
Glipizide and Metformin Hydrochloride Tablets (new)	32	4	1076
Glutaral Concentrate—*Specific gravity*	31	3	766
Glyburide Tablets—*Labeling* (add), *Dissolution* (add)	32	4	1080
Glyburide and Metformin Hydrochloride Tablets (new)	31	3	766
Gonadorelin Acetate (new)	30	4	1250
Goserelin Acetate (new)	32	3	792
Helium—*Definition, Packaging and storage*	31	4	1077
Hepatitis B Virus Vaccine Inactivated (delete)	31	6	1641
Hydrocodone Bitartrate—*USP Reference standards Ordinary impurities* (delete), *Related compounds* (add)	30	5	1628
Hydrocodone Bitartrate and Homatropine Methylbromide Tablets (new)	30	3	853
Hydrocortisone Tablets—*USP Reference standards, Uniformity of dosage units, Assay*	32	4	1083
Hydroxyzine Hydrochloride—*Definition, USP Reference standards, Chromatographic purity, Assay*	32	5	1456
Hypromellose—*Harmonization*	32	5	1573
Hypromellose Ophthalmic Solution—*Assay*	32	4	1084
Ibuprofen—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	796
Ibuprofen Oral Suspension—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	796
Ibuprofen Tablets—*USP Reference standards, Limit of ibuprofen related compound C, Assay*	32	3	798
Indinavir Sulfate—*Heavy metals, Method I,* (delete), *Heavy metals* (add), *Chromatographic purity, Assay*	32	2	345
Sodium Iodide I 123 Capsules—*Definition*	31	6	1642
Sodium Iodide I 123 Solution—*Definition, Radionuclidic purity, Bacterial endotoxins, pH*	31	6	1642
Sodium Iodide I 131 Solution—*pH*	31	6	1643
Iodoform—*Molecular weight*	32	1	115
Irbesartan—*Limit of azide, Related compounds, Assay*	32	4	1084
Irbesartan Tablets (new)	32	3	799
Irbesartan and Hydrochlorothiazide Tablets (new)	29	4	1036
Isosorbide Mononitrate Tablets (new)	29	5	1513
Isosorbide Mononitrate Extended-Release Tablets (new)	31	4	1082
Ivermectin—*Specific rotation, Limit of alcohol and formamide*	31	6	1645
Ketoprofen—*Assay*	31	3	772
Ketoprofen Extended-Release Capsules (new)	31	5	1378
Labetalol Hydrochloride Oral Solution (new)	32	1	116
Labetalol Hydrochloride Oral Suspension (new)	32	1	117
Lamivudine—*Assay*	32	2	346
Leflunomide (new)	31	5	1380
Leflunomide Tablets (new)	31	5	1383
Leuprolide Acetate (new)	30	3	882
Levocabastine Hydrochloride (new)	31	6	1647
Levodopa—*Related compounds*	32	4	1085
Levofloxacin (new)	32	2	347
Lidocaine and Prilocaine Cream (new)	31	4	1087
Lindane—*Definition, Assay*	31	6	1648
Lipid Injectable Emulsion (new)	32	2	350
Lisinopril Tablets—*Assay*	32	4	1086
Loperamide Hydrochloride Oral Solution—*Assay*	32	2	353
Lovastatin—*Assay*	32	1	118
Lovastatin Tablets—*Identification, Dissolution, Assay*	32	5	1458
Magaldrate and Simethicone Tablets—*Title* (name change)	29	6	1918
Magaldrate and Simethicone Chewable Tablets (new)	29	6	1919
Milk of Magnesia—*Limit of calcium* (delete)	32	2	353
Magnesium Carbonate and Citric Acid for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	419
Magnesium Chloride—*Identification*	31	2	420

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Magnesium Citrate Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	420
Magnesium Citrate for Oral Solution—*USP Reference standards* (add), *Content of anhydrous citric acid, Other requirements (delayed implementation to January 1, 2009)*	31	2	421
Magnesium Hydroxide—*Lead* (delete), *Limit of lead* (add)	32	4	1087
Magnesium Hydroxide Paste—*Definition, Soluble alkalies, Limit of lead* (add)	32	4	1088
Mangafodipir Trisodium—*Limit of residual solvents*	31	6	1650
Mannitol Injection—*Labeling*	32	2	263
Meloxicam (new)	31	1	57
Meloxicam Tablets (new)	32	5	1460
Metformin Hydrochloride Extended-Release Tablets (new)	31	3	772
Methylcellulose Ophthalmic Solution—*Identification*	31	3	780
Methylcellulose Oral Solution—*Identification*	31	3	780
Methylcellulose Tablets—*Identification*	31	3	780
Methyldopa Oral Suspension—*USP Reference standards, Limit of methyldopa-glucose reaction product* (delete)	32	2	354
Methylprednisolone—*Chromatographic purity*	32	2	354
Metolazone Oral Suspension (new)	32	1	119
Metoprolol Tartrate—*Chromatographic purity*	32	4	1089
Metoprolol Tartrate Oral Solution (new)	32	1	121
Metoprolol Tartrate Oral Suspension (new)	32	1	122
Metronidazole Benzoate—*USP Reference standards, Related compounds*	31	3	781
Miconazole Nitrate Cream—*Identification*	32	1	123
Mirtazapine—*Heavy metals*	31	6	1650
Mitoxantrone Injection—*Packaging and storage*	32	2	355
Modafinil (new)	30	5	1634
Modafinil Tablets (new)	30	5	1636
Morantel Tartrate—*pH*	32	2	355
Morphine Sulfate Extended-Release Capsules—*Packaging and storage* (add)	32	1	124
Mupirocin Calcium (new)	31	2	430
Mupirocin Cream (new)	31	2	432
Naphazoline Hydrochloride—*Definition, Assay*	31	4	1093
Naproxen Delayed-Release Tablets—*Packaging and storage*	32	1	124
Narasin Granular—*Molecular weight, Assay*	32	1	124
Narasin Premix—*Assay*	32	1	126
Naratriptan Hydrochloride—*Assay*	32	5	1462
Nefazodone Hydrochloride—*Related compounds*	32	5	1462
Nefazodone Hydrochloride Tablets (new)	32	3	804
Netilmicin Sulfate—*Definition, Assay*	32	4	1089
Nevirapine Oral Suspension (new)	32	4	1090
Nevirapine Tablets (new)	32	3	807
Nimodipine—*Identification, Related compounds*	32	2	360
Nitrous Oxide—*Definition, Packaging and storage, Assay*	31	4	1099
Norgestimate—*USP Reference standards, Chromatographic purity*	32	4	1094
Norgestimate and Ethinyl Estradiol Tablets (new)	29	1	87
Ofloxacin—*Chromatographic purity* (delete), *Related compounds* (add)	30	4	1274
Ondansetron Hydrochloride—*Limit of ondansetron related compound D, Assay*	32	1	126
Ondansetron Hydrochloride Oral Suspension (new)	32	1	127
Ondansetron Injection—*Chromatographic purity*	32	4	1096
Ondansetron Oral Solution—*Packaging and storage* (add), *Limit of ondansetron related compound D, Related compounds*	32	1	128
Ondansetron Orally Disintegrating Tablets—*Dissolution*	32	5	1463
Orphenadrine Citrate Injection—*Assay*	31	6	1651
Oxandrolone—*Ordinary impurities* (delete), *Related compounds* (add)	31	1	64
Oxandrolone Tablets—*Dissolution*	32	5	1464
Oxaprozin—*Packaging and storage* (add)	32	1	130
Oxaprozin Tablets—*Packaging and storage* (add)	32	1	130
Oxybutynin Chloride—*Related compounds*	32	3	810
Oxybutynin Chloride Extended-Release Tablets (new)	31	6	1652

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Oxycodone Hydrochloride Extended-Release Tablets (new)	31	4	1104
Oxygen—*Definition, Packaging and storage*	31	4	1107
Oxygen 93 Percent—*Definition, Packaging and storage*	31	4	1107
Paclitaxel—*USP Reference standards, Related compounds*	32	2	361
Pamidronate Disodium for Injection—*Packaging and storage, Bacterial endotoxins*	32	5	1465
Pancuronium Bromide Injection (new)	32	4	1097
Paricalcitol—*Identification, Chromatographic purity, Assay*	32	1	132
Paroxetine Hydrochloride—*Assay*	32	3	811
Pectin—*Identification*	31	3	783
Penicillamine Capsules—*Dissolution*	31	2	436
Pentazocine and Acetaminophen Tablets (new)	28	6	1838
Pentobarbital Sodium—*Labeling* (add), *USP Reference standards, Other requirements* (add)	31	1	73
Pentobarbital Sodium Injection—*Identification, Assay*	32	2	364
Permethrin (new)	32	4	1100
Permethrin Cream (new)	32	4	1102
Petrolatum (new)—*Harmonization*	28	2	569
White Petrolatum (new)—*Harmonization*	28	2	570
Phenytoin Tablets—*Title* (name change)	29	6	1965
Phenytoin Chewable Tablets (new)	29	6	1965
Piperacillin and Tazobactam Injection (new)	31	2	437
Piperacillin and Tazobactam for Injection (new)	31	2	439
Piroxicam Cream (new)	32	1	134
PEG 3350 and Electrolytes for Oral Solution—*Title, Definition, Assay for potassium and sodium*	32	4	1104
Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution—*USP Reference standards* (add), *Assay for anhydrous citric acid (delayed implementation to January 1, 2009)*	31	2	440
Potassium Bitartrate—*Limit of ammonia*	31	3	786
Potassium Citrate Extended-Release Tablets—*USP Reference standards* (add), *Assay (delayed implementation to January 1, 2009)*	31	2	443
Potassium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	444
Potassium Iodide Oral Solution—*Definition*	31	3	786
Potassium Perchlorate—*USP Reference standards* (delete), *Assay*	32	2	364
Potassium Sodium Tartrate—*Limit of ammonia*	31	3	787
Pravastatin Sodium (new)	32	3	813
Pravastatin Sodium Tablets (new)	32	3	817
Prednicarbate Cream (new)	32	3	819
Prednicarbate Ointment (new)	32	3	822
Prednisolone Sodium Phosphate—*USP Reference standards, Identification*	32	2	365
Promethazine Hydrochloride—*USP Reference standards, Related compounds*	32	4	1105
Promethazine Hydrochloride Tablets—*USP Reference standards, Related compounds, Assay*	32	4	1107
Pseudoephedrine Sulfate—*Ordinary impurities*	32	1	135
Pyrantel Pamoate—*Limit of iron*	32	5	1465
Pyridoxine Hydrochloride Injection—*Assay*	32	2	369
Quazepam Tablets—*USP Reference standards, Assay*	32	2	370
Quinapril Tablets—*Packaging and storage*	29	4	1071
Quinidine Sulfate Oral Suspension (new)	32	1	136
Ramipril—*Definition, Assay*	31	3	787
Oral Rehydration Salts—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	5	1399
Rifampin and Isoniazid Capsules—*Dissolution*	30	2	533
Rifampin, Isoniazid, and Pyrazinamide Tablets—*Dissolution*	30	2	534
Risperidone (new)	31	6	1659
Risperidone Tablets (new)	32	4	1109
Ritonavir—*Identification, X-ray diffraction* (add), *Related compounds*	32	4	1113
Ropivacaine Hydrochloride Injection (new)	32	2	374
Rubella and Mumps Virus Vaccine Live (delete)	31	6	1662
Saccharin Calcium—*Identification*	32	4	1114

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Saccharin Sodium—*Identification*	32	4	1114
Saquinavir Capsules—*Dissolution*	32	3	824
Schick Test Control (delete)	31	6	1662
Senna—*Title, Definition, Packaging and storage, Labeling* (add), *USP Reference standards* (add), *Botanic characteristics, Identification, Microbial enumeration* (add) *Loss on drying* (add), *Total ash* (add), *Assay* (add)	32	1	137
Senna Pods (new)	32	1	140
Sennosides—*Definition, Packaging and storage, Residue on ignition*	32	1	141
Sevoflurane (new)	30	1	178
Simvastatin—*Identification, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	32	1	141
Sodium Bicarbonate—*Normal carbonate, Limit of ammonia*	32	5	1465
Sodium Chloride—*Limit of phosphates*	31	5	1401
Sodium Chloride—*Identification, Loss on drying, Limit of potassium (postponed indefinitely)*	32	2	264
Sodium Fluoride—*Assay*	32	5	1466
Sodium Fluoride Oral Solution—*Assay*	32	5	1466
Sodium Fluoride and Phosphoric Acid Topical Solution (delete)	32	3	824
Spironolactone and Hydrochlorothiazide Tablets—*Dissolution*	32	2	376
Streptomycin Sulfate—*Assay*	32	5	1467
Sulfamethazine Granulated—*Assay*	31	3	797
Sumatriptan Succinate Oral Suspension (new)	32	1	144
Talc—*Packaging and storage* (add), *Limit of iron, Limit of calcium, Limit of aluminum*	31	6	1662
Tazobactam (new)	31	4	1116
Temazepam—*Identification*	32	1	145
Terbutaline Sulfate Inhalation Aerosol—*USP Reference standards, Assay*	31	2	450
Thalidomide—*Microbial limits, Chromatographic purity*	32	5	1467
Thalidomide Capsules—*Microbial limits* (add)	32	5	1468
Thiabendazole Tablets—*Title* (name change)	29	6	1991
Thiabendazole Chewable Tablets (new)	29	6	1991
Thimerosal—*Identification*	32	1	147
Thioridazine Hydrochloride—*Identification*	31	3	798
Tiagabine Hydrochloride—*Identification, Chromatographic purity*	32	5	1468
Tiamulin Fumarate—*Chemical name, Definition, Melting temperature, Chromatographic purity*	32	4	1115
Tilmicosin—*Definition, Related compounds, Assay*	31	3	798
Tizanidine Tablets (new)	32	1	147
Topiramate (new)	30	4	1307
Tramadol Hydrochloride (new)	31	2	458
Tramadol Hydrochloride Tablets (new)	31	2	462
Travoprost (new)	32	4	1115
Travoprost Ophthalmic Solution (new)	32	4	1118
Triamcinolone Acetonide—*USP Reference standards, Assay*	31	3	800
Triamcinolone Diacetate—*Definition, Identification*	32	4	1120
Tricitrates Oral Solution—*USP Reference standards* (add), *Assay for citrate (delayed implementation to January 1, 2009)*	31	2	465
Triclosan—*Assay*	32	2	377
Crystallized Trypsin—*Definition*	32	3	779
Ursodiol Capsules—*Dissolution*	31	3	800
Valganciclovir Hydrochloride (new)	32	2	379
Valganciclovir Tablets (new)	32	2	384
Valsartan (new)	32	1	150
Valsartan and Hydrochlorothiazide Tablets (new)	31	4	1123
Valproic Acid Injection (new)—*Title (delayed implementation to October 1, 2008)*	32	2	387
Vancomycin Hydrochloride—*USP Reference standards, Limit of monodechlorovancomycin* (add)	30	6	2055
Vasopressin—*Identification*	31	4	1127
Verapamil Hydrochloride—*USP Reference standards Identification, Chromatographic purity*	32	2	389
Verapamil Hydrochloride Injection—*USP Reference standards, Related compounds*	32	1	154
Verapamil Hydrochloride Oral Solution (new)	32	1	155
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Vinblastine Sulfate—*USP Reference standards*	32	5	1470
Vinblastine Sulfate for Injection—*USP Reference standards*	32	5	1470
Vincristine Sulfate—*USP Reference standards*	32	5	1470
Vincristine Sulfate Injection—*USP Reference standards*	32	5	1470
Vincristine Sulfate for Injection—*USP Reference standards*	32	5	1470
Vinorelbine Injection—*Related compounds, Assay*	32	5	1471
Vinorelbine Tartrate—*Related compounds, Assay*	32	5	1471
Pure Steam (new)	31	2	467
Water for Hemodialysis—*Bacterial endotoxins*	31	2	468
Sterile Water for Inhalation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add)	31	3	802
Sterile Water for Injection—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add)	31	3	803
Sterile Water for Irrigation—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add)	31	3	804
Sterile Purified Water—*pH* (delete), *Ammonia* (delete), *Calcium* (delete), *Carbon dioxide* (delete), *Chloride* (delete), *Sulfate* (delete), *Conductivity* (add)	31	3	804
Zidovudine Tablets—*USP Reference standards, Related compounds, Assay*	32	1	158
Zinc Chloride Injection—*Assay*	32	5	1473
<u>*Dietary Supplements Monographs*</u>			
Ademetionine Disulfate Tosylate (new)	31	2	469
Acesulfame Potassium—*Packaging and storage* (add), *Limit of fluoride*	31	3	811
Cat's Claw (new)	32	4	1120
Powdered Cat's Claw (new)	32	4	1124
Powdered Cat's Claw Extract (new)	32	4	1124
Cat's Claw Capsules (new)	32	4	1126
Cat's Claw Tablets (new)	32	4	1127
Black Cohosh (new)	32	4	1128
Powdered Black Cohosh (new)	32	4	1132
Powdered Black Cohosh Extract (new)	32	4	1133
Black Cohosh Fluidextract (new)	32	4	1134
Black Cohosh Tablets (new)	32	4	1135
Ginger—*Packaging and storage, Labeling, USP Reference standards, Identification, Microbial enumeration, Alcohol-soluble extractives, Limit of shogaols, Content of gingerols and gingerdiones*	32	1	160
Powdered Ginger—*Packaging and storage, USP Reference standards*	32	1	162
Ginger Capsules—*USP Reference standards, Content of gingerols, gingerdiones, and shogaols*	32	1	163
Ginger Tincture—*USP Reference standards, Thin-layer chromatographic identification test, Microbial enumeration, Content of gingerols*	32	1	163
Ginkgo—*Definition, Packaging and storage, USP Reference standards, Thin-layer chromatographic identification test, Microbial enumeration, Content of terpene lactones*	32	1	164
Powdered Ginkgo Extract (new)	32	1	166
Ginkgo Capsules (new)	32	1	172
Ginkgo Tablets (new)	32	1	174
Glucosamine Tablets—*Disintegration and dissolution*	32	4	1137
Glucosamine and Methylsulfonylmethane Tablets (new)	32	4	1137
Glucosamine, Chondroitin Sulfate Sodium and Methylsulfonylmethane Tablets (new)	32	4	1138
Tomato Extract Containing Lycopene—*Microbial enumeration, Limit of aflatoxins*	30	2	578
Maleic Acid—*Identification*	31	3	815
Maltose—*Water*	31	3	815
Maritime Pine—*Identification, Content of procyanidins*	32	4	1140
Maritime Pine Extract—*Identification, microbial enumeration, Content of procyanidins*	32	4	1142
Methylsulfonylmethane (new)	32	3	826
Methylsulfonylmethane Tablets (new)	32	3	827
Minerals Capsules—*Definition*	32	5	1474
Minerals Tablets—*Definition*	32	5	1474

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Fish Oil Containing Omega-3 Acids (new)	31	2	474
Fish Oil Containing Omega-3 Acids Capsules (new)	31	2	481
Olive Oil—*Definition, Labeling* (add), *Teaseed oil*	31	3	815
Phenoxyethanol—*Chromatographic purity, Assay*	31	3	816
Polyethylene Glycol (new)—*Harmonization*	31	3	897
Polyoxyl 10 Oleyl Ether—*Free ethylene oxide*	31	3	816
Polyoxyl 20 Oleyl Cetostearyl Ether—*Free ethylene oxide*	31	3	817
Sodium Benzoate—*USP Reference standards* (add), *Identification*	31	3	818
Sucrose (new)—*Harmonization*	31	3	902
Sugar Spheres—*Identification, Specific rotation*	31	3	819
Tagatose (new)	31	3	819
Thymol—*USP Reference standards* (add), *Identification*	31	3	821
Ubidecarenone—*USP Reference standards, Assay*	31	1	86
Ubidecarenone Capsules—*USP Reference standards, Assay*	31	1	86
Valerian—*Packaging and storage, Extractable matter, Microbial enumeration*	32	2	394
Powdered Valerian—*Packaging and storage, Labeling, Botanic characteristics*	32	2	395
Valerian Tablets—*Packaging and storage, USP Reference standards*	32	2	395
Oil- and Water-Soluble Vitamins with Minerals Capsules—*Definition*	32	5	1474
Oil- and Water-Soluble Vitamins with Minerals Oral Solution—*Definition*	32	5	1475
Oil- and Water-Soluble Vitamins with Minerals Tablets—*Definition*	32	5	1476
Water-Soluble Vitamins with Minerals Capsules—*Definition*	32	5	1476
Water-Soluble Vitamins with Minerals Oral Solution—*Definition*	32	5	1477
Water-Soluble Vitamins with Minerals Tablets—*Definition*	32	5	1477
Xanthan Gum—*Assay*	31	3	821
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⟨1⟩ Injections—*Labels and Labeling, Packaging*	32	2	402
⟨1⟩ Injections—*Packaging—Printing on Ferrules and Cap Overseals (delayed implementation to February 1, 2009)*	32	2	406
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	28	2	433
	28	3	839
	28	5	1468
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	29	5	1601
	29	6	2022
	30	2	613
	30	4	1338
	30	5	1674
	30	6	2092
	31	1	99
	31	2	507
	31	3	822
	31	4	1154
	31	5	1433
	31	6	1680
	32	1	181
	32	2	407
	32	3	829
	32	4	1161
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⟨41⟩ Weights and Balances—*Introduction*	32	2	514
⟨55⟩ Biological Indicators—Resistance Performance Tests—*Total Viable Spore Count, D-Value Determination*	30	1	212
⟨121⟩ Insulin Assays—*Appendix* (add)	30	5	1675
⟨231⟩ Heavy Metals—*Method II*	32	1	182
⟨267⟩ Porosimetry by Mercury Intrusion (new)—*Harmonization*	31	3	905
⟨311⟩ Alginates Assay—*System Suitability*	32	2	516
⟨345⟩ Assay for Citric Acid/Citrate and Phosphate (new)	31	2	514

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⟨381⟩ Elastomeric Closures for Injections—*Introduction, Characteristics, Identification Tests, Test Procedures (delayed implementation to January 1, 2006)*	30	1	220
⟨401⟩ Fats and Fixed Oils—*Acid Value (Free Fatty Acids)*	32	5	1492
⟨429⟩ Light Diffraction Measure of Particle Size (new)—*Harmonization*	31	4	1234
⟨466⟩ Ordinary Impurities—*Introduction, Reporting and Specifications* (add), *Methodology* (add), *Procedure*	32	5	1493
⟨467⟩ Residual Solvents—*Introduction; Classification of Residual Solvents by Risk Assessment; Methods for Establishing Exposure Limits; Options for Describing Limits of Class 2 Residual Solvents; Analytical Procedures* (add); *Reporting Levels of Residual Solvents* (add); *Limits of Residual Solvents; Identification, Control, and Quantification of Residual Solvents; Glossary*	32	5	1494
⟨611⟩ Alcohol Determination—*Introduction, Method IIa, Method IIb*	32	3	830
⟨616⟩ Bulk Density and Tapped Density—*Harmonization*	31	3	909
⟨621⟩ Chromatography—*Introduction, Thin-Layer Chromatography, Interpretation of Chromatograms, System Suitability, Chromatographic Reagents*	32	4	1163
⟨644⟩ Conductivity (new)	31	3	841
⟨660⟩ Containers—Glass (new)	32	4	1171
⟨661⟩ Containers—Plastics (entire chapter revised)	32	4	1176
⟨671⟩ Containers—Performance Testing—*Introduction, Multiple-Unit Containers for Capsules and Tablets, Multiple-Unit Containers for Capsules and Tablets (Without Closure)*(add), *Multiple-Unit Containers and Unit-Dose Containers for Liquids* (add), *Light Transmission Test* (add)	32	4	1193
⟨681⟩ Repackaging into Single-Unit Containers and Unit-Dose Containers for Nonsterile Solid and Liquid Dosage Forms (new)	32	4	1197
⟨699⟩ Density of Solids (new)—*Harmonization*	31	3	912
⟨721⟩ Distilling Range—*Method II*	32	4	1200
⟨729⟩ Globule Size Distribution in Lipid Injectable Emulsions (new)	31	5	1448
⟨730⟩ Plasma Spectrochemistry—*Sample Preparation, Sample Introduction, Standard Preparation, ICP, ICP–AES, ICP–MS, Glossary*	32	3	836
⟨785⟩ Osmolality and Osmolarity—*Osmolarity, Measurement of Osmolality*	32	3	850
⟨797⟩ Pharmaceutical Compounding—Sterile Preparations—*Introduction; Organization of This Chapter, Definitions* (add); *Responsibility of Compounding Personnel; CSP Microbial Contamination Risk Levels; Immediate Use CSPs* (add); *Single-Dose and Multiple-Dose Containers* (add); *Hazardous Drugs as CSPs* (add); *Radiopharmaceuticals as CSPs* (add); *Verification of Compounding Accuracy and Sterility; Personnel Training and Evaluation in Aseptic Manipulation Skills; Environmental Quality and Control; Suggested Standard Operating Procedures; Environmental Monitoring* (add); *Processing; Finished Preparation Release Checks and Tests; Storage and Beyond-Use Dating; Maintaining Sterility, Purity, and Stability of Dispensed and Distributed CSPs; Acronyms* (add), *Appendix*	32	3	852
⟨811⟩ Powder Fineness—*Title, Introduction* (add) *Harmonization*	31	1	228
⟨905⟩ Uniformity of Dosage Units—*Introduction, Content Uniformity, Weight Variation, Criteria*	32	4	1201
⟨921⟩ Water Determination—*Method I (Titrimetric)*	31	2	517
⟨941⟩ X-Ray Diffraction (new)—*Harmonization*	31	4	1241
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⟨1005⟩ Acoustic Emission (new)	32	5	1504
⟨1047⟩ Biotechnology-Derived Articles—Tests (delete)	32	2	516
⟨1052⟩ Biotechnology-Derived Articles—Amino Acid Analysis (new)	32	2	542
⟨1053⟩ Biotechnology-Derived Articles—Capillary Electrophoresis (new)	32	2	559
⟨1054⟩ Biotechnology-Derived Articles—Isoelectric Focusing (new)	32	2	568

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⟨1056⟩ Biotechnology-Derived Articles—Polyacrylamide Gel Electrophoresis (new)	32	2	580
⟨1057⟩ Biotechnology-Derived Articles—Total Protein Assay (new)	32	2	589
⟨1058⟩ Analytical Instrument Qualification (new)	32	2	595
⟨1065⟩ Ion Chromatography—*Apparatus*	32	3	899
⟨1070⟩ Emergency Medical Services Vehicles and Ambulances—Storage of Preparations (new)	32	2	605
⟨1079⟩ Good Storage and Shipping Practices—*Storage in Warehouses, Pharmacies, Trucks, Shipping Docks, and Other Locations; Special Handling; Shipment from Manufacturer to Wholesaler; Shipment from Manufacturer or Wholesaler to Pharmacy; Shipment from Pharmacy to Patient or Customer; Storage of Physician Samples Handled by Sales Representatives in Automobiles; Statements/Labeling of the Immediate Containers or Package Insert*	32	4	1208
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)	31	4	1167
⟨1082⟩ Genotoxicity Testing (new)	30	1	264
⟨1086⟩ Impurities in Official Articles—*Introduction, Initial IND Filing, NDA Filing, Post NDA Approval, ANDA Filing, Definitions*	32	5	1509
⟨1087⟩ Intrinsic Dissolution—*Title, Introduction, Experimental Procedure, Data Analysis and Interpretation*	30	6	2130
⟨1116⟩ Microbiological Evaluation of Clean Rooms and Other Controlled Environments—*Title, Introduction, Establishment of Clean Room Classifications, Importance of a Microbiological Evaluation Program for Controlled Environments, Physical Evaluation of Contamination Control Effectiveness* (add),*Training of Personnel, Critical Factors Involved in the Design and Implementation of a Microbiological Environmental Control Program, Establishment of Sampling Plan and Sites, Establishment of Microbiological Alert and Action Levels in Controlled Environments, Microbial Considerations and Action Levels for Controlled Environments, Methodology and Instrumentation for Quantitation of Viable Airborne Microorganisms, Methodology and Equipment for Sampling of Surfaces for Quantitation of Viable Microbial Contaminants in Controlled Environments, Culture Media and Diluents Used for Sampling or Quantitation, Identification of Microbial Isolates from the Environmental Control Program, Operational Evaluation of the Microbiological Status of Aseptically Filled Products in Clean Rooms and Other Controlled Environments* (delete), *An Overview of the Emerging Technologies for Advanced Aseptic Processing* (delete), *Conclusion* (add), *Glossary*	31	2	524
⟨1118⟩ Monitoring Devices—Time, Temperature, and Humidity—*Electronic Time–Temperature History Recorders*	32	3	900
⟨1120⟩ Raman Spectrometry (entire chapter revised)	32	4	1211
⟨1121⟩ Nomenclature—*Introduction, General Nomenclature Forms* (add), *Salt Nomenclature Policy* (add), *Policy for Postponement Schedules* (add)	32	4	1228
⟨1150⟩ Pharmaceutical Stability—*Controlled Room Temperature and Controlled Cold Temperature*	32	4	1232
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⟨1211⟩ Sterilization and Sterility Assurance of Compendial Articles—*Introduction, Methods of Sterilization, Sterility Testing of Lots, Performance, Observation, and Interpretation*	30	5	1729
⟨1217⟩ Tablet Breaking Force (new)	31	6	1695
⟨1222⟩ Terminally Sterilized Pharmaceutical Products—Parametric Release—*Introduction, General Review, Modes of Sterilization, Summary*	30	5	1741
⟨1226⟩ Verification of Compendial Procedures (new)	32	4	1232
⟨1231⟩ Water for Pharmaceutical Purposes—*Types of Water*	32	5	1528
⟨1232⟩ Instrumentation for Analysis of High Purity Pharmaceutical Waters (new)	30	5	1806
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Ethyl Acrylate and Methyl Methacrylate Copolymer Dispersion (new)	31	4	1141
Ethylcellulose Aqueous Dispersion—*Labeling, Identification*	31	6	1668
High Fructose Corn Syrup (new)	32	4	1151
Gamma Cyclodextrin (new)	31	3	812
Glyceryl Monostearate—*Labeling, USP Reference standards* (delete), *Assay for monoglycerides*	31	6	1669
Hydroxyethyl Cellulose (new)—*Harmonization*	30	2	709
Hydroxypropyl Betadex (new)	32	5	1481
Low-Substituted Hydroxypropyl Cellulose—*Harmonization*	30	1	338
Isomalt—*Identification, Related compounds*	32	4	1154
Magnesium Stearate—*Harmonization*	30	1	340
Nitrogen—*Definition, Packaging and storage, Assay*	31	4	1145
Nitrogen 97 Percent—*Definition, Packaging and storage, Assay*	31	4	1146
Oleyl Oleate (new)	31	6	1670
Palm Kernel Oil (new)	32	5	1486
Polacrilin Potassium—*CAS number, Chemical name*	31	6	1671
Polydextrose (new)	32	4	1155
Polyethylene Glycol—*Harmonization*	31	3	897
Polyethylene Oxide—*Packaging and storage, USP Reference standards, Identification, Heavy metals, Method II* (delete), *Heavy metals* (add), *Limit of free ethylene oxide, Organic volatile impurities, Method I* (delete), *Residual solvents* (delete)	32	2	398
Polyisobutylene—*Loss on drying*	32	3	828
Polyoxyl 10 Oleyl Ether—*Definition, Average polymer length*	32	5	1488
Polyoxyl 35 Castor Oil—*Viscosity*	31	6	1671
Polyvinyl Acetate (new)	32	2	400
Silicon Dioxide (new)—*Harmonization*	31	4	1229
Colloidal Silicon Dioxide (new)—*Harmonization*	31	4	1233
Tribasic Sodium Phosphate—*Loss on ignition*	32	2	402
Rice Starch (new)—*Harmonization*	30	2	721
Sucrose—*Harmonization*	31	3	902
Strawberry Syrup (new)	32	1	179
Tagatose (new)	30	5	1672
Tetrafluoroethane (new)	31	6	1672
Tributyl Citrate—*Assay*	32	1	179
Triethyl Citrate—*Assay*	32	1	180

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
[*PF* 32(1)–*PF* 32(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals*		
	Vol.	*No.*	*Page(s)*
General Notices and Requirements			
Tests and Assays (Foreign Substances and Impurities)	31	3	718
Preservation, Packaging, Storage, and Labeling (Repackaging Instructions)	31	3	718
USP Monographs			
Acetaminophen and Aspirin Tablets—*Dissolution*	30	1	41
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	43
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Phenylpropanolamine—*Dissolution*	30	1	42
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—*Dissolution*	30	1	44
Acetaminophen and Codeine Phosphate Capsules—*Dissolution*	30	1	45
Acetaminophen and Diphenhydramine Citrate Tablets—*Dissolution*	30	1	47
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	47
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	48
Acetohydroxamic Acid Tablets—*Dissolution*	30	1	49
Albendazole Oral Suspension—*Labeling* (delete)	30	4	1163
Albendazole Oral Suspension—*Labeling*	32	1	46
Albumin Human (entire submission)	29	4	992
Albuterol Tablets—			
Dissolution	30	1	50
Dissolution	31	1	40
Allopurinol—*USP Reference standards, Chromatographic purity, Related compounds, Assay*	28	5	1386
Alprazolam Tablets—*Dissolution*	30	5	1582
Amantadine Hydrochloride Capsules—*Dissolution*	30	1	51
Aminosalicylate Sodium Tablets—*Dissolution*	30	1	53
Amphetamine Sulfate Tablets—*Dissolution*	30	1	54
Ampicillin Capsules—*Dissolution*	30	1	55
Ampicillin Tablets—*Dissolution*	30	1	56
Ascorbic Acid Tablets—*Dissolution*	30	1	60
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules—*Dissolution*	30	1	60
Baclofen Tablets—*Dissolution*	30	1	61
Betamethasone Tablets—*Dissolution*	30	1	62
Butalbital, Acetaminophen, and Caffeine Tablets—*Dissolution*	30	1	80
Calcium Lactate Tablets—*Dissolution*	30	1	81
Calcium Pantothenate Tablets—*Dissolution*	30	1	81
Carboxymethylcellulose Sodium Suspension (entire submission)	30	3	812
Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules—*Dissolution*	30	1	83
Citalopram Hydrobromide—*Related compounds*	31	3	742
Citalopram Tablets (new)—*Dissolution, Related compounds*	31	3	745
Colchicine Tablets—*Dissolution*	30	1	91
Cyclizine Hydrochloride Tablets—*Dissolution*	30	1	91
Dextroamphetamine Sulfate Capsules—*Dissolution*	30	1	94
Dextroamphetamine Sulfate Tablets—*Dissolution*	30	1	94
Diethylcarbamazine Citrate Tablets—*Dissolution*	30	1	97
Dihydroergotamine Mesylate—*Identification C, Related alkaloids* (delete), *Chromatographic purity* (add)	29	6	1870
Diphenhydramine Hydrochloride Capsules—*Dissolution*	30	1	97
Diphenhydramine and Pseudoephedrine Capsules—*Dissolution*	30	1	98
Dyphylline and Guaifenesin Tablets—*Dissolution*	30	1	100
Estradiol Transdermal System (new)—*Drug release*	30	4	1201
Ethinyl Estradiol Tablets—*Related compounds*	31	2	402
Ethosuximide Capsules—*Dissolution*	30	1	102

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Fluvastatin Sodium—*Loss on drying* (add), *Water* (delete)	32	1	103
Fluticasone Propionate—*Content of acetone (Procedure)*	31	4	1070
Gabapentin Capsules (new) (entire submission)	28	2	298
Glyburide Tablets—*Dissolution*	29	2	418
Glycopyrrolate Tablets—			
Dissolution	30	1	105
Dissolution (Procedure, Tolerances)	31	4	1077
Guaifenesin Capsules—*Dissolution*	30	1	106
Guaifenesin Tablets—*Dissolution*	30	1	107
Hydrocodone Bitartrate and Acetaminophen Tablets—*Dissolution*	30	1	109
Indocyanine Green—*Definition, Assay*	29	6	1905
Irbesartan Tablets (new)—*Dissolution*	29	4	1035
Isosorbide Dinitrate Sublingual Tablets—			
Dissolution	30	1	113
Dissolution (Procedure, Tolerances)	31	5	1377
Diluted Isosorbide Mononitrate (entire submission)	31	4	1060
Kanamycin Sulfate Capsules—*Dissolution*	30	1	120
Levothyroxine Sodium Oral Solution (new)—*Preview*	31	3	938
Lisinopril Tablets—*Dissolution*	30	1	121
Loperamide Hydrochloride Tablets—*Dissolution*	30	5	1633
Magnesium Oxide—*Bulk density* (add)	29	4	1047
Mebendazole Oral Suspension—*Labeling*	32	1	119
Meclizine Hydrochloride Tablets—*Dissolution*	30	1	127
Meprobamate Tablets—*Dissolution*	30	1	129
Methenamine Tablets—*Dissolution*	30	1	130
Methocarbamol Tablets—*Dissolution*	30	1	130
Methylphenidate Hydrochloride Tablets—*Dissolution*	30	1	131
Morphine Sulfate Extended-Release Capsules—*Packaging and storage*	28	6	1822
Nadolol and Bendroflumethiazide Tablets—*Dissolution*	30	1	132
Nefazodone Hydrochloride (new)—*Related compounds*	31	4	1094
Nefazodone Hydrochloride Tablets (new) (entire submission)	31	4	1096
Neostigmine Bromide Tablets—*Dissolution*	30	1	133
Niacinamide Tablets—*Dissolution*	30	1	139
Ondansetron Orally Disintegrating Tablets (new)—*Disintegration, Dissolution*	30	6	2024
Oxaprozin—*Packaging and storage*	29	4	1059
Oxaprozin Tablets—*Packaging and storage*	29	4	1061
Oxybutynin Chloride Extended-Release Tablets (new) (entire submission)	30	4	1276
Oxycodone and Acetaminophen Capsules—*Dissolution*	30	1	151
Oxycodone and Acetaminophen Tablets—*Dissolution*	30	1	151
Oxycodone and Aspirin Tablets—*Dissolution*	30	1	152
PEG 3350 and Electrolytes for Oral Solution (entire submission)	31	5	1393
Penicillamine Capsules—*Dissolution*	30	1	153
Phentermine Hydrochloride Capsules—*Dissolution*	30	1	159
Phentermine Hydrochloride Tablets—*Dissolution*	30	1	160
Phenylpropanolamine Hydrochloride Capsules—*Dissolution*	30	1	161
Phenylpropanolamine Hydrochloride Tablets—*Dissolution*	30	1	162
Pimozide Tablets—*Dissolution*	30	1	164
Pindolol Tablets—*Dissolution*	30	1	165
Piperazine Citrate Tablets—*Dissolution*	30	1	165
Procyclidine Hydrochloride Tablets—*Dissolution*	30	1	169
Propantheline Bromide Tablets—*Dissolution*	30	1	170
Propoxyphene Hydrochloride and Acetaminophen Tablets—*Dissolution*	30	1	170
Pseudoephedrine Hydrochloride Tablets—*Dissolution*	30	1	172
Pyridoxine Hydrochloride Tablets—*Dissolution*	30	1	177
Pyrilamine Maleate Tablets—*Dissolution*	30	1	177
Ranitidine Oral Solution—*USP Reference standards, Identification, Antimicrobial effectiveness testing* (delete), *Chromatographic purity, Assay*	30	6	2036

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals*		
	Vol.	*No.*	*Page(s)*
Simvastatin—*Identification B, Chromatographic purity, Limit of lovastatin* (delete), *Assay*	31	3	792
Sodium Citrate and Citric Acid Oral Solution—*USP Reference standards* (add), *Assay for sodium citrate*	31	3	797
Sodium Salicylate Tablets—*Dissolution*	32	3	825
Sorbitol Solution—*Microbial limits* (add)	29	4	1078
Spironolactone Oral Suspension (new) (entire submission)	30	3	929
Spironolactone and Hydrochlorothiazide Oral Suspension (new) (entire submission)	30	3	930
Sumatriptan Succinate (new)—*Preview*	27	5	3157
Terbutaline Sulfate Tablets—*Dissolution*	31	1	76
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets—*Dissolution*	30	1	189
Thiamine Hydrochloride Tablets—*Dissolution*	30	1	190
Timolol Maleate Tablets—*Dissolution*	30	1	191
Titanium Dioxide (new) (entire submission)	30	4	1301
Titanium Dioxide (new) (entire submission)	30	4	1304
Triprolidine and Pseudoephedrine Hydrochlorides Tablets—*Dissolution*	30	1	192
Valproic Acid Injection (new) (entire submission)	31	3	801
	31	5	1412
Vecuronium Bromide for Injection (new)—*Preview*	25	4	8449
Dietary Supplements Monographs			
Ginkgo Capsules (new) (entire submission)	27	2	2238
Ginkgo Tablets (new) (entire submission)	27	2	2240
Powdered Ginkgo Extract (new) (entire submission)	27	2	2233
Asian Ginseng Capsules (new)—*Dissolution*	30	2	571
American Ginseng Capsules (new)—*Dissolution*	30	2	565
American Ginseng Tablets—*Dissolution*	30	2	567
Lutein—*Identification A, Zeaxanthin and other related compounds, Content of lutein*	31	4	1133
Lutein Preparation—*Identification A, Zeaxanthin and other related compounds, Content of lutein*	31	4	1134
Valerian Capsules (new)—*Disintegration and dissolution*	27	1	1825
USP General Test Chapters			
⟨1⟩ Injections—*Packaging*	31	1	192
⟨11⟩ USP Reference Standards			
USP 23-epi-26-Deoxyacetin RS	28	5	1468
USP Fluvastatin for System Suitability RS (add)	31	1	99
USP Human Albumin RS	29	6	2022
USP Polyoxyl 35 Castor Oil RS	30	5	1674
⟨41⟩ Weights and Balances (entire submission)	31	2	508
⟨267⟩ Porosimetry by Mercury Intrusion (new) (entire submission)	28	3	893
⟨386⟩ Environmentally Sensitive Preparations (new) (entire submission)	30	5	1680
⟨429⟩ Light Diffraction Measure of Particle Size (new) (entire submission)	28	3	895
⟨616⟩ Bulk Density and Tapped Density (entire submission)	28	3	901
⟨621⟩ Chromatography—*System Suitability (All revisions after the first two paragraphs, through the end up to Glossary)*	30	6	2094
⟨661⟩ Containers—*Test Methods and Acceptance Criteria for Polyethylene and Polypropylene Closure Resins and Molded Components* (add)	29	2	490
⟨699⟩ Density of Solids—*Preview*	28	2	603
⟨711⟩ Dissolution—*Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets* (delete), *Interpretation*	30	1	234
USP General Information Chapters			
⟨1058⟩ Analytical Instrument Qualification (new) (entire submission)	31	1	233
⟨1078⟩ Good Manufacturing Practices for Bulk Pharmaceutical Excipients (entire submission)	28	5	1504

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[*PF* 32(1)–*PF* 32(6)] *(Continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
⟨1080⟩ Bulk Pharmaceutical Excipients—Certificate of Analysis (new)—*Preview*	28	5	1650
⟨1089⟩ In Vitro, Absorption-Indicating Cell Culture System (new)—*Preview*	25	5	8733
⟨1092⟩ The Dissolution Procedure: Development and Validation (new)—*Preview*	30	1	351
⟨1195⟩ Significant Change Guide for Bulk Pharmaceutical Excipients (new)—*Preview*	28	5	1662
Dietary Supplements Chapters			
⟨2040⟩ Disintegration and Dissolution of Nutritional Supplements—*Preview*	28	5	1673
Reagents, Indicators, and Solutions			
1,4-Butanediol (add)—*Preview*	25	5	8747
Isoferulic Acid (add)	27	4	2837
1-Vinyl-2-pyrrolidone	31	1	108
Reference Tables			
Container Specifications			
Black Cohosh Tablets	27	4	2874
Citalopram Hydrobromide Tablets (add)	31	3	859
Description and Relative Solubility			
Magnesium Oxide	29	4	1262
Titanium Dioxide (add)	30	4	1405
NF Monographs			
Alfadex—*Packaging and storage*	30	1	202
Black Cohosh (entire submission)	28	5	1455
Powdered Black Cohosh (entire submission)	28	5	1460
Powdered Black Cohosh Extract (entire submission)	28	5	1461
Black Cohosh Tablets (entire submission)	28	5	1462
Corn Syrup (new) (entire submission)	28	2	403
High Fructose Corn Syrup (new) (entire submission)	28	2	408
Magnesium Stearate—*Microbial limits*	29	6	2018
Sodium Caprylate—*Packaging and storage*	30	3	990
Stearic Acid—*Microbial limits* (add)	29	2	480
Purified Stearic Acid—*Other requirements, Microbial limits*	29	3	706

†New cancellations in *PF* 32(6).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

MONOGRAPHS (NF)

Readers are requested to review the proposal carefully and to send comments to USP.

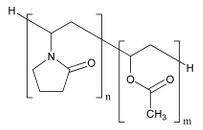
(EM2: K. Moore) RTS—C44007

BRIEFING

Copovidone. The Japanese Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of the compendial standards for the *Copovidone* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **OFFICIAL INQUIRY STAGE 4** document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Harmonization Stage 4 draft prepared by the Japanese Pharmacopoeia. Differences between the **OFFICIAL INQUIRY STAGE 4** document and the current *NF* monograph (see *NF 24* page 3316) include the following:

1. *Definition*—Nitrogen and vinyl acetate acceptance criteria are added. The K-value range is removed but indicated in the test for *K-value.*
2. *Description*—Consistent with Stage 4 document.
3. *Packaging and storage*—No change. The *USP* text is retained as a nonharmonized attribute.
4. *Labeling*—No change.
5. *Clarity and color of solution*—No change.
6. *Identification A*—A drying step added to infrared absorption ID; *Identification B*— A wet chemistry ID (colorimetric test with iodine TS) retained as a nonharmonized attribute.
7. *pH*—Added.
8. *Loss on drying*—No change.
9. *Residue on ignition*—No change.
10. *Limit of aldehydes*—A change in the use of reagents: pyrophosphate buffer instead of potassium phosphate buffer; additional details to sample preparation were also added.
11. *Limit of hydrazine*—Differences in preparation of the *Test solution* (no pH adjustment required) and new developing solution for evaluation by TLC (methanol/water) are added.
12. *Limit of peroxides*—No change.
13. *Limit of monomers*—The titration method is replaced with a new HPLC method consistent with the *Povidone* monograph.
14. *Nitrogen*—Modifications were made to the experimental procedure. Different reagents are used in the digestion procedure.
15. *K-value*—No change.
16. *Assay*—The test was formerly known as *Content of copolymerized vinyl acetate.* The calculation is modified to eliminate reference to the *Saponification Value* calculation in the *USP* general test chapter *Fats and Fixed Oils* ⟨401⟩.

Copovidone



$(C_6H_9NO)_n + (C_4H_6O_2)_m$

$(C_6H_9NO: \quad 111.14)_n + (C_4H_6O_2: \quad 86.09)_m$

Copolymer of 1-ethenylpyrrolidin-2-one and ethenyl acetate.

(Poly[(2-oxopyrrolidin-1-yl)ethylene-co-(1-acetoxyethylene)]) [*25086-89-9*].

» Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in the mass proportion of 3 : 2. It contains not less than 7.0% and not more than 8.0% of nitrogen (N:14.01) and not less than 35.3% and not more than 42.0% of vinyl acetate ($C_4H_6O_2$:86.09), calculated on the dried basis.

Packaging and storage—Preserve in tight containers. No storage requirements specified.

Labeling—Label it to indicate its nominal K-value.

USP Reference standards ⟨11⟩—*USP Copovidone RS.*

Clarity and color of solution—Dissolve 1.0 g in 10 mL of water: the solution is clear or slightly opalescent and colorless to pale yellow or pale red.

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: To 5 mL of a solution (1 in 50) add a few drops of iodine TS: a deep red color is produced.

pH ⟨791⟩ **:** between 3.0 and 7.0, in a solution (1 in 10).

Loss on drying ⟨731⟩**—**Dry 0.5 g at 105° for 3 hours: it loses not more than 5.0% of its weight.

Residue on ignition ⟨281⟩**:** not more than 0.1%.

Limit of aldehydes—

pH 9.0 Pyrophosphate buffer, 0.05 M—Transfer 8.7 g of monobasic potassium pyrophosphate to a 500-mL volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N potassium hydroxide to a pH of 9.0, dilute with water to volume, and mix.

Blank solution—Use water.

Standard solution—Dissolve 0.140 g of acetaldehyde ammonia trimer trihydrate in 200.0 mL of water, and mix. Pipet 1.0 mL of this solution into a 100-mL volumetric flask, dilute with *pH 9.0 Pyrophosphate buffer, 0.05 M* to volume, and mix.

Test solution—Transfer about 1 g of Copovidone, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *pH 9.0 Pyrophosphate buffer, 0.05 M,* dilute with *pH 9.0 Pyrophosphate buffer, 0.05 M* to volume, and mix. Insert a stopper into the flask, heat at 60° for 1 hour, and cool to room temperature.

Procedure—Pipet 0.5 mL each of the *Standard solution,* the *Test solution,* and the *Blank solution* into separate 1-cm cells. Add 2.5 mL of *pH 9.0 Pyrophosphate buffer, 0.05 M* and 0.2 mL of β-nicotinamide adenine dinucleotide TS to each cell. Mix by inversion, and stopper tightly. Allow to stand for 2 to 3 minutes at 22 ± 2°, and perform the test with these solutions with a suitable spectrophotometer, using water as the control solution. Determine the absorbances of the solutions at a wavelength of 340 nm. Add 0.05 mL of aldehyde dehydrogenase TS to each cell. Mix by inversion, and stopper tightly. Allow to stand for 5 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm. Calculate the percentage of aldehydes, expressed as acetaldehyde, in the portion of Copovidone taken by the formula:

$$10(C/W)\left[\frac{(A_{U2}-A_{U1})-(A_{B2}-A_{B1})}{(A_{S2}-A_{S1})-(A_{B2}-A_{B1})}\right]$$

in which C is the concentration, in mg per mL, of acetaldehyde in the *Standard solution,* calculated from the weight of the acetaldehyde ammonia trimer trihydrate with the factor 0.72; W is the weight, in g, calculated on the dried basis, of Copovidone taken to prepare the *Test solution;* A_{U1}, A_{S1}, and A_{B1} are the absorbances of the solutions obtained from the *Test solution,* the *Standard solution,* and the *Blank solution,* respectively, before the addition of the β-nicotinamide adenine dinucleotide TS; and A_{U2}, A_{S2}, and A_{B2} are the absorbances of the solutions obtained from the *Test solution,* the *Standard solution,* and the *Blank solution,* respectively, after addition of the aldehyde dehydrogenase TS: not more than 0.05% is found.

Limit of hydrazine—

Standard solution—Dissolve 0.09 g of salicylaldazine in toluene to make exactly 100 mL. Pipet 1 mL of this solution into a 100-mL volumetric flask, dilute with toluene to volume, and mix. Dissolve an accurately weighed quantity of salicylaldazine in toluene, and dilute quantitatively, and stepwise if necessary, with toluene to obtain a solution having a known concentration of 9 µg per mL.

Test solution—Transfer the equivalent of 2.5 g of dried Copovidone, accurately weighed, to a 50-mL centrifuge tube, add 25 mL of water, and mix to dissolve. Add 500 µL of a 1 in 20 solution of salicylaldehyde in methanol, stir, and warm in a water bath at 60° for 15 minutes. Allow to cool, add 2.0 mL of toluene, stopper tightly, shake vigorously for 2 minutes, and centrifuge. Use the clear upper toluene layer as the *Test solution.*

Procedure—Separately apply 10 µL of the *Test solution* and the *Standard solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of dimethylsilanized silica gel mixture with fluorescent indicator for thin-layer chromatography. Develop the chromatogram in a solvent system consisting of a mixture of methanol and water (2 : 1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and air-dry the plate. Locate the spot on the plate by examination under UV light at a wavelength of 365 nm: salicylaldazine appears as a fluorescent spot having an R_F value about 0.3, and the fluorescence of any salicylaldazine spot from the *Test solution* is not more intense than that produced by the spot obtained from the *Standard solution:* not more than 1 ppm is found.

Limit of peroxides—

Copovidone solution—Transfer the equivalent of 4.0 g of dried Copovidone, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test solution—Transfer 25.0 mL of *Copovidone solution* to a 50-mL beaker, add 2 mL of titanium trichloride–sulfuric acid TS, and mix. Allow to stand for 30 minutes at room temperature.

Blank solution—Transfer 25.0 mL of *Copovidone solution* to a 50-mL beaker, add 2 mL of 13% sulfuric acid, and mix.

Procedure—Determine the absorbance of the *Test solution* in a 1-cm cell at the wavelength of maximum absorbance at about 405 nm, with a suitable spectrophotometer, using the *Blank solution* as the blank: the absorbance is not more than 0.35 (corresponding to not more than 0.04%, expressed as hydrogen peroxide).

Limit of monomers (1-vinyl-2-pyrrolidone, vinyl acetate, and 2-pyrrolidone)—

Solution A—Prepare a mixture of water, acetonitrile, and methanol [90 : 5 : 5 (v/v/v)].

Solution B—Prepare a mixture of water, acetonitrile, and methanol [50 : 45 : 5 (v/v/v)].

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system* (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Separately dissolve 50 mg of 1-vinyl-2-pyrrolidone, 50 mg of vinyl acetate, and 300 mg of 2-pyrrolidone in methanol to make exactly 100 mL. Pipet 1 mL of this solution, add *Solution A* to make exactly 100 mL, and mix. Pipet 5 mL of this solution, add *Solution A* to make exactly 100 mL, and use this solution as the *Standard solution*.

Test solution—Dissolve about 250 mg of Copovidone, accurately weighed, into a 10-mL volumetric flask, add 1 mL of methanol, mix ultrasonically, dilute with water to volume, and mix. If necessary, filter this solution to remove undissolved particles.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector, a 235-nm detector, and a 4-mm × 25-mm guard column attached to a 4-mm × 25-cm analytical column that contains packing L7 with a 5-µm particle size. The column temperature is maintained at 30°. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–2	100	0	isocratic
2–26	100→80	0→20	linear gradient
26–27	80→0	20→100	linear gradient
27–36	0	100	isocratic
36–38	0→100	100→0	linear gradient

Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the resolution, *R,* between the 2-pyrrolidone, vinyl acetate, and 1-vinyl-2-pyrrolidone peaks is not less than 2.0; and the relative standard deviation for replicate injections of each analyte is not more than 2.0%.

[NOTE—According to the above operating conditions, the order of elution is 2-pyrrolidone, vinyl acetate, and 1-vinyl-2-pyrrolidone. After each injection with the *Test solution,* wash away the polymeric material of Copovidone from the guard column by passing the *Mobile phase* through the column backwards for about 30 minutes at the same flow rate applied in the test.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Test solution* and the *Standard solution,* and determine the peak areas of 1-vinyl-2-pyrrolidone, vinyl acetate, and 2-pyrrolidone. Calculate the content of 1-vinyl-2-pyrrolidone, vinyl acetate, and 2-pyrrolidone in Copovidone taken by the following formulas:

Content (ppm) of 1-vinyl-2-pyrrolidone

$$(A_{TA}/A_{SA}) \times 2.5/W$$

Content (ppm) of vinyl acetate

$$(A_{TB}/A_{SB}) \times 2.5/W$$

Content (%) of 2-pyrrolidone

$$(A_{TC}/A_{SC}) \times (15/W) \times 10^{-4}$$

in which W is the weight, in g, of Copovidone, calculated on the dried basis; A_{TA}, A_{TB}, and A_{TC} are the absorbances of the solutions of 1-vinyl-2-pyrrolidone, vinyl acetate, and 2-pyrrolidone, respectively, obtained from the *Test solution;* A_{SA}, A_{SB}, and A_{SC} are the absorbances of the solutions of 1-vinyl-2-pyrrolidone, vinyl acetate, and 2-pyrrolidone, respectively, obtained from the *Standard solution:* not more than 10 ppm of 1-vinyl-2-pyrrolidone is found, not more than 10 ppm vinyl acetate is found, and not more than 0.5% of 2-pyrrolidone is found.

Nitrogen, *Method II* ⟨461⟩—Proceed as directed in the chapter using an accurately weighed quantity of about 0.1 g of Copovidone except for the following: use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33 : 1 : 1) instead of potassium sulfate and cupric sulfate (10 : 1); omit the use of hydrogen peroxide; and heat until the solution has a clear, yellow-green color and the sides of the flask are free from carbonaceous material. Then heat for a further 45 minutes; add 20 mL of water, instead of 70 mL, after the second heating; and use bromocresol green–methyl red TS instead of methyl red–methylene blue TS. Titrate the distillate with 0.05 N sulfuric acid VS until the color of the solution changes from green through pale grayish blue to pale grayish red-purple: each mL of 0.5 N sulfuric acid VS is equivalent to 0.7004 mg of nitrogen.

K-value—Transfer an accurately weighed quantity of undried Copovidone, equivalent to about 1.0 g on the dried basis, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 1 hour. Determine the viscosity, using a capillary-tube viscosimeter of the Ubbelohde type (see *Viscosity* ⟨911⟩), of this solution at 25 ± 0.2°. Calculate the K-value of Copovidone by the formula:

$$\frac{1.5\log\eta - 1}{0.15 + 0.003w} + \frac{\sqrt{300w\log\eta + (w + 1.5w\log\eta)^2}}{0.15w + 0.003w^2}$$

in which w is the weight, in g, on the dried basis, of the specimen tested in each 100.0 mL of solution; and η is the kinematic viscosity of the test solution relative to that of water: the K-value is not less than 90.0% and not more than 110.0% of the nominal K-value stated on the label.

Assay—Weigh accurately about 2 g of Copovidone into a 250-mL borosilicate glass flask, add exactly 25 mL of 0.5 N alcoholic potassium hydroxide VS and a few glass beads, and heat under reflux for 30 minutes. Add 1 mL of phenolphthalein TS, and titrate the excess 0.5 N alcoholic potassium hydroxide immediately (while still hot) with 0.5 N hydrochloric acid VS. Perform a blank determination under the

same conditions (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Calculate the percentage of copolymerized vinyl acetate in the Copovidone taken by the formula:

$$0.1 \times \frac{86.09}{56.11} \times \frac{28.05(n_2 - n_1)}{w}$$

in which w is the weight, in g, of Copovidone, calculated on the dried basis; n_2 is the volume, in mL, of 0.5 N hydrochloric acid VS consumed for the blank determination; and n_1 is the volume, in mL, of 0.5 N hydrochloric acid VS consumed for the sample determination.

BRIEFING

Anhydrous Lactose, *NF 25* page 3357. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the Anhydrous Lactose monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION STAGE 6** document, is based on the corresponding monograph for Anhydrous Lactose that was prepared by USP. The USP draft was based in part on comments from EP and JP in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by USP.

Differences between the USP Adoption Stage 6 document and the current *NF* monograph for Anhydrous Lactose include the following:

1. *Definition*—Provided additional detail to maintain consistency with harmonized text.
2. *Packaging and storage*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text. No storage requirements specified.
3. *Labeling*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text.
4. *USP Reference standards*—No change.
5. *Clarity and color of solution*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text.
6. *Identification*—Test *A* is retained as a nonharmonized attribute. Tests *B* and *C* are retained as specific local attributes.
7. *Specific rotation*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text.
8. *Microbial limits*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text.
9. *Acidity or alkalinity*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text.
10. *Loss on drying*—No change.
11. *Water*—No change.
12. *Residue on ignition*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text.
13. *Heavy metals*—Retained as a nonharmonized attribute.
14. *Protein and light-absorbing impurities*—Removed from *Other requirements* section. Added detail to maintain consistency with the harmonized text.
15. *Content of alpha and beta anomers*—No change.

(DSN: K. Moore) RTS—C43927

No change:

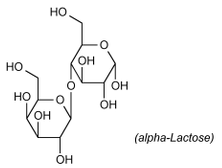
Anhydrous Lactose

Add the following:

Attribute	JP	EP	USP
Definition	+	+	+
Clarity and color of solution	+	+	+
Specific rotation	+	+	+
Acidity or alkalinity	+	+	+
Loss on drying	–	+	+
Water	+	+	+
Content of alpha and beta anomers	+	+	+
Residue on ignition	+	+	+
Protein and light-absorbing impurities	+	+	+

Legend: + will adopt and implement; – will not stipulate.
Nonharmonized attributes: Characters, Labeling, Microbial limits, Heavy metals, Packaging and storage, Identification (IR).
Specific local attributes: Identification B and C (USP), Particle size distribution (USP), Particle size distribution EP (FRC).

No change:



(alpha-Lactose)

Change to read:

» ~~Anhydrous Lactose is primarily beta lactose or a mixture of alpha and beta lactose.~~

Harmonization

▲Anhydrous Lactose is *O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose (β-lactose) or a mixture of *O*-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose and *O*-β-D-galactopyranosyl-(1→4)-α-D-glucopyranose (α-lactose).▲*NF26*

Add the following:

▲**Packaging and storage**—Preserve in tight containers.▲*NF26*

Change to read:

Labeling—Where the labeling indicates the relative quantities of alpha and beta lactose, determine compliance using *Content of alpha and beta anomers*.

▲Where the labeling states the particle size distribution, it also indicates the d_{10}, d_{50}, and d_{90} values and the range for each.▲*NF26*

No change:

USP Reference standards ⟨11⟩—*USP Dextrose RS. USP Fructose RS. USP Anhydrous Lactose RS. USP Sucrose RS.*

Add the following:

▲**Clarity and color of solution**—A solution of 1 g in 10 mL of boiling water is clear and nearly colorless. Determine the absorbance of this solution at a wavelength of 400 nm. The absorbance divided by the path length, in cm, is not more than 0.04.▲*NF26*

No change:

Identification—
A: *Infrared Absorption* ⟨197K⟩.
B: Proceed as directed in *Identification* test *B* under *Lactose Monohydrate,* except to use USP Anhydrous Lactose RS instead of USP Lactose Monohydrate RS in *Standard solution A* and *B* and to use Anhydrous Lactose in the *Test solution*.
C: Proceed as directed in *Identification* test *C* under *Lactose Monohydrate*.

Add the following:

▲**Specific rotation** ⟨781⟩—Dissolve 10 g by heating in 80 mL of water to 50°. Allow to cool, and add 0.2 mL of 6 N ammonium hydroxide. Allow to stand for 30 minutes, and dilute with water to 100 mL: the specific rotation, calculated on the anhydrous basis, determined at 20°, is between +54.4° and +55.9°.▲*NF26*

Add the following:

▲**Microbial limits** ⟨61⟩—The total aerobic microbial count does not exceed 100 cfu per g, the total combined molds and yeasts count does not exceed 50 cfu per g, and it meets the requirements of the test for absence of *Escherichia coli*.▲*NF26*

Add the following:

▲**Acidity or alkalinity**—Dissolve 6 g by heating in 25 mL of carbon dioxide-free water, cool, and add 0.3 mL of phenolphthalein TS: the solution is colorless, and not more than 0.4 mL of 0.1 N sodium hydroxide is required to produce a red color.▲*NF26*

No change:

Loss on drying ⟨731⟩—Dry it at 80° for 2 hours: it loses not more than 0.5% of its weight.

No change:

Water, *Method I* ⟨921⟩: not more than 1.0%, determined on a preparation containing anhydrous lactose in a mixture of methanol and formamide (2 : 1).

Add the following:

▲**Residue on ignition** ⟨281⟩: not more than 0.1%, determined on a specimen ignited at a temperature of 600 ± 50°.▲*NF26*

No change:

Heavy metals, *Method II* ⟨231⟩: 5 µg per g.

Add the following:

▲**Protein and light-absorbing impurities** ⟨851⟩—Measure the light absorption of a 1% (w/v) solution in the range of 210 nm to 300 nm. The absorbance divided by the path length, in cm, is not more than 0.25 in the range of 210 nm to 220 nm and is not more than 0.07 in the range of 270 nm to 300 nm.▲*NF26*

No change:

Content of alpha and beta anomers—
Silylation reagent—Prepare a mixture of pyridine and trimethylsilylimidazole (72 : 28).
Resolution mixture—Prepare a mixture of alpha lactose monohydrate and beta lactose having an anomeric ratio of about 1 : 1 based on the labeled anomeric contents of the alpha lactose monohydrate and the beta lactose.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 4-mm × 0.9-m glass column packed with 3% liquid phase G19 on support S1A. The column temperature is maintained at about 215°, and the injection port and the detector temperatures are maintained at about 275°. The carrier gas is helium, flowing at a rate of about 40 mL per minute.

Derivatization procedure—Transfer about 1 mg of Anhydrous Lactose to a 5-mL reaction vial equipped with a screw cap, add 0.45 mL of dimethyl sulfoxide, seal the vial tightly with a screw cap, and mix on a vortex mixer to dissolve. Add 1.8 mL of *Silylation reagent,* seal the vial tightly with a screw cap, and mix gently. Transfer about 1 mg of *Resolution mixture* to a second 5-mL reaction vial equipped with a screw cap, add 0.45 mL of dimethyl sulfoxide, seal the vial tightly with a screw cap, and mix on a vortex mixer to dissolve. Add 1.8 mL of *Silylation reagent,* seal the vial tightly with a screw cap, and mix gently. Maintain both vials at room temperature for 20 minutes before using.

Procedure—Inject a 2.0-µL portion of the derivatized *Resolution mixture* into the chromatograph, and record the areas for the major peaks: the relative retention times are about 0.7 for the silyl derivative of alpha lactose and 1.0 for the silyl derivative of beta lactose; and the resolution, *R,* between the two peaks is not less than 3.0. Similarly inject a 2.0-µL portion of the derivatized Anhydrous Lactose into the chromatograph, and record the areas for the major peaks. Determine the percentage of alpha anomer in the portion of Anhydrous Lactose taken by the formula:

$$100r_a / (r_a + r_b)$$

in which r_a is the response of the alpha anomer silyl derivative peak, and r_b is the response of the beta anomer silyl derivative peak. Determine the percentage of beta anomer in the portion of Anhydrous Lactose taken by the formula:

$$100r_b / (r_a + r_b)$$

in which the terms are as defined above.

Delete the following:

~~***Other requirements**—It meets the requirements for *Packaging and storage*, *Labeling*, *Clarity and color of solution*, *Specific rotation* ⟨781⟩, *Microbial limits* ⟨61⟩, *Acidity or alkalinity, Residue on ignition* ⟨281⟩, and *Protein and light-absorbing impurities* under *Lactose Monohydrate*.~~ ▲*NF26*

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

Briefings Each Preview is preceded by a Briefing in the following format:

BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How To Use PF*), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:

(DSN: L. Evans) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

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Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in the *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

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Abstract—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

References—Consult a current copy of the *Pharmacopeial Forum* and the *ACS Style Guide* for assistance with reference style.

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12601 Twinbrook Pkwy.
Rockville, MD 20852

Comparative Study of the Chromatographic and Bioassay Procedure for the Determination of Vasopressin Potency*

Hullahalli R. Prasanna,[1] Joseph P. Hanig,[2] and Karl P. Flora[1,3*]

ABSTRACT Vasopressin is a bioactive peptide hormone available as two chemically distinct forms: lysine vasopressin, an antidiuretic, and arginine vasopressin, an antidiuretic and neurotransmitter. Lysine forms are commercially available in intravenous and nasal spray preparations. Previously the *United States Pharmacopeia* (*USP*) measured vasopressin potency by monitoring blood pressure in rats following intravenous administration of the drug. In *USP 29* (with an effective date of January 1, 2007), *USP* subsequently replaced this bioassay with a high-performance liquid chromatographic (HPLC) procedure. We have compared two commercially marketed vasopressin formulations, injection and nasal spray, by the current HPLC and former bioassay procedures. The results indicate a good correlation between the two procedures. HPLC analysis of the nasal spray samples revealed the presence of significant amounts of methyl- and propylparabens that were present in these preparations as excipients.

INTRODUCTION

Vasopressin and oxytocin are bioactive peptide hormones of significant clinical importance (*1*). Vasopressin is present as two chemically distinct forms: lysine vasopressin, a known antidiuretic, and arginine vasopressin, a compound with antidiuretic as well as neurotransmitter activity (*2*). The lysine vasopressin forms are commercially available in the U.S. The vasopressin peptide hormones are synthesized in the hypothalamus and paraventricular nucleus of primates (*3*) and are transported to the posterior pituitary for storage and eventual release. Vasopressin is released as a response to hypo-osmolality, hypovolemia, hypotension, emotional stress, change from prone or sitting to upright posture, and by many pharmacological agents (*4*). For pharmaceutical use, vasopressin as the lysine form is prepared by chemical synthesis. It was previously isolated from the pituitary of domestic animals. Several investigators have developed chromatographic procedures for both qualitative and quantitative evaluation of vasopressin and oxytocin (*5–9*). Based on this work, USP replaced the bioassay procedure with a high-performance liquid chromatography (HPLC) procedure that appeared in *USP 29* with an official date of January 1, 2007. Despite this advance, results are still expressed in units because the physical standard for the new procedure remains a World Health Organization (WHO) standard with assigned value expressed in IU/mL. USP intends to replace this standard with a fully characterized official USP Reference Standard so that results can be expressed in terms of mass. In the case of oxytocin, excellent correlation between chromatographic and bioassay methods has been observed for the determination of potency (*8*). This report presents the results of our comparisons between the current *USP* HPLC procedure for the determination of vasopressin potency and the previous bioassay procedure (*10*) for two different formulations (injectable and nasal spray) of commercially marketed lysine vasopressin. Evaluation of the HPLC method suggests a possible modification of the recent *USP* monograph.

MATERIALS AND METHODS

Chromatographic apparatus

The HPLC system used was a Hewlett-Packard model 1050 quaternary pump, a model 1050 autosampler, and a model 1050 diode array or variable wavelength ultraviolet detector. The data collected were processed using Chemstation software (Hewlett-Packard, Avondale, PA).

Reagents and supplies

The following reagents and solvents were obtained from the suppliers indicated and were used as received: acetonitrile (HPLC grade), methanol (HPLC grade) and glacial acetic acid (reagent grade) (J.T.Baker, Phillipsburg, NJ); dibasic ammonium phosphate (LR grade, Fisher Scientific, Fair Lawn NJ); sodium acetate, methyl- and propylparaben (Aldrich Chemical, Milwaukee, WI); absolute ethyl alcohol (Pharma Products, Bayonne, NJ); and chlorobutanol (Sigma Chemical, St. Louis, MO). Deionized water (NANOpure, Branstead/Thermolyne Corp., Dubuque, IA) was used in the preparation of reagents and the mobile phase. The lysine vasopressin products were collected as routine post-marketing surveillance samples from individual companies. Vasopressin samples analyzed were of two formulation types, injection and nasal spray. Sample diluent was prepared by dissolving 5.0 g of chlorobutanol in 5.0 mL of glacial acetic acid, 5.0 g of ethyl alcohol, 1.1 g of sodium acetate, and 1000 mL of water and thoroughly mixed. This diluent was used to dissolve arginine- or lysine-containing reference standards obtained from WHO. Standard solutions were prepared by adding 1.0 mL of sample diluent to a glass ampoule containing a freeze-dried plug of vasopressin WHO standard (arginine or lysine) to give a final vasopressin concentration of 7.7 International Units (IU)/mL (arginine form) or 8.2 IU/mL (lysine form). Dilutions were made to ob-

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[2] Division of Applied Pharmacology and Toxicological Research, Both in the Center for Drug Evaluation and Research, Food and Drug Administration.

[3] Deceased.

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tain two other standard concentrations. These concentrations were based on the potencies assigned to the standard materials supplied by WHO. Samples and standards prepared in this manner were suitable for direct injection into the HPLC system. The paraben standards were dissolved in methanol at 1 mg/mL and were diluted with the vasopressin diluent to concentrations suitable for the assay.

Chromatography

Chromatographic assay of Vasopressin as the lysine form was accomplished on a stainless steel column (4.6 mm × 25 cm) containing USP-designated packing L1 (Spherisorb ODS, 5 µm, Beckman Instruments, Inc., Fullerton, CA). The composition of the isocratic mobile phase consisted of 870 mL of 0.05 M ammonium phosphate buffer, pH 3.0, and 130 mL of acetonitrile. The two solutions were individually filtered using 0.45-µm nylon membrane filter and then mixed. Each sample was chromatographed for 90 min at a flow rate of 1.0 mL/min. Detection was accomplished using ultraviolet (UV) at 220 nm with both a variable wavelength and diode array detectors. Diode array UV scans were run and recorded on the components observed in the injected samples. The flow rate was chosen to yield the approximate retention times for vasopressin described in the *USP* monograph (*10*). All separations were accomplished at ambient temperature. The injection volume was 20 µL for all samples and standards.

Bioassay procedure

The rat blood pressure bioassay required for the determination of the potencies of vasopressin was preformed as described in the *USP* monograph (*10*).

RESULTS AND DISCUSSION

Chromatographic techniques of sufficient accuracy, selectivity, precision, and sensitivity have recently been described for quantifying biologically active peptides, including oxytocin and vasopressin. When methods of potency determination for biologically active molecules are replaced by physicochemical procedures, it is important to establish a correlation between the old and the new procedures. The excellent correlation between the chromatographic and the bioassay determinations of potency of oxytocin (*8, 9*) suggested that a correlation for vasopressin could also be established.

Establishment of an HPLC method with a known correlation to the bioassay procedure would facilitate the determination of the potency and purity of commercially marketed products. The observations also could be helpful in evaluating the need for testing in animals to determine the potency of the samples. A chromatographic method may allow the estimation of both process and product impurities and excipients, which would not be possible in the bioassay. Recognizing these possibilities, we evaluated the current *USP* chromatographic analysis and compared it to the bioassay procedure using several commercially marketed samples of vasopressin.

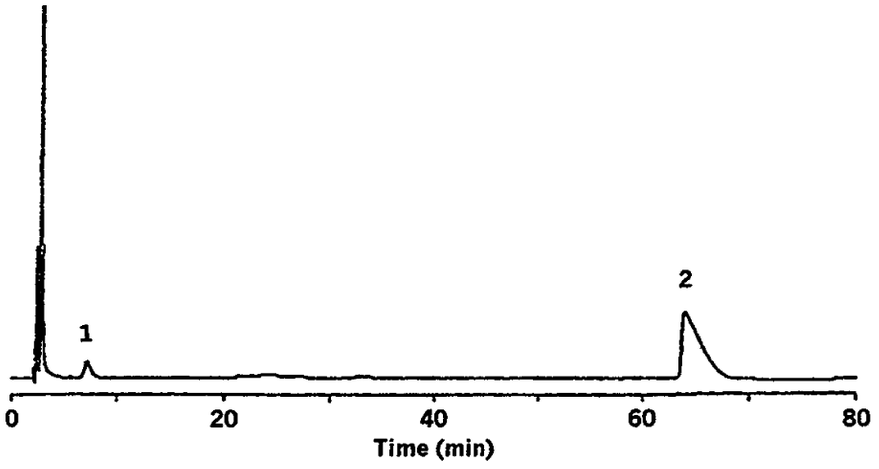

Figure 1. Typical Chromatographic profile of WHO arginine vasopressin standard. Peak 1 = vasopressin; peak 2 = chlorobutanol.

Figure 1 depicts a typical chromatographic profile of the WHO arginine vasopressin standard. In this run 2.0 IU/μL was injected, and experimental conditions were *USP* monograph procedures as described in the Methods section. Although *USP* recommends a 60-min run for each sample for complete elution, under our experimental conditions chlorobutanol, which is contained in the sample diluent, elutes between 65 and 68 min. Therefore, to avoid contamination of subsequent vasopressin samples a run time of 90 min was chosen. The system suitability criteria specified in the monograph were easily met: Resolution between vasopressin and the nearest peak was not less than 1.5 (ratio), and the relative standard deviation (for both retention time as well as peak area) for 10 replicate injections was not more than 2%. Precision data for vasopressin peak area and retention time are presented in *Table 1*.

Table 1. Precision of HPLC vasopressin assay[1]

Retention time (min) (Mean ±RSD[2])	Peak area (Mean ±RSD)
5.5 ±09.004 (<0.1%)	317 ±2.96 (<1.0%)

[1] Ten 20-μL replicates of WHO argenine vasopressin standard (0.164 IU/20 μL) were analyzed separately for 90 min by HPLC.
[2] Relative standard deviation.

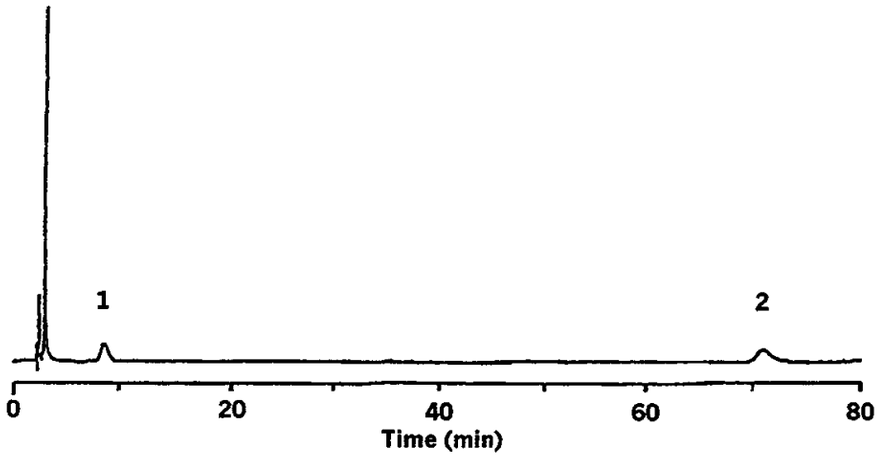

Figure 2. Chromatogram of a commercially marketed injectable sample of vasopressin. Peak 1 = vasopressin; peak 2 = chlorobutanol.

Figure 2 shows a chromatogram of a commercially marketed injectable sample of lysine vasopressin. The sample was diluted with diluent (~ 2.0 units/mL), and 20 μL of the diluted sample was injected. Experimental conditions were *USP* monograph procedures as described in the Methods section. The position of the vasopressin peak agrees well with that of the one noted for the WHO standard. For the assay of the marketed samples of the nasal spray (lysine vasopressin) the appropriate lysine-containing WHO reference standard was used. The *USP* procedure applied here did not chromatographically resolve the arginine and lysine vasopressin standard when mixed in equal amounts. An examination of the chromatograms for the nasal spray product reveals a distinct additional peak eluting at about 37–39 minutes in addition to the expected vasopressin and chlorobutanol peaks (*Figure 3*). In this experiment 20 μL of the sample was injected. Experimental conditions were *USP* monograph procedures as described in the Methods section.

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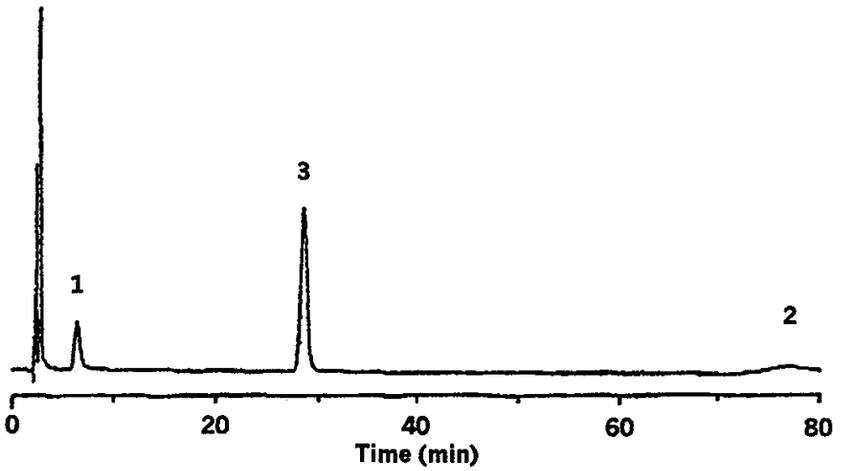

Figure 3. Chromatogram of a commercially marketed sample of vasopressin nasal spray. Peak 1 = vasopressin; peak 2 = chlorobutanol; peak 3 = methylparaben.

At the detection wavelength specified in the *USP* monograph, the area of this peak was severalfold that of the parent vasopressin peak. The package insert for the commercially marketed nasal spray preparation indicates the presence of unspecified amounts of methyl- and propylparaben (methyl or propyl esters of 4-hydroxybenzoic acid) added as preservatives along with chlorobutanol, in addition to other excipients. Authentic samples of methyl- and propylparaben were chromatographed under the same chromatographic conditions to ascertain their elution characteristics. The results indicate that methylparaben elutes at an elution volume consistent with the additional peak observed in the commercial nasal spray samples. When nasal spray samples were spiked with authentic methylparaben, the peaks coeluted. Also, diode array ultraviolet scans of the additional peak observed in the nasal spray and the peak observed with authentic methylparaben produced similar ultraviolet spectra.

However, under the *USP* HPLC assay conditions propylparaben did not elute. In order to confirm the presence of propylparaben in the marketed nasal spray product, the acetonitrile content in the mobile phase was increased to 25%, and 40 µL of the diluted sample was injected (see Methods section). *Figure 4* shows the assay of the marketed nasal spray formulation under these conditions.

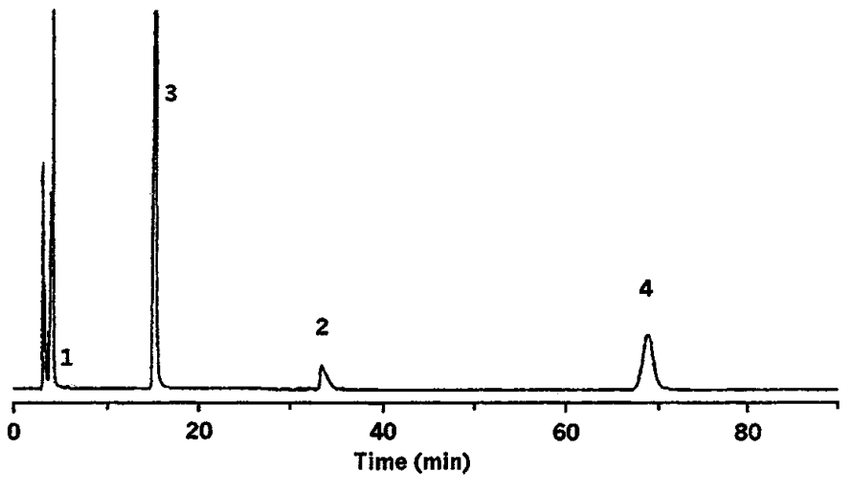

Figure 4. Chromatogram of a commercial sample of vasopressin nasal spray. Peak 1 = vasopressin; peak 2 = chlorobutanol; peak 3 = methylparaben; peak 4 = propylparaben.

An additional peak eluting later than the characteristically tailing peak for chlorobutanol is observed. Diode array scans of the peaks labeled in *Figure 4* are consistent with methyl- and propylparaben. To further confirm the identity of these peaks, we spiked samples of nasal spray formulation with authentic samples of suitable amounts of both methyl- and propylparabens. The chromatographic profile observed in *Figure 5* indicates the coelution of methyl- and propylparaben with the additional peaks observed in the nasal spray product. The mobile phase contained 25% acetonitrile (see the Methods section), and 40 µL of the diluted sample was injected.

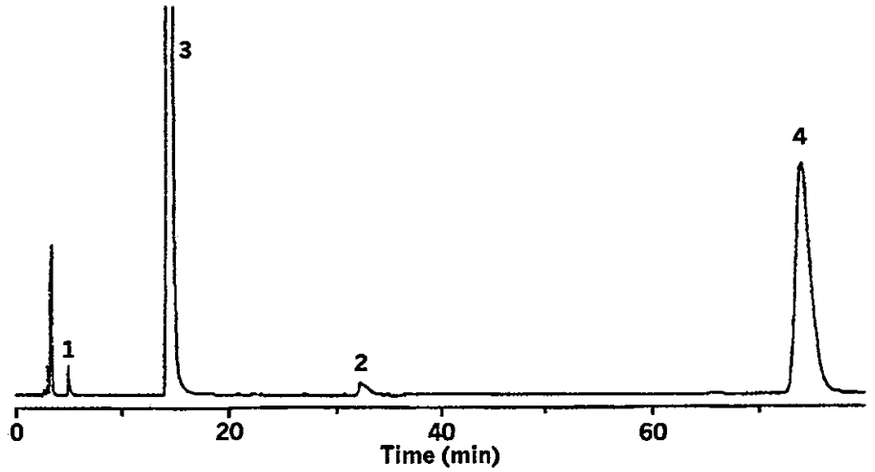

Figure 5. Chromatogram of a commercial sample of vasopressin nasal spray spiked with 50 µg each of methyl- and propylparaben. Peak 1 = vasopressin; peak 2 = chlorobutanol; peak 3 = methylparaben; peak 4 = propylparaben.

The chromatographic identification of the preservatives methyl- and propylparabens in the samples is noteworthy and could be of potential clinical significance. Studies reported elsewhere indicate that parabens can alter the balance of estrogens in animals and humans. The estrogenic aspect of parabens is suspected to increase the risk of breast cancer in humans (*11, 12*). Therefore the identification and quantitation of parabens present as excipients in the commercial nasal spray products in vasopressin samples would be helpful in assessing the quality of the vasopressin samples.

The results obtained from the comparative study undertaken between the chromatographic and bio-identity procedure of commercially marketed samples of vasopressin are presented in *Table 2.*

Table 2. Comparison of HPLC and Bioidentity Methods for the Evaluation of Potency of Vasopressin

	Activity/mL (IU/mL)			Percent of Labeled Content	
		HPLC[†]			
Formulation[*]	Labeled	Mean ±SD	Bioassay	Bioassay	HPLC
Injectable 1	20	22.3 ±0.25	20.37	102	112
Injectable 2	20	23.6 ±0.56	22.00	110	118
Injectable 3	20	18.7 ±0.22	21.30	107	94
Nasal Spray 1	50	47.9 ±1.79	47.20	94	96
Nasal spray 2	50	47.9 ±1.80	51.4	103	96
Nasal Spray 3	50	51.5 ±1.26	NA[‡]	NA	103

[*] Three separate samples of injectable and nasal spray variety obtained from three different manufacturers were used in the analysis.
[†] Vasopressin was measured in triplicate by HPLC and in duplicate for the bioassay.
[‡] NA = Not Analyzed.

When the results are expressed as a percent of the labeled potency, four of six samples meet the newly specified *USP* limits of 90–110% for vasopressin potency as determined by the HPLC assay, whereas all the results of the biological procedure were within the established range (85–120%). These results establish a good correlation measured by both procedures.

SUMMARY

This report demonstrates a good correlation between the chromatographic and bioassay methods for the evaluation of potency of lysine vasopressin in commercially marketed samples. The chromatographic method easily meets the specified system suitability criteria for both retention time and the peak area. The method was robust for potency determination and showed acceptable precision. However, the monograph notes that small changes in the mobile phase composition could result in significant changes in the elution volume of vasopressin. This is perhaps understated because elution volumes were sensitive to different batches of mobile phase prepared in exactly the same way. A similar elution time for vasopressin could be ensured only by using the same batch of mobile phase (*Table 1*). Therefore, large batches of mobile phase may be prepared to cover the analysis of a given set of samples.

The elution of methylparaben in the commercial nasal spray preparation is of some concern because it is not addressed or acknowledged in the *USP* monograph. Perhaps of greater concern is the apparent nonelution of the highly UV-absorbing propylparaben. In our application of the *USP* system propylparaben did not appear to elute either within the 90-min run time or as much as 90 min later. It is not known if this would be the case with other L1 columns. The modification proposed in this study, such as increasing the of time of running the chromotograph (90 min as opposed to 60 min) and additionally a change in the strength of acetonitrile to 25% in the mobile phase demonstrates that both parabens may be eluted, but under these conditions vasopressin elutes with other components of the sample diluent. A possible solution would be to run the system isocratically until after the elution of vasopressin and then to apply a gradient to elute chlorobutanol and the parabens. However, given the sensitivity of the elution of vasopressin to small changes in the mobile phase, significant reequilibration times after the gradient may be required, and this feature will also avoid elution of propylparabens in subsequent injections as a residual component of previous operations.

The results observed in this study indicate that the HPLC method is suitable for the assay of vasopressin in marketed formulations of both injectable and nasal spray varieties. In the revised monograph *USP* should include these features of the assay, identifying the excipient peaks in the nasal spray product, along with a method for detecting them as outlined in this study. We note that USP is working to advance an official USP Reference Standard for both lysine and arginine vasopressin with content (purity) expressed in terms of mass. This will allow a full transition to a standards-based as opposed to a procedures-based approach, with results expressed in terms of mass instead of units.

ACKNOWLEDGMENTS

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Determination of Signal-to-Noise Ratio in the Establishment of Quantitation Limit Requirements for Chromatographic Methods in *USP* Monographs—Approaches for Calculation and Implementation

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ABSTRACT USP has postponed indefinitely implementation of the requirements of the text pertaining to detection sensitivity in General Chapter *Chromatography, System Suitability* ⟨621⟩ (*1*). Although the central issue pertains to the impact of the proposal on older procedures that were not initially developed to meet proposed quantitation limit requirements, a more fundamental issue pertains to the appropriate calculation of quantitation limits and the application of such requirements in the monographs. The USP Expert Committee on General Chapters has discussed the issue and proposes to approach the topic first with a test case to gather public feedback about implementing signal-to-noise requirements for chromatographic monographs. This *Stimuli* article outlines the fundamental principles of calculating quantitation limits and considers the current requirements of the *European Pharmacopoeia* and the *Japanese Pharmacopoeia*. The article provides a suggested approach for determining the quantitation limit for monographs and also proposes a process to implement Quantitation Limit Requirements in current and new monographs.

INTRODUCTION

Proposals to establish Quantitation Limits requirements for *USP* monographs were originally published in *Pharmacopeial Forum* in 2004 (*2*). The proposal included a *Quantitation Limit Solution* at a 0.05% concentration level relative to the amount of drug substance in the *Test Preparation* for drug substance and a 0.1% level relative to the amount of drug substance in the *Test Preparation* for the drug product. The proposed requirement was that the signal-to-noise (S/N) ratio for the drug substance peak obtained with the *Quantitation Limit Solution* should not be less than 10. The purpose of the requirement was to ensure that appropriate quantitation limits could be met for calculating impurity levels in the drug substance and drug product *Test Preparations*. Recently, USP has postponed indefinitely the implementation of the requirements of the text pertaining to quantitation limits in General Chapter *Chromatography, System Suitability* ⟨621⟩. This *Stimuli* article explores the calculation of detection sensitivity and approaches to calculate quantitation limits in current and new monographs.

TERMINOLOGY

The draft USP proposal for the addition of detection sensitivity requirements relates to those monographs that have chromatographic-related specifications. The logic behind the requirement is to ensure that the procedure provides adequate quantitation capability to accurately quantify organic impurities (related compounds). The provision for such calculations as part of system suitability ensures that related compounds of interest can be quantified accurately each time the procedure is implemented in a laboratory. The literature is replete with discussions of detection limits, including discussions of limits of quantitation and limits of detection (*3*–*7*). USP had originally proposed the terminology *detection sensitivity* in considerations of quantitation limits. The term *sensitivity* is normally reserved for the slope of the calibration curve (*8*), and the term *detection* usually refers to detectability of peaks rather than the ability to accurately quantify them. In order to avoid confusion of terms, we suggest that the *USP*-proposed terminology of "detection sensitivity" be changed to "quantitation limit requirements" because the proposed measurement examines the limit of quantitation for the procedure.

THEORETICAL BACKGROUND

Although the purpose of this brief article is not to discuss the myriad treatments of detection limits, it is helpful to briefly review some approaches to gain an appreciation of the subject.

The detector output signal from HPLC experiment is the sum of the signal due to the presence of the analyte plus any signal due to the instrument background or blank contribution (*5*):

$$O_{total} = O_{analyte} + O_{blank} \qquad (1)$$

where O is the signal output of the measurement.

Equation 1 can be rewritten as:

$$O_{total} = (bC_x) + a_L + O_{blank} \qquad (2)$$

when expressed in terms of concentration (where b is given by the slope of the response of the analyte of interest, the sensitivity), C_X is the concentration of the analyte, and a_L is a constant relating the linear function of signal and analyte concentration). The analyte signal is given then as:

$$O_{analyte} = bC_x + a_L \qquad (3)$$

At the quantitative concentration limit (assuming for ease of argument that $a_L = 0$), then:

$$O_{total} = bC_x + 0 + O_{blank} \qquad (4)$$

$$O_{total} = bC_x + O_{blank} \qquad (5)$$

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or:

$$C_x = [O_{total} - O_{blank}]/\, b \qquad (6)$$

At the limit of quantitation, $C_x = C_{limit}$.

Then:

$$C_{limit} = (O_{total} - O_{blank})/\, b \qquad (7)$$

or:

$$O_{total} - O_{blank} = C_{limit}\, b. \qquad (8)$$

The blank signal has associated with it the variability σ and is estimated by the measured standard deviation s from a sample population.

The determination limit (*9*) is given by:

$$O_{total} - O_{blank} = C_{limit}\, b = Ks \qquad (9)$$

where $(O_{total} - O_{blank})$ is the true value of the net signal, and K is a constant determined by the level of acceptable risk, typically set at $K = 10$ for quantitative analysis.

$$C_{limit}\, b = Ks = 10s \qquad (10)$$

$$C_{limit} = (10s)/(b) \qquad (11)$$

CURRENT COMPENDIAL PERSPECTIVES

The *Japanese Pharmacopoeia* does not require measurement of the limit of quantitation on a routine basis for its monographs, although the quantitation limit is given as described in equation 11 in *General Information Chapter for Validation of Analytical Procedures* (*10*).

The *European Pharmacopoeia* (*EP*) requires S/N (*11*) measurements for minor components in some of its product monographs. The *Chromatographic Separation Techniques* chapter of *EP* defines the S/N ratio as:

$$S/N = (2H)/h \qquad (12)$$

where H is the height of the peak of interest and h is the range of the background noise. The value of the *S/N* ratio requirement is monograph dependent and is listed specifically for each monograph. *EP* considers "the background noise in a chromatogram obtained after injection or application of a blank, observed over a distance equal to 20 times the width at half-height of the peak in the chromatogram obtained with the prescribed reference solution and, if possible, situated equally around the place where this peak would be found." The expression "if possible" serves to emphasize the importance of good science in selecting the appropriate portion of the baseline that best represents the baseline noise where the peak of interest elutes. The analyst may begin with a consideration of *EP*'s suggestions and then make appropriate adjustments based on scientific merits.

The *USP* chapter on *Validation of Compendial Methods* ⟨1225⟩ (*12*) indicates that a typically acceptable ratio is 10:1 for the quantitation limit. Other references indicate that this is a generally acceptable level or define the limit as 10 times the standard deviation of the lowest detectable signal (*13, 14*).

SELECTION OF CALCULATION APPROACH

The situations shown in equations 11 and 12 are only two examples of calculation approaches for determination of quantitation limits. The first approach involves the measurement of the standard deviation of the noise, and several injections are required. In the second approach, that of *EP,* the sensitivity determination may be based on as few as one or two injections. Although more accurate analysis can be performed using elaborate statistical analysis, the potential need to perform this calculation on a routine basis requires a practical and simple approach. Other approaches also exist: the measurement of the peak-to-peak noise as described by IUPAC (8), ASTM (*15*), Dolan (*16*), Hinshaw (*17*), the root-mean-square noise (*16*), and the statistical approach described by Miller and Miller (*18*). Whereas the scientific merits of these other approaches are clear, the advantages of harmonization of compendial chapters between *USP* and *EP,* as well as the simplicity of the *EP* approach prevailed in the final analysis.

In addition, with the advent of software programs that enable automatic calculation of quantitation limits, flexibility should be provided to allow such advances. As *EP* indicates in section 2.2.46, "With some equipment, certain parameters, such as the signal-to-noise ratio, can be calculated using software provided by the manufacturer. It is the responsibility of the user to ensure that the calculation methods used in the software are compatible with the requirements of the *European Pharmacopoeia*. If not, the necessary corrections must be made."

Finally, the purpose of the quantitation limits solutions is to ensure that adequate S/N levels exist to ensure analysts' ability to accurately quantitate low-level impurities as described in various monographs. Multiple approaches are possible, but a simple approach is preferred in order to promote harmonized approaches. Arguments can be made that *EP*'s is not the most technically robust approach, but its simplicity, acceptable precision, and the positive outcomes of compendial harmonization lend support to this approach.

IMPLEMENTATION

To resolve the issue, we propose to introduce a *Quantitation Limit Solution* as part of the system suitability test in those chromatographic procedures pertaining to the USP *Impurities* test procedure. The *Quantitation Limit Solution* is a solution of the drug substance generally at a 0.05% concentration level relative to the concentration of the *Test Preparation* for drug substances and generally a 0.1% level relative to the amount of drug substance in the *Test Preparation* for drug products. The *Quantitation Limit Solution* concentration level depends on the quantitation requirements of the procedure. The system is considered suitable for the analysis if the signal-to-noise (S/N) ratio for the drug substance peak obtained with the *Quantitation Limit Solution* is not less than 10. The addition of a *Quantitation Limit Solution* to a monograph ensures that accurate quantitation of related substances can be made at the procedure's specified quantitation level. Implementation of *Quantitation Limit Solution* in current monographs, however, is not practical without additional development and validation of current methods. In fact, it may not be sufficient only to demonstrate the validity of a method at a single working sample concentration. In order to circumvent sensitivity issues

caused by differences in detector sensitivities between laboratories, analysts may need to validate a larger linear concentration range for the active component in order to allow assay concentration changes to meet *Quantitation Limit Solution* requirements that depend on detector sensitivity. For example, instead of giving a simple target concentration for the preparation of the sample solution, it may be helpful to provide a range of concentrations in which the procedure has been demonstrated to be accurate, linear, and precise. To ensure that the instrument is operating in the linear range of the test method, a second sample solution at 50% of the working sample concentration could be tested at the time the procedure is run to ensure a linear response when the higher range of the assay concentration target is used in order to meet the *Quantitation Limit Solution* requirements.

Future monographs should include *Quantitation Limit Solution* as part of the validated method. The validation should include the components discussed above.

CONCLUSION

The inclusion of a *Quantitation Limit Solution* in monographs that require impurity determination should become a standard practice for *USP* monographs that include an impurity limit requirement. The general requirement should be included in ⟨621⟩ and should apply to monographs in which the application of a *Quantitation Limit Solution* has been validated. None of the various approaches to calculating the S/N ratio has overriding advantages from a scientific perspective, and hence the choice with *EP* of a harmonized approach presents advantages in the global pharmaceutical environment. Additional suggestions for validation of methods that include a *Quantitation Limit Solution* may be included in ⟨1225⟩ based on public feedback.

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Monograph Redesign Proposal

Todd L. Cecil, *USP*[*]

ABSTRACT This *Stimuli* article presents proposed style, format, and content changes to the *USP–NF* monograph. This article seeks input from readers of *Pharmacopeial Forum* and *USP–NF*.

INTRODUCTION

During the USP Annual Scientific Meeting in September 2005 in San Diego, attendees discussed changes to *USP–NF* to enhance usability. The discussion emphasized the need for changes in monograph style, format, and content. Subsequently, USP staff prepared a new monograph template based on this discussion and presented it to members of the *USP* Council of Experts. With this further input, the template was refined. Presented herewith are *USP* official monographs for Acepromazine Maleate and Acebutolol Hydrochloride Capsules using the new template. Comments will be accepted through February 1, 2007.

STYLE

Concise wording

Despite USP's goal of unambiguous, clear, and concise statements in its publications, the style of writing in *USP–NF* has increasingly relied on extensive descriptions of test procedures and other requirements. The proposed presentation reduces the number of words for these descriptions. Also, procedures would be moved to General Chapters when feasible.

Cross-references

Common tests, procedures, and acceptance criteria in the drug substance and corresponding dosage monograph(s) will be repeated to avoid cross-referencing.

Sections

The International Conference on Harmonization (ICH) Q6A and B guidances categorized tests in a specification into Universal (Description, Identification, Impurities, and Assay) and Specific tests. The proposed template follows this categorization. Similarly, in accordance with ICH, the template provides an Impurity test(s), with procedures for organic, inorganic, and residual solvent impurities. The terms *related compound, chromatographic purity, ordinary impurities,* and the like are eliminated. The proposed template aligns acceptance criteria with the corresponding test; e.g., the Assay test acceptance criteria are moved to the Assay test part of the template. The monograph's Description section in the proposed template includes information described in ICH Q6A as well as information from the Description and Solubility section of *USP–NF*. As before, the latter is informational only and is not intended to be enforced.

Solutions

When possible, the description of the solutions is shortened to include the analyte, solvent, and concentration in SI units. When solvents are complex mixtures, additional description of component solutions is included. Preparation details are excluded. This change allows greater flexibility to the analyst in preparing solution volumes that are appropriate to the task.

PROPOSED CHANGES TO FORMAT

USP traditionally uses combinations of fonts, italics and boldface, and capitalization–lower case to present information. This complexity is often lost on users and only makes the text hard to read and understand. In the proposed template, these combinations are reduced or eliminated. Instead, the proposed template uses a sans serif font that is designed to signal information locus without the need to read entire passages. The template also relies on indenting, including hanging indents with boldface headers, to aid in location of information. The outcome is closer to an outline than a text. Larger type size with more white space is also used to aid comprehension. Although they are not shown in the draft monographs included in this article, lines (rules) may be used to demarcate the beginning and end of a monograph and also to identify commentary within a monograph.

PROPOSED CHANGES TO CONTENT

Content changes are kept to a minimum, but the proposed presentation eliminates calculations. Although discussion of this possibility is underway, comments are solicited now and are expected to be useful.

SUMMARY

Based on comments about this *Stimuli* article and further deliberations, conversion to the new presentation may occur in *USP 32–NF 27* in 2009.

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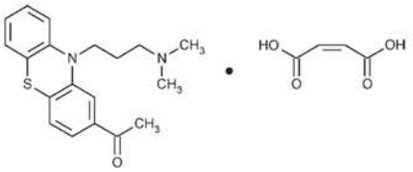
Stimuli to the Revision Process

DRAFT MONOGRAPHS

Acepromazine Maleate



DESCRIPTION

$C_{19}H_{22}N_2OS \cdot C_4H_4O_4$ 442.53

Ethanone, 1-[10-[3-(dimethylamino)propyl]-10*H*-phenothiazin-2-yl]-, (*Z*)-2-butenedioate (1:1).

10-[3-(Dimethylamino)propyl]phenothiazin-2-yl methyl ketone maleate (1:1) [3598-37-6].

IDENTIFICATION

A: *Infrared Absorption* ⟨197K⟩

B: The retention time of the major peak in the chromatogram of the Assay Test solution corresponds to that in the chromatogram of the Assay Standard solution, as obtained in the Assay.

IMPURITIES

Residue on ignition ⟨281⟩: not more than 0.2%

Specified and Unspecified Impurities

[NOTE—Conduct this test without exposure to daylight, and with the minimum necessary exposure to artificial light.]

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Test solution: 20.0 mg/mL acepromazine maleate in methanol and diethylamine (19:1)

Standard solution: 0.1 mg/mL acepromazine maleate in methanol and diethylamine (19:1)

Application volume: 10 µL

Developing solvent system: *n*-heptane, isobutyl alcohol, and diethylamine (75:17:8)

Detection/visualization: short-wavelength UV light

Impurities Acceptance Criteria—No spot, except for the principal spot and origin, is not more intense than the spot in the chromatogram obtained from Standard solution (0.5%).

ASSAY

Solvent A: triethylamine and water (6:700), adjusted to pH 2.5 with phosphoric acid

Mobile phase: Solvent A and acetonitrile (70:30) Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution: 1 mg/mL USP Acepromazine Maleate RS in 0.05 *N* hydrochloric acid

Standard solution: 0.1 mg/mL of USP Acepromazine Maleate RS: from a 1 to 10 dilution of Standard stock solution with water

Test stock solution: 1 mg/mL acepromazine maleate in 0.05 *N* hydrochloric acid

Test solution: 0.1 mg/mL acepromazine maleate: from a 1 to 10 dilution of Test stock solution with water

Chromatographic system—
Mode: liquid chromatography
Detector: 280 nm
Column: 4-mm × 15-cm: 5-µm L7 packing
Flow rate: about 1 mL/minute
Injection size: about 10 µL

System Suitability—
Sample—Standard Solution
Suitability Acceptance Criteria—
column efficiency: NLT 1500 theoretical plates
relative standard deviation of acepromazine maleate: NMT 2.0%
tailing factor: NMT 2.5

Assay Acceptance Criteria—Acepromazine Maleate contains not less than 98.0% and not more than 101.0% of $C_{19}H_{22}N_2OS \cdot C_4H_4O_4$, calculated on the anhydrous basis.

SPECIFIC TESTS

Melting range ⟨741⟩: between 136° and 139°

pH ⟨791⟩: between 4.0 and 5.5, in a 10 mg/mL solution

Water, *Method I* ⟨921⟩: NMT 1.0%

ADDITIONAL REQUIREMENTS

Packaging and storage—Preserve in well-closed containers, protected from light. Store at room temperature.

Labeling—Label it to indicate that it is for veterinary use only.

USP Reference standards ⟨11⟩:
USP Acepromazine Maleate RS

Acepromazine Maleate Tablets

Acepromazine Maleate Tablets contains acepromazine maleate.

[NOTE—Throughout the following procedures, protect test or assay specimens, the Reference Standard, and solutions containing them, by conducting the procedures without delay, under subdued light, or using low-actinic glassware.]

IDENTIFICATION

A: *Infrared Absorption* ⟨197K⟩

Test sample—To a quantity of powdered Tablets equivalent to about 20 mg of acepromazine maleate, add 2 mL of water and 3 mL of 2 N sodium hydroxide, and extract with two 5-mL portions of cyclohexane. Combine the cyclohexane extracts and evaporate to dryness under vacuum, using gentle heat, if necessary.

B: The retention time of the major peak in the chromatogram of the Assay preparation corresponds to that in the chromatogram of the Standard preparation, as obtained in the Assay.

ASSAY

Solvent 1—Add 6 mL of triethylamine to 700 mL of water and adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Solvent 1 and acetonitrile (70:30) Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution: 1 mg/mL of USP Acepromazine Maleate RS in 0.05N hydrochloric acid

Standard solution: Dilute 5 mL of Standard Stock solution with water to 50 mL

Test solution—Transfer not fewer than 10 Tablets, accurately counted, to a 200-mL volumetric flask. Add about 100 mL of 0.05 N hydrochloric acid, and sonicate for about 10 minutes. Shake by mechanical means for about 30 minutes, dilute with 0.05 N hydrochloric acid to volume, and mix. Quantitatively dilute an accurately measured volume of this solution with water to obtain a solution containing about 0.1 mg of acepromazine maleate per mL. Pass a portion of this solution through a filter having a 0.5-µm or finer porosity, and use the filtrate as the Assay preparation.

Chromatographic system—
Mode: liquid chromatography
Detector: UV 280 nm
Column: 4-mm × 15-cm column that contains packing L7
Flow rate: about 1 mL/min
Injection size: about 10 µL

System Suitability—
Sample—Standard Solution
Suitability Acceptance Criteria—
column efficiency: NLT 1500 theoretical plates
relative standard deviation: NMT 2.0%
tailing factor: NMT 2.5

Calculate the quantity, in mg, of acepromazine maleate ($C_{19}H_{22}N_2OS{\cdot}C_4H_4O_4$) in each Tablet taken by the formula:

$$(LC/D)(r_U / r_S)$$

in which L is the labeled quantity, in mg, of acepromazine maleate in each Tablet; C is the concentration, in mg per mL, of USP Acepromazine Maleate RS in the Standard preparation; D is the concentration, in mg per mL, of acepromazine maleate in the Assay preparation, based on the labeled quantity per Tablet, the number of Tablets taken, and the extent of dilution; and r_U and r_S are the acepromazine peak responses obtained from the Assay preparation and the Standard preparation, respectively.

Assay Acceptance Criteria—Acepromazine Maleate Tablets contains not less than 90.0% and not more than 110.0% of $C_{19}H_{22}N_2OS{\cdot}\ C_4H_4O_4$.

ADDITIONAL REQUIREMENTS

Packaging and storage—Preserve in tight, light-resistant containers and store at controlled room temperature.

Labeling—Label the Tablets to indicate that they are for veterinary use only.

USP Reference standards ⟨11⟩:
USP Acepromazine Maleate RS

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

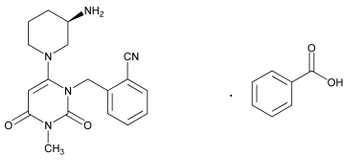
USP Dictionary of USAN and International Drug Names
2006 USP DICTIONARY SUPPLEMENT 4

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2006 edition of the USP Dictionary (USPD) up-to-date. The cumulative contents of the supplements to the current (2006) edition will be included in the next complete edition of the Dictionary.

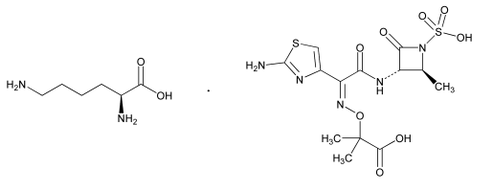
Newly Approved United States Adopted Names (USAN), Released for Publication

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

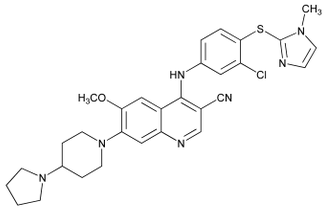
Alogliptin Benzoate [*2006*] (al″ oh glip′ tin). $C_{18}H_{21}N_5O_2 \cdot C_7H_6O_2$. 461.51. (1) Benzonitrile, 2-[[6-[(3*R*)-3-amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl]methyl]-, monobenzoate; (2) 6-[(3*R*)-3-Aminopiperidin-1-yl]-1-(2-cyanobenzyl)-3-methylpyrimidin-2,4(1*H*,3*H*)-dione monobenzoate; (3) 2-[[6-[(3*R*)-3-Amino-1-piperidinyl]-3,4-dihydro-3-methyl-2,4-dioxo-1(2*H*)-pyrimidinyl]methyl]benzonitrile monobenzoate. *CAS-850649-62-6*. *Treatment of type 2 diabetes.* (Takeda) ✧*SYR-322*



Aztreonam Lysine [*2005*] (az′ tree oh nam lye′ seen). $C_{13}H_{17}N_5O_8S_2 \cdot C_6H_{14}N_2O_2$. 581.62. (1) L-Lysine, mono[2-[[(*Z*)-[1-(2-amino-4-thiazolyl)-2-[[(2*S*,3*S*)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoate]; (2) L-Lysine, mono[2-[[(*Z*)-[1-(2-aminothiazol-4-yl)-2-[[2*S*,3*S*)-2-methyl-4-oxo-1-sulfoazetidin-3-yl]amino]-2-oxoethylidene]amino]oxy]-2-methylpropanoate. *CAS-827611-49-4*. *Antimicrobial.* Cayston (Corus) ✧*Corus1020*

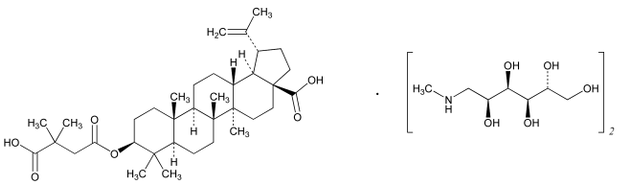


Balamapimod [*2006*] (bal a map′ i mod). $C_{30}H_{32}ClN_7OS$. 574.14. (1) 3-Quinolinecarbonitrile, 4-[[3-chloro-4-[(1-methyl-1*H*-imidazol-2-yl)thio]phenyl]amino]-6-methoxy-7-[4-(1-pyrrolidinyl)-1-piperidinyl]-; (2) 4-[[3-Chloro-4-[(1-methyl-1*H*-imidazol-2-yl)sulfanyl]phenyl]amino]-6-methoxy-7-[4-(pyrrolidin-1-yl)piperidin-1-yl]quinoline-3-carbonitrile. *CAS-863029-99-6*. *Oncology.* (Wyeth) ✧*MKI-833*

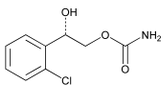


Belagenpumatucel-L [*2006*] (bel″ a jen″ pum a too′ sel). Allogeneic vaccine cocktail of TGF-β blocked, whole non-small cell lung cancer tumor cells. *Cell therapy treatment of non-small cell lung cancer.* Lucanix ✧

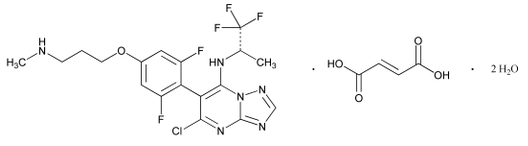
Bevirimat Dimeglumine [*2006*] (be vir′ i mat). $C_{36}H_{56}O_6 \cdot 2C_7H_{17}NO_5 \cdot$ 975.25. (1) Lup-20(29)-en-28-oic acid, 3-(3-carboxy-3-methyl-1-oxobutoxy)-, (3β)-, compd. with 1-deoxy-1-(methylamino)-D-glucitol (1:2); (2) Bis[1-deoxy-1-(methylamino)-D-glucitol] 3β-(3-carboxylato-3-methylbutanoyloxy)lup-20(29)-en-28-oate. *CAS-823821-85-8*. *Treatment of HIV infection.* (Panacos) ✧*PA-457; PA-457N; PA103001; PA103001-01; PA103001-04; PA-457 di-NMG; DSB*2NMG*



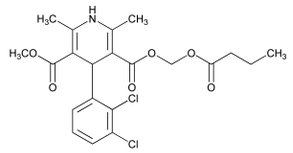
Carisbamate [*2006*] (kar is bam′ ate). $C_9H_{10}ClNO_3$. 215.63. (1) 1,2-Ethanediol, 1-(2-chlorophenyl)-, 2-carbamate, (1*S*)-; (2) (+)-(2*S*)-2-(2-Chlorophenyl)-2-hydroxyethyl carbamate. *CAS-194085-75-1*. *Novel neurotherapeutic agent for the treatment of epilepsy and other CNS disorders.* (Johnson & Johnson) ✧*YKP-509; RWJ-333369; JNJ-10234094*



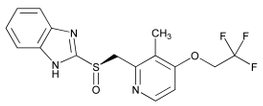
Cevipabulin Fumarate [*2006*] (se vip″ a bue′ lin). $C_{18}H_{18}ClF_5N_6O \cdot C_4H_4O_4 \cdot 2H_2O$. 616.92. (1) [1,2,4]Triazolo[1,5-*a*]pyrimidin-7-amine, 5-chloro-6-[2,6-difluoro-4-[3-(methylamino)propoxy]-phenyl]-*N*-[(1*S*)-2,2,2-trifluoro-1-methylethyl]-, (2*E*)-2-butenedioate (1:1), dihydrate; (2) 5-Chloro-6-[2,6-difluoro-4-[3-(methylamino)propoxy]phenyl]-*N*-[(1*S*)-2,2,2-trifluoro-1-methylethyl]-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine (2*E*)-but-2-enedioate (1:1) dihydrate. *CAS-849550-69-2*. *Treatment of cancer.* (Wyeth) ✧*TTI-237*



Clevidipine Butyrate [*2006*] (clev eye′ di peen). $C_{21}H_{23}Cl_2NO_6$. 456.32. [Clevidipine is INN.] (1) 3,5-Pyridinedicarboxylic acid, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, methyl (1-oxobutoxy)methyl ester; (2) (Butanoyloxy)methyl methyl (4*RS*)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.*CAS-167221-71-8; CAS-166432-28-6* [clevidipine]. *Antihypertensive.* Clevelox (Medical Arts) ✧*H324/38*



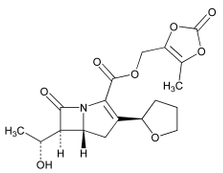
Dexlansoprazole [*2006*] (dex″ lan soe′ pra zole). $C_{16}H_{14}F_3N_3O_2S$. 369.36. (1) 1*H*-Benzimidazole, 2-[(*R*)-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-; (2) (+)-2-[(*R*)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1*H*-benzimidazole; (3) 2-[(*R*)-[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1*H*-benzimidazole. *CAS-138530-94-6*. INN. *Non-erosive GERD, healing of erosive esophagitis, and maintenance of healing of erosive esophagitis.* (Takeda) ✧*T-168390; TAK-390*



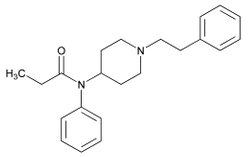
Disomotide [*2005*] (dye soe mor′ tide). $C_{47}H_{74}N_{10}O_{14}S$. 1035.21. (1) L-valine, L-isoleucyl-L-methionyl-L-α-aspartyl-L-glutaminyl-L-valyl-L-prolyl-L-phenylalanyl-L-seryl-; (2) [186-L-Methionine]-melanocyte protein Pmel 17 (human melanoma-associated ME20 antigen)-(185-193)-peptide. *CAS-181477-43-0*. INN. *Melanoma peptide vaccine.* (Medarex) ✧*MPS-22*

IMDQVPFSV

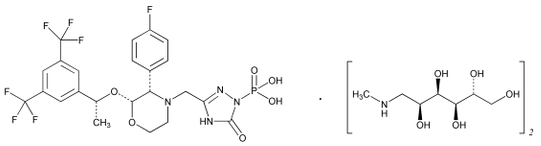
Faropenem Medoxomil [*2006*] (far″ oh pen′ em). $C_{17}H_{19}NO_8S$. 397.40. [Faropenem is INN.] (1) 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[(2*R*)-tetrahydro-2-furanyl]-, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5*R*,6*S*); (2) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl (5*R*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[(2*R*)-tetrahydrofuran-2-yl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate. *CAS-141702-36-5; CAS-106560-14-9* [faropemnem]. *Treatment of bacterial infections.* (Replidyne); (Nippon Soda); (Tropon GmbH) *[Name previously used: Fropenem.]* ✧*A0026*



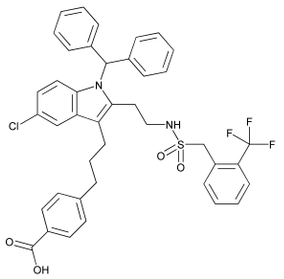
Fentanyl [*2006*] (fen′ ta nil). $C_{22}H_{28}N_2O$. 336.47. (1) Propanamide, *N*-phenyl-*N*-[1-(2-phenylethyl)-4-piperidinyl]; (2) *N*-(1-Phenethylpiperidin-4-yl)-*N*-phenylpropionamide. *CAS-437-38-7*. *Analgesic.* Sublimaze (McNeil); Duragesic (ALZA) ✧



Fosaprepitant Dimeglumine [*2005*] (fos″ a pre′ pi tant). $C_{23}H_{22}F_7N_4O_6P \cdot 2C_7H_{17}NO_5$. 1004.83. [Fosaprepitant is INN.] (1) D-Glucitol, 1-deoxy-1-(methylamino)-, [3-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate (2:1) (salt); (2) Bis(1-deoxy-1-(methylamino)-D-Glucitol) [3-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-2,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]phosphonate. *CAS-265121-04-8; CAS-172673-20-0* [fosaprepitant]. *Antiemetic.* (Merck) ✧*MK-0517*



Giripladib [*2006*] (jir ip′ la dib). $C_{41}H_{36}ClF_3N_2O_4S$. 745.25. (1) Benzoic acid, 4-[3-[5-chloro-1-(diphenylmethyl)-2-[2-[[[[2-(trifluoromethyl)phenyl]methyl]sulfonyl]amino]ethyl]-1*H*-indol-3-yl]propyl]-; (2) 4-[3-[5-Chloro-1-(diphenylmethyl)-2-[2-[[[2-(trifluoromethyl)benzyl]sulfonyl]amino]ethyl]-1*H*-indol-3-yl]propyl]benzoic acid. *CAS-865200-20-0*. *Treatment of pain and symptomatic management of arthritis.* (Wyeth) ✧*PLA-695*



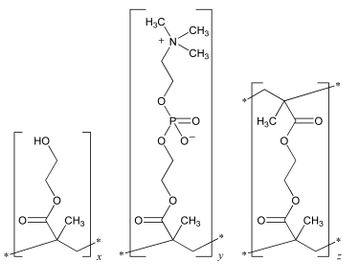
Hyaluronidase (Ovine) [*2004*] (hye″ al ure on′ i dase). **USP** [Injection]. $C_{2600}H_{4040}N_{696}O_{774}S_{23}$ (peptide). (1) Hyaluronidase (sheep testis isoenzyme); (2) Hyaluronidase (glycoprotein, sheep testis isoenzyme). Molecular weight is approximately 58,170 daltons. *CAS-488712-31-8; CAS-9001-54-1*. INN; BAN; JAN. *Clearance of vitreous hemorrhage.* Diffusin (Ortho Pharmaceutical†); Enzodase (Bristol-Myers Squibb†); Hyazyme (Abbott†); Vitrase (Biozyme Laboratories Ltd., UK); Wydase (Wyeth-Ayerst) [NOTE—The source of the product (ovine, porcine, etc.) must be indicated in the labeling.]✧ *HYO6A*

LDFRAPPLIS NTSFLWAWNA PAERCVKIFK LPPDLRLFSV KGSPQKSATG
QFITLFYADR LGYYPHIDEK TGNTVYGGIP QLGNLKNHLE KAKKDIAYYI
PNDSVGLAVI DWENWRPTWA RNWKPKDVYR DESVELVLQK NPQLSFPEAS
KIAKVDFETA GKSFMQETLK LGKLLRPNHL WGYYLFPDCY NHNYNQPTYN
GNCSDLEKRR NDDLDWLWKE STALFPSVYL NIKLKSTPKA AFYVRNRVQE
AIRLSKIASV ESPLPVFVYH RPVFTDGSST YLSQGDLVNS VGEIVALGAS
GIIMWGSLNL SLTMQSCMNL GNYLNTTLNP YIINVTLAAK MCSQVLCHDE
GVCTRKQWNS SDYLHLNPMN FAIQTGKGGK YTVPGKVTLE DLQTFSDKFY
CSCYANINCK KRVDIKNVHS VNVCMAEDIC IEGPVKLQPS DHSSSQNEAS
TTTVSSISPS TTATTVSPCT PEKQSPECLK VRCLEAIANV TQTGCQGVKW
KNTSSQSSIQ NIKNQTTY

USP DI Category: Spreading agent.

Linaclotide Acetate [*2006*] (lin″ a kloe′ tide). $C_{59}H_{79}N_{15}O_{21}S_6.C_2H_4O_2$. 1586.79. (1) L-Tyrosine, L-cysteinyl-L-cysteinyl-L-α-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-, cyclic (1→6),(2→10),(5→13)-tris(disulfide), monoacetate (salt); (2) L-Cysteinyl-L-cysteinyl-L-α-glutamyl-L-tyrosyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl-L-tyrosine cyclic (1→6),(2→10),(5→13)-tris(disulfide) monoacetate (salt). *CAS-851199-60-5*. *Treatment of gastrointestinal disorders including irritable bowel syndrome with constipation* (*IBS-C*) *and chronic constipation* (*CC*). (Microbia) ✧*MM-416775*

Omafilcon A [*1995*] (oh ma fil′ kon). $(C_6H_{10}O_3)_x(C_{11}H_{22}NO_6P)_y(C_{10}H_{14}O_4)_z$. (1) 2-Hydroxyethyl 2-methyl-2-propenoate polymer with 4-hydroxy-*N*,*N*,*N*,10-tetramethyl-9-oxo-3,5,8-trioxa-4-phosphaundec-10-en-1-aminium inner salt 4-oxide and 1,2-ethanediyl bis(2-methyl-2-propenoate); (2) 2-Hydroxyethyl methacrylate polymer with choline hydroxide, 2-hydroxyethyl hydrogen phosphate, inner salt, methacrylate and ethylene dimethacrylate. *CAS-144056-32-6. Contact lens material (hydrophilic). Proclear (Biocompatibles)* [NOTE—The water content of the contact lens material is 59 ± 1% at ambient temperature (23 ± 2°C), and the oxygen permeability is 25 ± 1 × 10^{-11} (cm^2/sec)(ml O_2/ml × mm Hg) at 35°C (Dk value).]✧



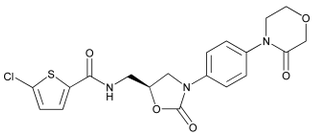
Ovemotide [*2005*] (oh ven′ oh tide). $C_{46}H_{71}N_9O_{14}$. 974.11. (1) L-Valine, L-tyrosyl-L-leucyl-L-α-glutamyl-L-prolylglycyl-L-prolyl-L-valyl-L-threonyl-; (2) [264-L-Valine]melanocyte protein Pmel 17 (human melanoma-associated ME20 antigen)-(256-264)-peptide. *CAS-181477-91-8*. INN. *Melanoma peptide vaccine.* (Medarex) ✧*MPS-21*

Y L E P G P V T V

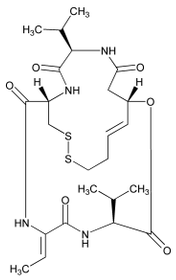
Rinfabate [*2006*] (rin′ fa bate). (1) Insulin-like growth factor-binding protein-3 (human); (2) Recombinant human insulin-like growth factor-binding protein 3. Molecular weight is approximately 28,732 daltons. *CAS-405341-12-0*. *Anti-cancer agent.* (Insmed Therapeutic Proteins) ✧*rhIGFBP-3*

GASSAGLGPV VRCEPCDARA LAQCAPPPAV CAELVREPGC GCCLTCALSE
GQPCGIYTER CGSGLRCQPS PDEARPLQAL LDGRGLCVNA SAVSRLRAYL
LPAPPAPGNA SESEEDRSAG SVESPSVSST HRVSDPKFHP LHSKIIIIKK
GHAKDSQRYK VDYESQSTDT QNFSSESKRE TEYGPCRREM EDTLNHLKFL
NVLSPRGVHI PNCDKKGFYK KKQCRPSKGR KRGFCWCVDK YGQPLPGYTT
KGKEDVHCYS MQSK

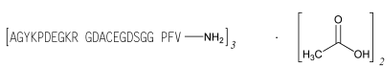
Rivaroxaban [*2006*] (ri va rox′ a ban). $C_{19}H_{18}ClN_3O_5S$. 435.88. (1) 2-Thiophenecarboxamide, 5-chloro-*N*-[[(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]-; (2) 5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide. *CAS-366789-02-8*. INN. *Prophylaxis of venous thromboembolism.* (Bayer HealthCare) ✧*BAY 59-7939*



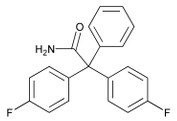
Romidepsin [*2006*] (Roe″ mi dep′ sin). $C_{24}H_{36}N_4O_6S_2$. 540.70. (1) Cyclo[(2*Z*)-2-amino-2-butenoyl-L-valyl-(3*S*,4*E*)-3-hydroxy-7-mercapto-4-heptenoyl-D-valyl-D-cysteinyl], cyclic (3→5)-disulfide; (2) (1*S*,4*S*,7*Z*,10*S*,16*E*,21*R*)-7-Ethylidene-4,21-bis(1-methylethyl)-2-oxa-12,13-dithia-5,8,20,23-tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone. *CAS-128517-07-7*. INN. *Antitumor/anticancer drug.* Chromadax (Gloucester) ✧*FR901228; FK228*



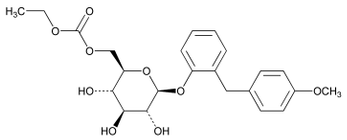
Rusalatide Acetate [*2006*] (roo sal′ a tide). $(C_{97}H_{147}N_{29}O_{35}S)_3.(C_2H_4O_2)_2$. 7054.00. (1) L-Valinamide, L-alanylglycyl-L-tyrosyl-L-lysyl-L-prolyl-L-α-aspartyl-L-α-glutamylglycyl-L-lysyl-L-arginylglycyl-L-α-aspartyl-L-alanyl-L-cysteinyl-L-α-glutamylglycyl-L-α-aspartyl-L-serylglycylglycyl-L-prolyl-L-phenylalanyl-, acetate (3:2) (salt); (2) L-Alanylglycyl-L-tyrosyl-L-lysyl-L-prolyl-L-α-aspartyl-L-α-glutamylglycyl-L-lysyl-L-arginylglycyl-L-α-aspartyl-L-alanyl-L-cysteinyl-L-α-glutamylglycyl-L-α-aspartyl-L-serylglycylglycyl-L-prolyl-L-phenylalanyl-L-valinamide, acetate (3:2) salt. *CAS-875455-82-6*. *Promotes healing of bone, skin wounds, cartilage, cardiovascular tissue and ligaments/tendons.* Chrysalin (OrthoLogic) ✧*TP 508; TRAP-508*



Senicapoc [*2006*] (sen″ i kay′ pok). $C_{20}H_{15}F_2NO$. 323.34. (1) Benzeneacetamide, 4-fluoro-α-(4-fluorophenyl)-α-phenyl-; (2) 2,2-Bis(4-fluorophenyl)-2-phenylacetamide. *CAS-289656-45-7*. *Treatment of disorders mediated by a calcium activated intermediate conductance potassium ion channel antagonist.* (Icagen); (McNeil-PPC) ✧*ICA-17043*

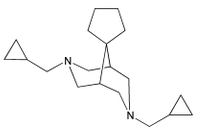


Sergliflozin [*2006*] (ser″ gli floe′ zin). $C_{23}H_{28}O_9$. 448.46. (1) β-D-Glucopyranoside, 2-[(4-methoxyphenyl)methyl]phenyl, 6-(ethyl carbonate); (2) 2-(4-Methoxybenzyl)phenyl 6-*O*-(ethoxycarbonyl)-β-D-glucopyranoside. *CAS-408504-26-7*. *Treatment of type 2 diabetes.* (GlaxoSmithKline) ✧*GW869682X*

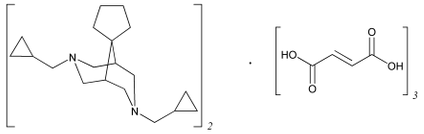


Sipuleucel-T [*2005*] (sye″ pul oo′ sel). Product is a specific active immunotherapeutic composed of antigen-loaded autologous antigen presenting cells designed to stimulate a T cell immune response specific for the tumor-associated antigen prostatic acid phosphatase (PAP). *Treatment of prostate cancer.* Provenge (Dendreon) ✧*APC8015*

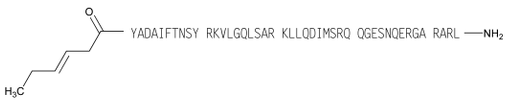
Tedisamil [*2005*] (te dis′ a mil). $C_{19}H_{32}N_2$. 288.47. (1) Spiro[cyclopentane-1,9′-[3,7]diazabicyclo[3.3.1]nonane], 3′,7′-bis(cyclopropylmethyl)-; (2) 3′,7′-Bis(cyclopropylmethyl) spiro[cyclopentane-1,9′-[3,7]diazabicyclo[3.3.1]nonane]. *CAS-90961-53-8*. INN. *Antiarrhythmic agent (K⁺channel blocker)*. (Solvay Pharmaceuticals) ✧*KC8857*



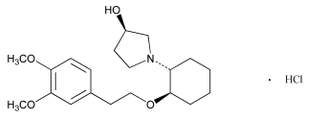
Tedisamil Sesquifumarate [*2005*] (ted″ i′ sam il ses″ kwi fue′ ma rate). $2C_{19}H_{32}N_2 \cdot 3C_4H_4O_4$. 925.16. (1) Spiro[cyclopentane-1,9′-[3,7]diazabicyclo[3.3.1]nonane], 3′,7′-bis(cyclopropylmethyl)-, (2*E*)-2-butenedioate (2:3); (2) Bis[3′,7′-bis(cyclopropylmethyl)-spiro[cyclopentane-1,9′-[3,7]diazabicyclo[3.3.1]nonane]] dihydrogen tris[(2*E*-but-2-enedioate]. *CAS-150501-62-5*. *Antiarrhythmic agent (K⁺ channel blocker);* (Solvay Pharmaceuticals) ✧*KC8857*



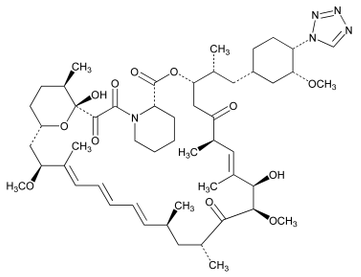
Tesamorelin [*2006*] (tes″ a moe rel′ in). $C_{221}H_{366}N_{72}O_{67}S$. 5135.78. (1) L-Leucinamide, *N*-[(3*E*)-1-oxo-3-hexenyl]-L-tyrosyl-L-alanyl-L-α-aspartyl-L-alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucylglycyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-α-aspartyl-L-isoleucyl-L-methionyl-L-seryl-L-arginyl-L-glutaminyl-L-glutaminylglycyl-L-α-glutamyl-L-seryl-L-asparaginyl-L-glutaminyl-L-α-glutamyl-L-arginylglycyl-L-alanyl-L-arginyl-L-alanyl-L-arginyl-; (2) (3*E*)-Hex-3-enoylsomatoliberin (human). *CAS-218949-48-5*. *Reduction of visceral adipose tissue in patients receiving antiretroviral therapy.* (Theratechnologies) ✧*TH9507*



Vernakalant Hydrochloride [*2006*] (ver nayk′ a lant). $C_{20}H_{31}NO_4 \cdot HCl$. 385.93. (1) 3-Pyrrolidinol, 1-[(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl]-, hydrochloride, (3*R*)-; (2) (3*R*)-1-[(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl]pyrrolidin-3-ol hydrochloride. *CAS-748810-28-8*. *Treatment of patients with atrial fibrillation and atrial flutter.* (Astellas); (Cardiome) ✧*RSD1235*



Zotarolimus [*2005*] (zoe ta roe′ li mus). $C_{52}H_{79}N_5O_{12}$. 966.21. (1) Rapamycin, 42-deoxy-42-(1*H*-tetrazol-1-yl)-, (42*S*)-; (2) (1*R*, 9*S*, 12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*, 35*R*)-1,18-Dihydroxy-19,30-dimethoxy-12-[(1*R*)-2-[(1*S*,3*R*,4*S*)-3-methoxy-4-(1*H*-tetrazol-1-yl)cyclohexyl]-1-methylethyl]-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentone. *CAS-221877-54-9*. INN. *Drug component of phosphorycholine polymer coated drug-eluting stent currently under evaluation for the prevention of coronary restenosis following stent replacement.* (Abbott) ✧*ABT-578*



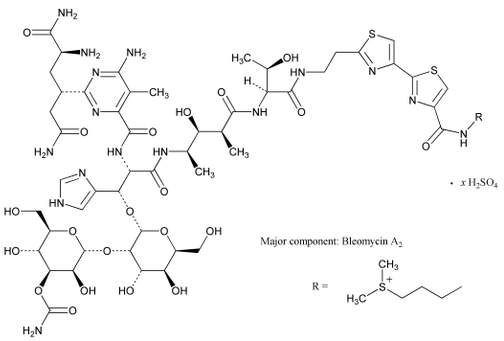
Nomenclature

Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

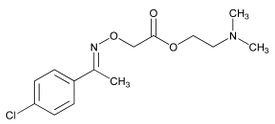
Bleomycin Sulfate

Change the chemical structure to read:



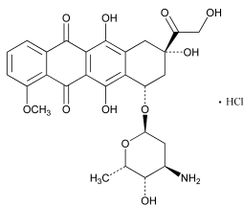
Cloximate

Change the chemical structure to read:



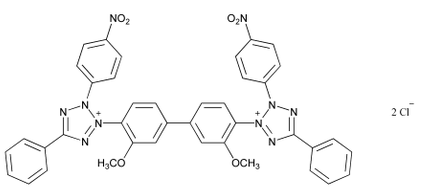
Epirubicin Hydrochloride

Change the chemical structure to read:



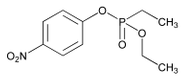
Nitroblue Tetrazolium Chloride

Add the chemical structure to read:



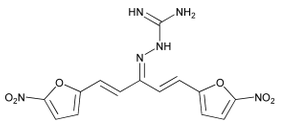
***p*-Nitrophenyl-*O*-ethyl Ethylphosphonate**

Add the chemical structure to read:



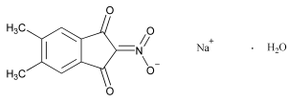
Nitrovin

Add the chemical structure to read:



Nivimedone Sodium

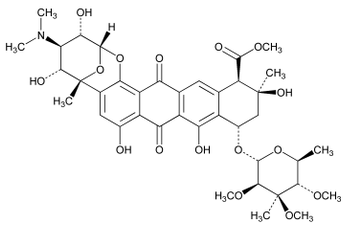
Add the chemical structure to read:



Nogalamycin

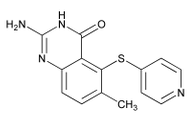
Change the molecular formula and weight and the chemical structure to read:

$C_{39}H_{49}NO_{16}$. 787.80.



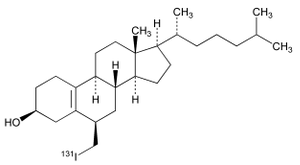
Nolatrexed

Add the chemical structure to read:



Norcholestenol Iodomethyl

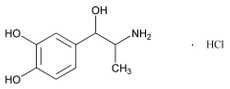
Add the chemical structure to read:



Nordefrin Hydrochloride

Add the chemical information and structure to read:

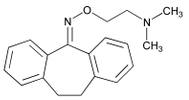
$C_9H_{13}NO_3 \cdot HCl$. 219.67.
(±)-α-(1-Aminoethyl)-3,4-dihydroxybenzyl alcohol hydrochloride.



Noxiptiline

Change the chemical name and structure to read:

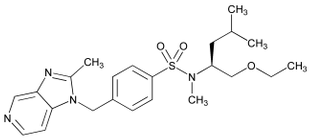
10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-one *O*-[(2-dimethylamino)ethyl]oxime.



Nupafant

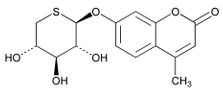
Change the chemical name and structure to read:

N-[(*S*)-1-(Ethoxymethyl)-3-methylbutyl]-*N*-methyl-α-(2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)-*p*-toluenesulfonamide.



Odiparcil

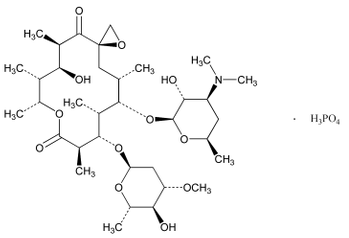
Add the chemical structure to read:



Oleandomycin Phosphate

Add the CAS numbers and change the chemical structure to read:

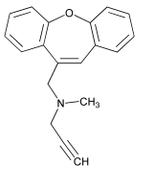
CAS-7060-74-4; CAS-3922-90-5 [oleandomycin].



Omigapil

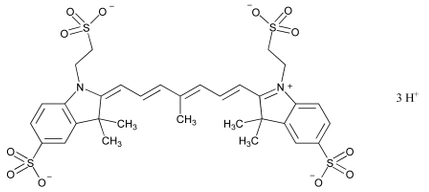
Change the chemical name and add the chemical structure to read:

N-(Dibenzo[*b,f*]oxepin-10-ylmethyl)-*N*-methylprop-2-yn-1-amine.



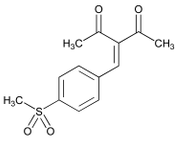
Omocianine

Add the chemical structure to read:



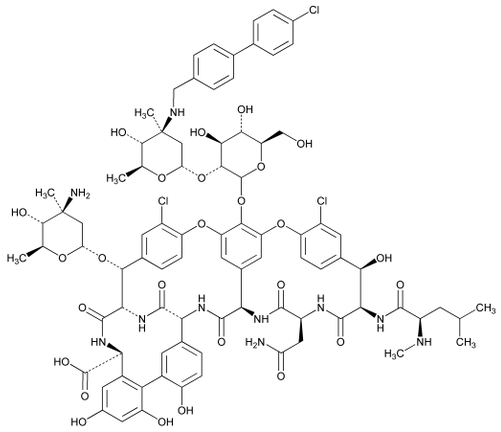
Orazipone

Add the chemical structure to read:



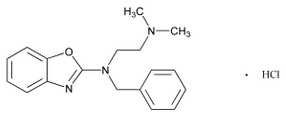
Oritavancin

Change the chemical structure to read:



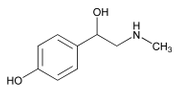
Oxadimedine Hydrochloride

Change the chemical structure to read:



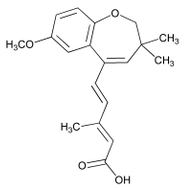
Oxedrine

Add the chemical structure to read:



Oxeglitazar

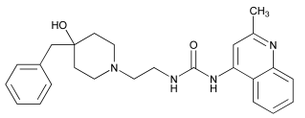
Add the chemical structure to read:



Palosuran

Add the molecular weight and the chemical structure to read:

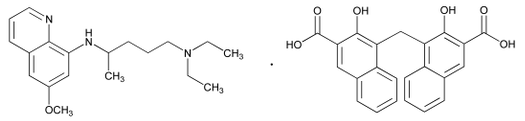
418.53



Pamaquine Naphthoate

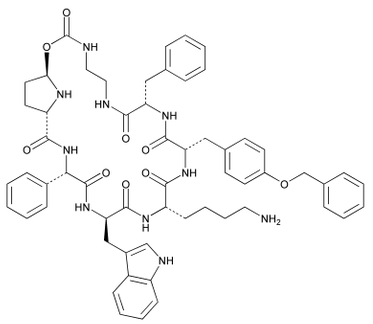
Add the chemical names and change the chemical structure to read:

(1) Quinoline, 6-methoxy-8-(1-methyl-4-diethylamino)butylamino, methylene-bis-β-hydroxynaphthoate; (2) N^1,N^1-Diethyl-N^4-(6-methoxyquinolin-8-yl)pentane-1,4-diamine pamoate.



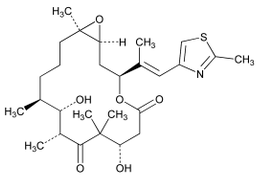
Pasireotide

Add the chemical structure to read:



Patupilone

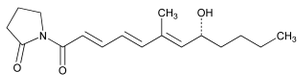
Add the chemical structure to read:



Pecilocin

Add the chemical information and change the chemical structure to read:

$C_{17}H_{25}NO_3$. 291.39. 2-Pyrrolidinone, 1-(8-hydroxy-6-methyl-2,4,6-dodecatrienoyl)-, (*E,E,E*)-(*R*)-.



Pegademase Bovine

Delete the chemical structure

Pegaspargase

Delete the chemical structure

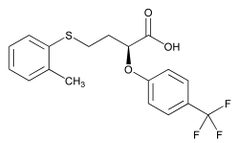
Pegoterate

Delete the chemical structure

Pemaglitazar

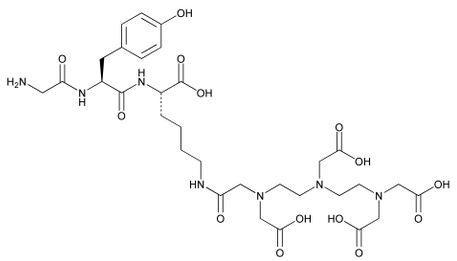
Change the chemical name and add the chemical structure to read:

(2*S*)-4-[(2-Methylphenyl)sulfanyl]-2-[4-(trifluoromethyl)phenoxy]butanoic acid.



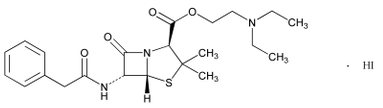
Pendetide

Add the chemical structure to read:



Penethamate Hydriodide

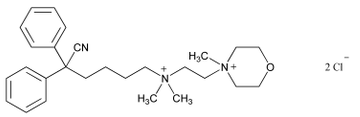
Add the chemical structure to read:



Pentacynium Chloride

Change the chemical name and add the chemical structure to read:

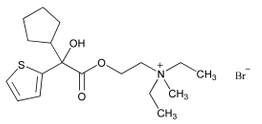
N-[*N*′-(5-Cyano-5,5-diphenylpentyl)-*N*′-dimethylammoniummethyl]-*N*-methylmorpholinium dichloride.



Penthienate Bromide

Add the chemical information and structure to read:

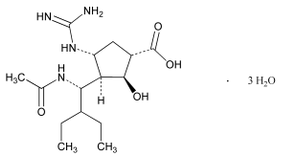
$C_{18}H_{30}BrNO_3S$. 420.40. (1) Diethyl(2-hydroxyethyl)methylammonium bromide α-cyclopentyl-2-thiopheneglycolate; (2) 2-(2-Cyclopentyl-2-hydroxy-2-(thiophen-2-yl)acetoxy)-*N,N*-diethyl-*N*-methylethanaminium bromide.



Peramivir

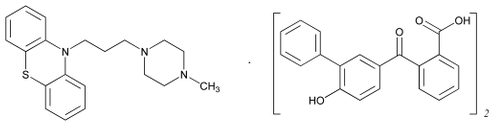
Change the chemical information and structure to read:

$C_{15}H_{28}N_4O_4 \cdot 3H_2O$. (1*S*,2*S*,3*R*,4*R*)-3-[(1*S*)-1-Acetylamino-2-ethylbutyl]-4-[(aminoiminomethyl)amino]-2-hydroxycyclopentanecarboxylic acid.



Perazine Fendizoate

Add the chemical structure to read:



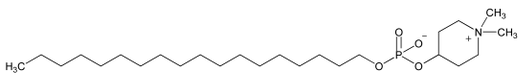
Perflisobutane

Add the chemical structure to read:

Perifosine

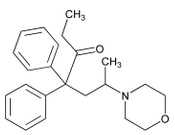
Change the chemical name and add the chemical structure to read:

1,1-Dimethylpiperidinium-4-yl octadecyl phosphate, inner salt.



Phenaxodone

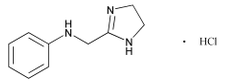
Add the chemical structure to read:



Phenamazoline Hydrochloride

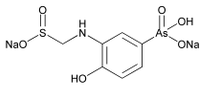
Add the chemical name and change the chemical structure to read:

N-((4,5-Dihydro-1*H*-imidazol-2-yl)methyl)aniline hydrochloride.



Phenarsone Sulfoxylate

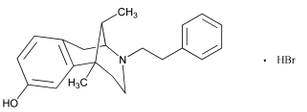
Add the chemical structure to read:



Phenazocine Hydrobromide

Add the chemical information and change the chemical structure to read:

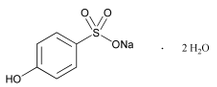
$C_{22}H_{27}NO \cdot HBr$. 402.37. 2′-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan.



Phenolsulphonate Sodium

Add the chemical information and structure to read:

$C_6H_5NaO_4S \cdot 2H_2O$. 232.19. Sodium 4-hydroxybenzenesulfonate, dihydrate. *CAS-10580-19-5*.



Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO).

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

Proposed International Nonproprietary Names

The following 68 names have been selected by the World Health Organization (WHO) as Proposed International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information,* Vol. 20, No. 2, 2006.

Any comments or formal objections to the proposed names should be addressed to Helene Biernacki, Research Associate, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Proposed INN	Therapeutic Indication
Abagovomab	*Immunological agent, Antineoplastic*
Iodofiltic Acid (^{123}I)	*Radiopharmaceutical*
Aclidinium Bromide	*Muscarinic receptor antagonist*
Afimoxifene	*Anti-estrogen*
Aflibercept	*Angiogenesis inhibitor*
Aleglitazar	*Antidiabetic*
Alferminogene Tadenovec	*Gene therapy product—stimulates angiogenesis*
Apilimod	*Immunomodulator*
Apricitabine	*Antiviral*
Atacicept	*Immunomodulator*
Azilsartan	*Angiotensin II receptor antagonist*
Bavituximab	*Antineoplastic*
Bedoradrine	*β_2-adrenoceptor agonist*
Beperminogene Perplasmid	*Gene therapy product—stimulates angiogenesis for tissue repair*
Beroctocog Alfa	*Blood coagulation factor*
Bremelanotide	*Melanocortin receptor agonist*
Bucelipase Alfa	*Enzyme*
Camobucol	*Anti-inflammatory*
Capadenoson	*Adenosine A_1 receptor agonist*
Catramilast	*Phosphodiesterase IV inhibitor*
Cediranib	*Angiogenesis inhibitor*
Denibulin	*Antineoplastic*
Dexelvucitabine	*Antiviral*
Efungumab	*Immunomodulator*
Elacytarabine	*Antineoplastic*
Elocalcitol	*Vitamin D analogue*
Elsibucol	*Anti-inflammatory*
Epoetin Theta	*Anti-anaemic*
Ferroquine	*Antimalarial*
Fluticasone Furoate	*Steroidal anti-inflammatory*
Fosalvudine Tidoxil	*Antiviral*
Gamithromycin	*Antibiotic (veterinary use)*
Ilepatril	*Antihypertensive*
Imisopasem Manganese	*Anti-inflammatory*
Inakalant	*Anti-arrhythmic*
Lapaquistat	*Squalene synthase inhibitor*
Levonadifloxacin	*Antibacterial*
Lexatumumab	*Antineoplastic*
Lificiguat	*Guanylate cyclase activator*
Lobeglitazone	*Antidiabetic*
Lorcaserin	*Serotonin receptor agonist*
Mifamurtide	*Antineoplastic*
Migalastat	*Alpha-galactosidase A enzyme inhibitor*
Mirodenafil	*Vasodilator*
Motavizumab	*Immunomodulator*
Naproxcinod	*Anti-inflammatory*
Omtriptolide	*Antineoplastic*
Pafuramidine	*Antiparasitic*
Piraxostat	*Xanthine oxydase inhibitor*
Pramiconazole	*Antifungal*
Prinaberel	*Beta estrogen receptor agonist*
Rilonacept	*Immunomodulator*
Rosabulin	*Antineoplastic*
Sagopilone	*Antineoplastic*
Sodelglitazar	*Antidiabetic*
Sofigatran	*Thrombin inhibitor*
Succinobucol	*Anti-inflammatory*
Taribavirin	*Antiviral*
Tezampanel	*AMPA/KA glutamate receptor antagonist*
Ticagrelor	*Platelet aggregation inhibitor*
Tigapotide	*Antineoplastic*
Tipelukast	*Leukotriene receptor antagonist*
Tomopenem	*Antibiotic*
Tylvalosin	*Antibiotic*
Vabicaserin	*Serotonin receptors agonist, antipsychotic*
Vapitadine	*Tricyclic histamine H_1 receptor antagonist*
Veliflapon	*5-Lipoxygenase activating protein (FLAP) antagonist*
Volinanserin	*Serotonin receptor antagonist*

Recommended International Nonproprietary Names

The following 74 nonproprietary names have been selected by the World Health Organization (WHO) as Recommended International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information,* Vol. 20, No. 3, 2006.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Alcaftadine	Dilopetine	Mavacoxib	Sitagliptin
Amibegron	Disomotide	Nilotinib	Sontuzumab
Antithrombin Alfa	Dutacatib	Nimotuzumab	Sotirimod
Apadenoson	Eltrombopag	Obatoclax	Stamulumab
Aplaviroc	Eprodisate	Ocrelizumab	Tadocizumab
Avosentan	Fimasartan	Oglemilast	Talotrexin
Axitinib	Fosaprepitant	Olaparib	Telaprevir
Bosutinib	Fospropofol	Orvepitant	Tiplasinin
Brecanavir	Gabapentin Enacarbil	Ovemotide	Tramiprosate
Capeserod	Goxalapladib	Ozarelix	Transferrin Aldifitox
Casopitant	Incyclinide	Paquinimod	Tucotuzumab Celmoleukin
Celivarone	Indantadol	Parogrelil	Velafermin
Cevoglitazar	Ipilimumab	Pazopanib	Verpasep Caltespen
Darapladib	Iratumumab	Relacatib	Vicriviroc
Dasatinib	Larotaxel	Rilapladib	Vorinostat
Denagliptin	Lisdexamfetamine	Rolipoltide	Zibotentan
Denosumab	Lodenafil Carbonate	Romidepsin	Zotarolimus
Dexamethasone Cipecilate	Masilukast	Rotigaptide	
Diaplasinin		Sapacitabine	
		Simotaxel	

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