Commentary

USP 39–NF 34, Second Supplement

June 1, 2016

In accordance with USP's Rules and Procedures of the Council of Experts ("Rules") and except as provided in Section 7.02 Accelerated Revision Processes, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary* (*USP–NF*) for public review and comment in the *Pharmacopeial Forum (PF),* USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be republished in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without republication in *PF,* a summary of comments received and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of the USP Web site at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference between the contents of the Commentary and the official text, the official text prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the Commentary, shall prevail.

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Comments were received for the following when they were proposed in Pharmacopeial Forum

General Chapters:

- <2> Oral Drug Products—Product Quality Tests
- <3> Topical and Transdermal Drug Products—Product Quality Tests
- <4> Mucosal Drug Products—Product Quality Tests
- <212> Oligosaccharide Analysis
- <341> Antimicrobial Agents—Content
- <771> Ophthalmic Products—Quality Tests
- <1004> Mucosal Drug Products-Performance Tests
- <1029> Good Documentation Guidelines
- <1063> Shear Cell Methodology for Powder Flow Testing
- <1130> Nucleic Acid-Based Techniques—Approaches for Detecting Trace Nucleic Acids (Residual DNA Testing)
- <1228.3> Depyrogenation by Filtration
- <1228.5> Endotoxin Indicators for Depyrogenation
- <1229.13> Sterilization-in-Place
- <1231> Water for Pharmaceutical Purposes
- <2040> Disintegration and Dissolution of Dietary Supplements

Monographs:

- Acetaminophen Suppositories
- Acetazolamide Compounded Oral Suspension
- Allopurinol Compounded Oral Suspension
- Amiodarone Hydrochloride Compounded Oral Suspension
- Amitraz Concentrate for Dip
- Amlodipine Compounded Oral Suspension
- Aripiprazole
- Atenolol Compounded Oral Solution
- Azathioprine Compounded Oral Suspension
- Baclofen Compounded Oral Suspension
- Benzalkonium Chloride Solution
- Bethanechol Chloride Compounded Oral Solution
- Bethanechol Chloride Compounded Oral Suspension
- Bismuth Subsalicylate Oral Suspension
- Calcium Propionate
- Captopril Compounded Oral Solution
- Captopril Compounded Oral Suspension
- Cetirizine Hydrochloride Orally Disintegrating Tablets
- Chloroquine Phosphate Compounded Oral Suspension
- Ciprofloxacin
- Ciprofloxacin Hydrochloride
- Clonazepam Compounded Oral Suspension
- Codeine Phosphate Compounded Oral Solution
- Compounding Monographs—General
- Dapsone Compounded Oral Suspension
- Desloratadine
- Desloratadine Orally Disintegrating Tablets
- Desloratadine Tablets
- Diclofenac Sodium
- Diltiazem Hydrochloride Extended-Release Capsules
- Diltiazem Hydrochloride Compounded Oral Solution
- Diltiazem Hydrochloride Compounded Oral Suspension
- Dipyridamole Compounded Oral Suspension
- Dolasetron Mesylate Compounded Oral Solution
- Dolasetron Mesylate Compounded Oral Suspension
- Doxapram Hydrochloride
- Enalapril Maleate Compounded Oral Suspension
- Flecainide Acetate Compounded Oral Suspension
- Flucytosine Compounded Oral Suspension
- Ganciclovir Compounded Oral Suspension

- Granisetron Hydrochloride Compounded Oral Suspension
- Hydralazine Hydrochloride Compounded Oral Solution
- Hydrochloric Acid Compounded Injection
- Ibuprofen Tablets
- Indomethacin Compounded Topical Gel
- Isradipine Compounded Oral Suspension
- Ketoconazole Compounded Oral Suspension
- Labetalol Hydrochloride Compounded Oral Suspension
- Lisinopril
- Lisinopril Compounded Oral Suspension
- Magnesium Aluminum Silicate
- Metolazone Compounded Oral Suspension
- Metoprolol Tartrate Compounded Oral Solution
- Metronidazole Gel
- Naratriptan Compounded Oral Suspension
- Niacin
- Octreotide Acetate
- Ondansetron Compounded Hydrochloride Oral Suspension
- Oral Rehydration Salts
- Oxymorphone Hydrochloride Extended-Release Tablets
- Oxymorphone Hydrochloride Tablets
- Pentoxifylline Compounded Oral Suspension
- Phenobarbital Compounded Oral Suspension
- Polyethylene Glycol
- Polyethylene Glycol 3350
- Polyvinyl Acetate Dispersion
- Potassium Bromide Compounded Oral Solution, Veterinary
- Progesterone Compounded Vaginal inserts
- Promethazine Hydrochloride
- Promethazine Hydrochloride Tablets
- Propylthiouracil Compounded Oral Suspension
- Pyrazinamide Compounded Oral Suspension
- Pyrimethamine Compounded Oral Suspension
- Quinidine Sulfate Compounded Oral Suspension
- Rifabutin Compounded Oral Suspension
- Rifampin Compounded Oral Suspension
- Ropinirole Extended-Release Tablets
- Sildenafil Compounded Citrate Oral Suspension
- Sodium Bromide Compounded Injection, Veterinary
- Sodium Bromide Compounded Oral Solution, Veterinary
- Sodium Hypochlorite Compounded Topical Solution
- Sodium Phenylbutyrate Compounded Oral Suspension
- Sotalol Hydrochloride Compounded Oral Suspension
- Sprionolactone and Hydrochlorothiazide Compounded Oral Suspension
- Sulfamethoxazole and Trimethoprim Oral Suspension
- Sumatriptan Compounded Oral Suspension
- Tacrolimus
- Tacrolimus Capsules
- Tacrolimus Compound Oral Suspension
- Temozolomide Compounded Oral Suspension
- Terbinafine Compounded Oral Suspension
- Terbutaline Sulfate Compounded Oral Suspension
- Tetracycline Hydrochloride Oral Suspension
- Tiagabine Hydrochloride Compounded Oral Suspension
- Tramadol Hydrochloride and Acetaminophen Compounded Oral Suspension
- Tramadol Hydrochloride Compounded Oral Suspension
- Trihexyphenidyl Hydrochloride Tablets
- Ursodiol Compounded Oral Suspension
- Valacyclovir Compounded Oral Suspension
- Verapamil Hydrochloride Compounded Oral Solution
- Verapamil Hydrochloride Compounded Oral Suspension
- Zolmitriptan Orally Disintegrating Tablets

No comments were received for the following proposal when they were proposed in Pharmacopeial Forum:

General Chapters:

- <5> Inhalation and Nasal Drug Products General Information and Product Quality Tests
- <121.1> Physicochemical Analytical Procedures for Insulins
- <782> Vibrational Circular Dichroism Spectroscopy
- <1782> Vibrational Circular Dichroism Spectroscopy—Theory and Practice
- <2750> Manufacturing Practices for Dietary Supplements

Monographs:

- Alprazolam Oral Suspension
- Aminobenzoate Potassium
- Aminobenzoate Sodium
- Amitraz
- Antithrombin Iii Human
- Azelastine Hydrochloride
- Chlordiazepoxide Hydrochloride For Injection
- Chlorobutanol
- Chlorothiazide Oral Suspension
- Chlorothiazide Tablets
- Codeine Sulfate Tablets
- Compounding Monographs - General
- Diatrizoate Sodium
- Diclofenac Potassium
- Dolasetron Mesylate Injection
- Dolasetron Mesylate Tablets
- Doxapram Hydrochloride Injection
- Extended Insulin Zinc Suspension
- Guaifenesin
- Half-Strength Lactated Ringer's and Dextrose Injection
- Hydroxyprogesterone Caproate Injection
- Imipramine Pamoate Capsules
- Insulin Injection
- Insulin Zinc Suspension
- Iopanoic Acid
- Iopanoic Acid Tablets
- Ipodate Sodium
- Ipodate Sodium Capsules
- Isophane Insulin Suspension
- Lactated Ringer's and Dextrose Injection
- Lactated Ringer's Injection
- Mangafodipir Trisodium
- Mangafodipir Trisodium Injection
- Mannitol
- Methylcobalamin Tablets
- Methylergonovine Maleate
- Metoprolol Tartrate Oral Suspension
- Metronidazole Extended-Release Tablets
- Modified Lactated Ringer's and Dextrose Injection
- Morphine Sulfate Compounded Suppositories
- Multiple Electrolytes and Dextrose Injection Type 1
- Multiple Electrolytes and Dextrose Injection Type 2
- Multiple Electrolytes and Dextrose Injection Type 3
- Multiple Electrolytes and Dextrose Injection Type 4
- Multiple Electrolytes and Invert Sugar Injection Type 1
- Multiple Electrolytes and Invert Sugar Injection Type 2
- Multiple Electrolytes and Invert Sugar Injection Type 3
- Multiple Electrolytes Injection Type 1
- Multiple Electrolytes Injection Type 2
- Mupirocin Calcium
- Naratriptan Hydrochloride Oral Suspension
- Northern Schisandra Fruit Dry Extract
- Oxymorphone Hydrochloride Injection
- Oxymorphone Hydrochloride Suppositories
- Pergolide Compounded Oral Suspension Veterinary
- Piroxicam Compounded Cream
- Potassium Benzoate
- Potassium Chloride in Dextrose And Sodium Chloride Injection
- Potassium Chloride In Dextrose Injection
- Potassium Chloride in Lactated Ringer's And Dextrose Injection
- Potassium Chloride In Sodium Chloride Injection
- Powdered Red Clover Extract
- Powdered St. John's Wort Extract
- Promethazine Hydrochloride Injection

- Promethazine Hydrochloride Oral Solution
- Prompt Insulin Zinc Suspension
- Ringer's and Dextrose Injection
- Shellac
- Schizochytrium Oil
- Sodium Cetostearyl Sulfate
- Sulconazole Nitrate
- Theophylline
- Theophylline Oral Solution
- Theophylline Compounded Oral Suspension
- Thiotepa For Injection
- Urea
- Valproic Acid
- Vinblastine Sulfate for Injection

General Chapter/Section(s): <2> Oral Drug Products—Product Quality Tests/ Multiple Sections
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 4

General

Comment Summary #1: The commenter suggested a test for Volatile Content for the non-active moiety of certain dosage forms of drug substance.
Response: Comment not incorporated. This will be addressed during the next revision of General Chapter <2>.
Comment Summary #2: The commenter suggested that additional consideration be given to content uniformity of "half tablets" in the situation of scored tablets.
Response: Comment not incorporated. This will be addressed during the next revision of General Chapter <2>.

Introduction

Comment Summary #3: The commenter suggested modifying the scope of the General Chapter not to omit the semi-solid oral dosage forms, like pastes intended for animals and described in General Chapter <1151> *Pharmaceutical Dosage Forms* by revising the sentence to read, "Oral drug products primarily fall into two main categories: solids and liquids."
Response: Comment incorporated.
Comment Summary #4: The commenter suggested reviewing the text, "Some of the tests indicated in this chapter may be performed on an in-process basis or omitted as routine tests based on process validation. However, the product must meet USP compendial requirements when sampled and tested, once the product is on the market," because it is entirely redundant with *General Notices* 3.10*. Applicability of Standards* and will create inconsistency and confusion.
Response: Comment not incorporated. This will be addressed during the next revision of General Chapter <2>.
Comment Summary #5: The commenter suggested reviewing the applicability of the General Chapter, because no drug product monograph makes reference to <2> and therefore there is potential for misinterpretation.
Response: Comment not incorporated. This will be addressed during the next revision of General Chapter <2> and other similar general chapters.

Introduction/Drug Product Quality Tests and Performance Tests

Comment Summary #6: The commenter recommended deleting the term, "soluble tablets," because the glossary in General Chapter <1151> indicates that soluble tablets are a "not preferred" dosage form term.
Response: Comment incorporated.

Product Quality Tests for Oral Drug Products/Universal Tests

Expert Committee-initiated Change #1: The title was revised to "Universal Tests for Oral Drug Products" to make it more specific to oral drug products and aligned with the content of each basic test description, and to differentiate it from the *General Notices* 5*. Monograph Components*.

Product Quality Tests for Oral Drug Products/Universal Tests/Description
Comment Summary #7: The commenter suggested deleting the section *Description,* because in *General Notices* 5.30*. Description and Solubility*, it is stated that the *Description* section is not considered a test.
Response: Comment not incorporated. It is a description of a qualitative measurement, only included for completeness and it clarifies that it is not a standard by itself.

Product Quality Tests for Oral Drug Products/Universal Tests/Identification, Assay, Impurities
Comment Summary #8: The commenter suggested including the information provided for each of these basic types of tests in *General Notices* 5*. Monograph Components*, rather than repeating, if considered useful.
Response: Comment not incorporated. This information is more specific for oral drug products. See *General Notices* section 3.10 on the applicability of general chapters.

Product Quality Tests for Oral Drug Products/Specific Tests for Tablets/Disintegration
Expert Committee-initiated Change #2: The two references to the *European Pharmacopeia* will be addressed during the next revision of the General Chapter <2>.

Product Quality Tests for Oral Drug Products/Specific Tests for Tablets/Uniformity of Dosage Units
Comment Summary #9: The commenter suggested including the test of *Uniformity of Dosage Units* in other dosage form types, and not only for Tablets. It could be included as *Universal Tests* or in other particular dosage forms.
Response: Comment not incorporated. This concern was not part of the current revision, and will be addressed during the next revision of the General Chapter <2>.

Product Quality Tests for Oral Drug Products/Uncoated Tablets
Comment Summary #10: The commenter suggested revising the heading to read "Specific Tests for Uncoated Tablets" to be consistent with other subheadings in the *Drug Product Quality Tests and Performance Tests*.
Response: Comment incorporated.

Comment Summary #11: The commenter suggested deleting the references to the terms "boluses" and "soluble tablets" from the list of uncoated tablets, because they are "not preferred" dosage form terms, as described in General Chapter <1151> *Pharmaceutical Dosage Forms*.
Response: Comment incorporated.

Product Quality Tests for Oral Drug Products/Uncoated Tablets/Buccal, Sublingual, and Orally Disintegrating (Orodispersible) Tablets
Comment Summary #12: The commenter recommended deleting the word "orodispersible," because General Chapter <1151> has identified this as a "not preferred" dosage form term.
Response: Comment incorporated.

Expert Committee-initiated Change #3: The content of this section was updated to reflect that General Chapter <4> *Mucosal Drug Products—Product Quality Tests* is already official, instead of published in *PF*.

Product Quality Tests for Oral Drug Products/Uncoated Tablets/Disintegrating and Dispersible Tablets
Comment Summary #13: The commenter recommended deleting the entire section, as both “disintegrating tablets” and “dispersible tablets” are described as “not preferred” dosage form terms in General Chapter <1151>.
Response: Comment incorporated.

Product Quality Tests for Oral Drug Products/Uncoated Tablets/Disintegrating and Dispersible Tablets/Dispersion fineness
Comment Summary #14: The commenter suggested adding a maximum amount of acceptable residue to the *Dispersion fineness* test.
Response: Comment partially incorporated. The test was deleted.

Product Quality Tests for Oral Drug Products/Uncoated Tablets/Tablets for Oral Solution and Tablets for Oral Suspension/Dispersion fineness
Comment Summary #15: The commenter suggested adding a maximum amount of acceptable residue to the *Dispersion fineness test.*
Response: Comment partially incorporated. The test was deleted.

Expert Committee-initiated Change #4: The content of this section was updated to include a definition of Tablets for Oral Solution and Tablets for Oral Suspension for informational purposes and completeness.

Product Quality Tests for Oral Drug Products/Coated Tablets
Comment Summary #16: The commenter suggested revising the heading to read “Specific Tests for Coated Tablets” to be consistent with other subheadings in the *Drug Product Quality Tests and Performance Tests*.
Response: Comment incorporated.
Comment Summary #17: The commenter recommended deleting “inactive and insoluble filler” from the list of various substances used in the coating because use of the term “filler” in this context is inconsistent with how it is normally used. Alternatively, the phrase may be revised to “inactive and insoluble ingredients.”
Response: Comment partially incorporated. The phrase was revised to “inactive and insoluble excipients.”

Product Quality Tests for Oral Drug Products/Specific Tests for Capsules
Comment Summary #18: The commenter recommended revising the definition of “Two-piece capsules” to delete “in a range of standard sizes” to allow for the use of a non-standard capsule.
Response: Comment incorporated.

Product Quality Tests for Oral Drug Products/Specific Tests for Capsules/Disintegration

Comment Summary #19: The commenter recommended deleting the reference to the *European Pharmacopeia* for additional information about the disintegration test for modified-release capsules. If this information is needed, it should be proposed for addition to the *USP–NF*.

Response: Comment not incorporated. This will be addressed during the next revision of General Chapter <2>.

Product Quality Tests for Oral Drug Products/Specific Tests for Granules

Comment Summary #20: The commenter recommended deleting the reference to the *European Pharmacopeia* for additional information about the disintegration test for effervescent granules.

Response: Comment not incorporated. This will be addressed during the next revision of the General Chapter <2>.

Product Quality Tests for Oral Drug Products/Specific Tests for Liquids/pH

Comment Summary #21: The commenter recommended revising the sentence, "Although it is less critical than in ophthalmic preparations, the pH of a liquid formulation can affect flavor and stability" to "Although it is less critical than in ophthalmic preparations, the pH of an oral liquid formulation can affect flavor and stability."

Response: Comment partially incorporated. The sentence was revised to "The pH of an oral liquid formulation can affect flavor and stability."

Comment Summary #22: The commenter recommended revising the sentence, "The uptake of atmospheric CO_2 and pH change of oral liquid products is only relevant to aqueous-based products" to "The uptake of atmospheric CO_2 and pH change of oral liquid products are only relevant to aqueous-based products," because there are two subjects.

Response: Comment partially incorporated. The sentence was revised to, "The uptake of atmospheric CO_2 and consequent pH change of oral liquid products is only relevant to aqueous-based products."

Product Quality Tests for Oral Drug Products/Types of Liquid Dosage Forms/Oral Solutions, and Powders and Granules for Solution

Comment Summary #23: The commenter recommended deleting the word "Oral" from the subheading, because oral is a route and not a dosage form.

Response: Comment incorporated.

Product Quality Tests for Oral Drug Products/Types of Liquid Dosage Forms/Powders and Granules for Syrups and Powders for Oral Drops

Comment Summary #24: The commenter recommended deleting the term "Syrup," because the preferred term in <1151> is "Solution," and also deleting the term "Drop," because the appropriate dosage form terminology is "solution" or "suspension."

Response: Comment incorporated. The title was revised to "Powders and Granules for Solutions."

General Chapter/Section(s): <3> Topically Applied Drug Products—Product Quality Tests/Multiple Sections
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 3

Product Quality Tests for Topical and Transdermal Drug Products/Specific Tests/Particle Size
Comment Summary #1: The commenter suggested replacing the statement, "…should be examined for evidence of particle size alteration," with "…should be examined for evidence of particle alteration…."
Response: Comment incorporated.

Specific Tests for Topically Applied Semisolid Drug Products/Uniformity in Containers/Uniformity of Active Ingredients/Multiple unit tubes that contain 5 g or more of product
Comment Summary #2: The commenters suggested adding additional instructions on how to proceed if Stage 1 acceptance criteria are not met.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested clarifying the text in this section, because the way it was written did not prevent users from performing Stage 3 testing, if either Stage 1 or Stage 2 acceptance criteria are met. If Stage 1 or Stage 2 are met then it also meets the requirement to proceed to Stage 3.
Response: Comments incorporated.
Comment Summary #4: The commenter suggested modifying the text to indicate that addition tubes should be tested to comprise of a total of three samples from each of the 10 tubes and indicated that the way the text is written someone could interpret that one could proceed straight from Stage 1 to Stage 3.
Response: Comment incorporated. Directions were added regarding the number of tubes to test depending on whether Stage 2 was completed.

Specific Tests for Topically Applied Semisolid Drug Products/Uniformity in Containers/Uniformity of Active Ingredients/Multiple unit tubes that contain less than 5 g of product
Comment Summary #5: The commenters suggested adding additional instructions on how to proceed if Stage 1 acceptance criteria are not met.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested clarifying the text in this section, because the way it was written did not prevent users from performing Stage 3 testing, if either Stage 1 or Stage 2 acceptance criteria are met. If Stage 1 or Stage 2 is met then it also meets the requirement to proceed to Stage 3.
Response: Comments incorporated.
Comment Summary #7: The commenter suggested modifying the text to indicate that addition tubes should be tested to comprise of a total of three samples from each of the 10 tubes and indicated that the way the text is written someone could interpret that one could proceed straight from Stage 1 to Stage 3.

Response: Comment incorporated. Directions were added regarding the number of tubes to test depending on whether Stage 2 was completed.
Comment Summary #8: The commenter recommended adding additional criterion related to the non-passing of Stage 1.
Response: Comment not incorporated. It was determined that the existing criteria are sufficient.
Comment Summary #9: The commenter suggested changing the names of the sections "*Microbial Limits*" and "*Antimicrobial Preservative Content*" to the titles of the respective General Chapters.
Response: Comment not incorporated. The titles of the sections follow USP template.

General Chapter/Section(s): <4> Mucosal Drug Products—Product Quality Tests/Introduction
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 1
Comment Summary #1: The commenter requested clarification of the applicability of the tests in the General Chapter.
Response: Comment incorporated.

Product Quality Tests for Mucosal Drug Products
Comment Summary #2: The commenter requested alignment of the discussion of identification in the General Chapter with that in <771> *Ophthalmic Products—Quality Tests.*
Response: Comment incorporated. The text, "positive identification of the drug substance or substances" was removed. The reference to *General Notices* and the Requirements section 5.40 were retained.
Comment Summary #3: The commenter indicated that impurities are not controlled by an appropriate test, but rather that acceptable limits are established.
Response: Comment incorporated.
Comment Summary #4: The commenter indicated that for drug product monographs, process impurities are identified, but disregarded when determining degradation impurities. Process impurities are limited in the drug substance monograph.
Response: Comment incorporated.
Comment Summary #5: The commenters indicated that reference made to <771> *Ophthalmic Ointments* should be corrected. The correct reference is <771> *Ophthalmic Products—Quality Tests*
Response: Comment incorporated.
Comment Summary #6: The commenter requested that, under ophthalmic products, the reference made to the attribute, foreign, and particulate matter be restated to conform to the text in <771>.
Response: Comment incorporated.

General Chapter/Section(s): <212> Oligosaccharide Analysis/Multiple Sections
Expert Committee: General Chapters—Biological Analysis
No. of Commenters: 2

Introduction
Comment Summary #1: The commenter suggested removing the phrase "may be a helpful but not mandatory resource" for general chapters numbered <1000> to <1999>, because similar wording is included in the revised *General Notices*, Section 3.10.
Response: Comment incorporated.
Comment Summary #2: The commenter requested clarification on when validation is needed by suggesting the following edits to the text, "Furthermore, validation is required when the procedure is optimized outside the allowed parameter limits defined in *Chromatography* <621>*, System Suitability* for a specific product (see *Validation of Compendial Procedures* <1225>)."
Response: Comment partially incorporated. The text was revised to state, "Furthermore, validation is required when the procedure is optimized for a specific product, (e.g. outside the allowed parameter limits defined in *Chromatography* <621>*, System Suitability*) (see *Validation of Compendial Procedures* <1225>).

Sample Preparation
Comment Summary #3: The commenter suggested clarifying whether the *Sample Preparation* section is for all of the procedures that follow.
Response: Comment incorporated. The following statement was added to the beginning of the section, "The sample preparation is for all of the procedures that follow."
Comment Summary #4: The commenter suggested clarifying whether the use of a control sample is in addition to or instead of the Reference Standard (RS) described in a *Note* at the beginning of the section.
Response: Comment incorporated. Both RS and a control sample are needed. The *Note* was revised to state, "In addition to RS, a control sample with a known glycan profile should be included in the overall procedure to confirm correct performance of the analysis. A reaction blank control only containing the buffer matrix of the glycoprotein sample can also be included in the overall procedure."
Comment Summary #5: The commenter recommended adding an example of an ultrafiltration membrane with a molecular weight cutoff of 10 kDa to the section of *Digestion with PNGase F*, *Method 1 using an ultrafiltration membrane with a molecular weight cutoff of 30 kDa*.
Response: Comment incorporated. An example is provided in the footnote. As a consequence, the footnotes are re-numbered accordingly.

Separation and Identification of OligosaccharidesNormal Phase Chromatography/HILIC
Comment Summary #6: The commenter recommended the following edits to the text, **Normal Phase Chromatography/**~~*INormal Phase Chromatography/*~~**HILIC**
Response: Comment incorporated.

Capillary Electrophoresis
Comment Summary #7: The commenter requested the following revision for *Standard solution* and *Sample solution* sections for consistency: *APTS-labeled standard solution* prepared as directed in the test for ~~*8-Aminopyrene-1,3,6-trisulfonic Acid (APTS) Labeling for CE Separation*~~ *APTS Labeling for Capillary Electrophoresis Separation*.
Response: Comment incorporated.
Comment Summary #8: The commenter recommended correcting the migration orders of G1Fa and G1Fb to G1Fb and G1Fa in the *Table 15*.
Response: Comment incorporated.

General Chapter/Section(s): <341> Antimicrobial Agents—Content/Multiple Sections
Expert Committee: Monographs—Chemical Medicines Monographs 1
No. of Commenters: 3
Comment Summary #1: The commenter suggested converting the General Chapter to an informational chapter with a number above <1000>.
Response: Comment not incorporated. The procedures in the General Chapter are used in official USP monographs.
Comment Summary #2: The commenter requested including information on the liner used for gas chromatographic analysis of phenol and benzyl alcohol, and for handling of deposits/thermal degradation in the liner.
Response: Comment not incorporated. Liners are commonly used in gas chromatographic procedures and because different products have different formulation matrices. It is up to the analyst to select a liner that is suitable for the product under test.
Comment Summary #3: The commenter recommended replacing the term “agent” to “antimicrobial agent” throughout the General Chapter for clarity.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended including the names of four homologous esters of p-hydroxybenzoic acid for clarity.
Response: Comment incorporated.
Comment Summary #5: The commenter recommended clarifying the phrase, “Unless otherwise directed” by changing to “Unless otherwise directed by the individual monograph”, and changing the phrase “corresponds closely” to “about the same as” under *General Gas and Liquid Chromatographic Methods*.
Response: Comment incorporated.
Comment Summary #6: The commenter requested including details for determination of ethylparaben and butylparaben similar to methylparaben and propylparaben.
Response: Comment not incorporated. The Expert Committee determined that the statement included in the General Chapter for analysis of ethylparaben and butylparaben is sufficient.
Comment Summary #7: The commenter indicated that the methods suggested in the General Chapter may not be able to resolve a particular antimicrobial agent from other compounds present in the formulation matrix.
Response: Comment not incorporated. The procedures listed in the General Chapter are consistent with submissions from manufacturers with FDA approval. It is the responsibility of individual manufacturers to develop alternate method for their

formulation if necessary. Such methods would need to be validated as indicated in *General Notices* 6.30. *Alternative and Harmonized Methods and Procedures.*
Comment Summary #8: The commenter suggested that the gas chromatographic procedure for phenol may not work well for phenol allergenic extracts in 50% glycerol, where phenol is present at 4 mg/mL.
Response: Comment not incorporated. The Expert Committee will consider revising the General Chapter in the future upon the receipt of supporting data.
Comment Summary #9: The commenter indicated that thimerosal may decompose to thiosalicylic acid and dithiosalicylic acid with dissociation of ethyl mercury. This is particularly pronounced in proteinaceous solutions such as vaccines and can lead to changes in acceptance criteria.
Response: Comment not incorporated. It is the responsibility of individual manufacturers to develop alternate method for their formulation if necessary. Such methods would need to be validated as indicated in *General Notices* 6.30. *Alternative and Harmonized Methods and Procedures.*
Comment Summary #10: The commenter indicated that the sample preparation is not included in the tests for benzyl alcohol and phenol.
Response: Comment not incorporated. A statement is already included in the beginning of the relevant sections indicating how to prepare sample solutions if these are not listed in individual test procedure/monograph.

General Chapter/Section(s): <771> Ophthalmic Products—Quality Tests/Multiple Sections
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 5
Comment Summary #1: A commenter requested clarification on the following requirement when applied to pre-filled syringes, “It is mandatory that the immediate containers for ophthalmic products be sealed and tamper-proof so that sterility is ensured at the time of the first use.” Taking into account that pre-filled syringes for ophthalmic use must be packed in blisters so as to guarantee sterility and that the blister must be opened in aseptic conditions just before the time of use.
Response: Comment incorporated. The text will be revised and a cross-reference to the *Container-Closure Integrity* section will be added. The revision will be published in *Pharmacopeial Forum* (PF) 42(4) [Jul.–Aug. 2016].
Comment Summary #2: The commenter questioned the reasons for having only one procedure to evaluate or measure viscosity in the *Specific Tests section* under *Viscosity*.
Response: Comment not incorporated. The commenter was referring to the first version of the General Chapter. The final version has three different procedures to measure viscosity.
Comment Summary #3: Under *Antimicrobial Preservatives***,** the commenter suggested including an additional exemption for antimicrobial agents, “products that are packed in multi-dose container systems which employ measures to prevent microbial contamination of the container content during storage and in-use period by means of a tip seal mechanism or sterile filtration barriers.”

Response: Comment not incorporated. When the Expert Committee developed this General Chapter, it decided to address requirements based on products already approved by FDA to be marketed in the USA. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment Summary #4: The commenter suggested accepting the use of a single chromatographic retention time as identification test.
Response: Comment not incorporated. The identification of the product should be done by one specific procedure. If the procedure does not have enough specificity, the identification needs to be done by at least two orthogonal identification tests.
Comment Summary #5: The commenter suggested clarifying whether the intent of leachables and extractables was to be a one-time development or a routine test.
Response: Comment incorporated. The text will be revised to indicate that the leachables and extractables assessment should be done during product development and should be reassessed if any changes are made to the product, including manufacturing process, formulation, packaging material, etc. The revision will be published in *PF* 42(4) [Jul.–Aug. 2016].
Comment Summary #6: The commenter suggested including information on how the drop size should be determined (i.e., angle, number of drops, etc.) and stating the acceptable variability.
Response: Comment incorporated. The text will be revised to indicate that any appropriate validated procedure can be used to determine drop size. The revision will be published in *PF* 42(4) [Jul.–Aug. 2016].
Comment Summary #7: The commenter suggested adding the tests for number of drops, surface tension, and dissolution.
Response: Comment not incorporated. Ophthalmic solutions and suspensions are sold by volume and not by number of drops. The parameter that needs to be evaluated is *Minimum Fill* as stated in the General Chapter. Surface tension is product specific and it is the manufacturer's responsibility to evaluate if this parameter needs to be controlled. In the introductory paragraph to the *Drug Product Quality* section it states, "The performance tests (dissolution/drug release) are addressed by Ophthalmic Products—Performance Tests <1771>."
Comment Summary #8: The commenter suggested revising the text under *Antioxidant Content* to denote that antioxidant content should always be measured.
Response: Comment not incorporated. This is already covered by the General Chapter.
Comment Summary #9: The commenter suggested adding a test for globule size distribution.
Response: Comment not incorporated. This topic is covered in the *Particle Size and particle Size Distribution* procedures.

General Chapter/Sections(s): <1004> Mucosal Drug Products—Performance Tests/Aerosols and Nasal Sprays
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 1
Comment Summary #1: The commenter suggested adding lingual aerosols to the list of products for which performance tests are largely concerned with droplet or particle size.
Response: Comment incorporated.

Product Quality Tests/Creams, Gels, and Ointments
Comment Summary #2: The commenter requested the provision of the full name of <1724> *Semisolid Drug Products–Performance Tests.*
Response: Comment not incorporated. Current USP style is not to give the full general chapter name for successive references in a general chapter once the full name of the referenced chapter has been provided.

Product Quality Tests/Lozenges
Comment Summary #3: The commenter indicated that Apparatus 1 has been used in performance testing of lozenge products and requested its addition in this section.
Response: Comment incorporated.

Product Quality Tests/*Suspensions*
Comment Summary #4: The commenter suggested correcting a misspelling in the section title.
Response: Comment incorporated.

General Chapter/Section(s): <1029> Good Documentation Guidelines/Multiple Sections
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 5

Principles of Good Documentation
Comment Summary #1: The commenter requested rewording the sentence, “All corrections to the original entries should be initialed and dated, with an explanation included in cases where the reason for the change is not obvious” to “All corrections to the original entries should be initialed and dated <u>(or captured within an electronic audit trail)</u>, with an explanation included in cases where the reason for the change is not obvious” to clarify that an electronic audit trail entry satisfies the same condition via *Code of Federal Regulations,* Title 21 (21 CFR), Part 11 electronic signatures.
Response: Comment incorporated.
Comment Summary #2: The commenter requested rewording the sentence, “Records should be retained per regulatory requirements and be readable during the retention time” to “Records should be retained per regulatory requirements <u>(or where applicable, via an alternative documented process)</u> and be readable during the retention time,” because not all items captured within a “Document Management Process” have regulatory requirements.

Response: Comment not incorporated, The General Chapter already provides guidance on this topic.
Comment Summary #3: The commenter requested moving a bullet point from the *Data Collection and Recording* section and revising it to state, “GMP records such as batch records, test methods, and specifications should be given unique identifiers and should undergo appropriate review and signature by a second person to confirm the accuracy, compliance, and completeness of the entries. For GMP documents version control should be used,” because it fits better in the context related to GMP records.
Response: Comment not incorporated. The Expert Committee determined that there was no need to further elaborate on which documents should be included, and that moving the text will not improve the flow of the General Chapter.

Data Collection and Recording
Comment Summary #4: The commenter suggested restating or clarifying the following sentence, “The use of transient records must not be used for documentation of GMP activities,” because a “transient” record is not defined.
Response: Comment partially incorporated. The sentence was deleted.
Comment Summary #5: The commenter suggested rewording the sentence, “If the record is in an electronic system and the system provides traceability of who filled each field and when, the field can be left blank” to “If the record is in an electronic system and the system provides traceability of who filled each field and when, the field can be left blank. <u>This is only true if the electronic version is the official copy,</u>” because if the electronic system is used and a paper copy is printed and serves as the official copy, all GMP rules need to apply to that paper copy.
Response: Comment not incorporated. The Expert Committee determined that the proposed clarification is not needed.
Comment Summary #6: The commenter suggested revising the sentence, “All GMP records should undergo appropriate review and signature by a second person to confirm the accuracy, compliance, and completeness of the entries” to ensure application of a second person review should apply only to documents that have a direct impact on product quality, integrity, purity and safety (e.g. laboratory test records to ensure that correct tests were conducted, results are accurate and the correct standard was used in determining test results).
Response: Comment partially incorporated. The sentence was revised to state, “All GMP records <u>for data collection</u> should undergo appropriate review and signature by a second person to confirm the accuracy, compliance, and completeness of the entries,”
Comment Summary #7: The commenter requested moving a bullet point from current section to the *Principles of Good Documentation* section, because it fits better in the context related to GMP records.
Response: Comment not incorporated. The Expert Committee determined that moving the text would not improve the flow of the General Chapter.
Comment Summary #8: The commenter requested clarifying the signature/initialization of electronically compiled instrument data print outs (e.g. data printouts directly transferred to a governing electronic data record without producing a paper copy).

Response: Comment incorporated. The sentence was revised to “All multiple-page data sheets or instrument printouts in paper form should be signed/initialed on the first or last page with a note indicating the total number of pages.”

Different Types of GMP Documents/Equipment-Related Documentation
Comment Summary #9: The commenter suggested separating the “Use and maintenance logs” bullet point into two separate bullets to allow flexibility within the industry to document equipment use outside of logbooks (e.g. documentation of equipment within the analytical notebook or batch record).
Response: Comment incorporated. The bullet points were revised for additional clarification.

Different Types of GMP Documents/Deviations and Investigations
Comment Summary #10: The commenter suggested rewording the bullet point regarding root-cause investigation and trend data analysis to apply to several different types of trending analysis programs.
Response: Comment incorporated. The bullet point was divided in two and they were revised for additional clarification.
Expert Committee-initiated Change #1: The bullet point “Impact assessment” was added to this section and removed from the *Protocols and Reports* section.

Different Types of GMP Documents/Batch Records
Comment Summary #11: The commenter suggested rewording the bullet point regarding review and approval to include signature requirements per CFR 211.186
Response: Comment partially incorporated. The bullet point was revised to state, “Review and approval.”

Different Types of GMP Documents/Certificate of Analysis
Comment Summary #12: The commenter suggested adding the phrase “as appropriate” in several bullet points.
Response: Comment not incorporated. The preceding sentence starts with the word “Typically;” therefore addition of the phase “as appropriate” is not necessary.

Different Types of GMP Documents/Standard Operating Procedures
Comment Summary #13: The commenter requested rewording the bullet point “Revision history” to “Revision history, including justification of changes” to include the justification for any changes.
Response: Comment not incorporated. This change is already part of the change control.

Different Types of GMP Documents/Analytical Procedures
Comment Summary #14: The commenter requested rewording the bullet point “Revision history” to “Revision history, including justification of changes” to include the justification for any changes.
Response: Comment not incorporated. This change is already part of the change control.

Different Types of GMP Documents/Protocols and Reports
Comment Summary #15: The commenter suggested adding the phrase, "for report only" to this section, because it will usually only be relevant in the report.
Response: Comment incorporated.
Expert Committee-initiated Change #2: The bullet point "Impact assessment" was removed from this section and added to the *Deviations and Investigations* section.

Retention of Documents
Comment Summary #16: The commenter recommended removing the sentence "however, it should be at least 1 year after the batch expiration date," because many countries, as well as industry, have a standard retention time of 10 years, 20 years, or the lifetime of the product for documents. A statement of "at least 1 year" is minimal compared to what is actually practiced.
Response: Comment not incorporated. The current wording is consistent with applicable GMP.

General Chapter/Section(s): <1063> Shear Cell Methodology for Powder Flow Testing/Multiple Sections
Expert Committee: General Chapters—Physical Analysis
No. of Commenters: 1
Comment Summary #1: The commenter recommended providing more detail or removing the paragraph last paragraph of Section 4.1 *Sample Preparation* starting "Some pharmaceutical powders…" because it is in contradiction to the best fit approach with regards to choosing processes relevant testing conditions.
Response: Comment not incorporated. The text is not a contradiction, but rather it is supportive of the argument for testing under relevant process conditions. If fresh material is being handled in the process and it is thought to age, then it is important to test fresh material so that it is representative of the material in the process.
Comment Summary #2: The commenter recommended changing the number of pre-shear normal stress levels specified in Section 5. *Selection of Test Conditions* from four to three.
Response: Comment not incorporated. Four pre-shear points is consistent with the ASTM standard which also recommends four pre-shear normal stress levels. If the flow function is linear then three points should be sufficient; however, if there is non-linearity then at least four points would be needed to describe the curve. The Expert Committee also noted that current text states "should" and not "must."
Comment Summary #3: The commenter indicated that the General Chapter was written with the annular shear tester as the basis and suggested that it might be advantageous and less prone to misinterpretation to make the General Chapter more generic.
Response: Comment not incorporated. The Expert Committee concluded that the General Chapter is not biased to one type of shear cell over any other(s).
Comment Summary #4: The commenter requested revising *Table* 1, *General Classification of Flow Character,* to read: <1 Nonflowing, <2 Very cohesive.

Response: Comment not incorporated. The General chapter uses (and references) the terminology introduced by the original author of this classification scheme, Jenike. More recent variations of the classification scheme are less well-known and in the Expert Committees' opinion do not provide significant additional benefits.
Expert Committee-initiated Change #1: Due to the character entities not being mapped correctly, when the General Chapter content was being processed for online *PF*, the preprocessor converted the sigma and the delta to the capital sigma (Σ) and delta (*Δ)* instead of the lowercase sigma (σ) and delta (δ), respectively. The symbols are corrected in the official text. USP is modifying symbols presented in the *PF* version of the file to their intended mathematical operators.
Expert Committee-initiated Change #2: In *Appendix*, the definition for Arching was revised to state "The formation of a bridge of powder across an opening caused by, for example, attractive interactions between particles."
Expert Committee-initiated Change #3: In *Introduction*, the sentence "When the shear cell data are combined with unconfined yield strength, wall friction data, and bulk density data, they can be used …" was revised to state "When the shear cell data are combined, they can be used…"
Expert Committee-initiated Change #4: The current *Introduction* was split into two parts, with the second part existing under the heading of "Scope." This section begins with the phrase, "This chapter focuses on the three most…"
Expert Committee-initiated Change #5: In *Theory and Principles*, in the first sentence of the last paragraph, the word "friction" was added to the statement "the wall friction (particle–wall)."
Expert Committee-initiated Change #6: The "Φ' and μ_w = function of the applied stress (σ_w)" were replaced with "Note that Φ', and hence μ_w often are a function of the applied normal stress σ_w."
Expert Committee-initiated Change #7: In *Test Procedure,* after the numbered steps the phrase "Steps 1-4…" was changed to "Steps 1-5…"
Expert Committee-initiated Change #8: In *Appendix,* in the Comments column for "Cohesion" "unconsolidated" was replaced with "unconfined".
Expert Committee-initiated Change #9: In *Appendix,* in the Symbol and SI Units column for "Effective angle of friction" "σ" was changed to "δ".

General Chapter/Sections:	<1130> Nucleic Acid-Based Techniques—Approaches for Detecting Trace Nucleic Acids (Residual DNA Testing)
Expert Committee:	General Chapters—Biological Analysis
No. of Commenters:	2

General Comments
Comment Summary #1: The commenter requested including content which emphasizes the importance of the DNA standard used in the qPCR method.
Response: Comment not incorporated. The sequence specificity is discussed in detail, which the Expert Committee believes is one of the most important considerations for a DNA standard.

Comment Summary #2: The commenter stated that it was unclear why the hybridization method has been reintroduced compared to the previous public inquiry in *Pharmacopeial Forum* 40(2) [Mar.–Apr. 2014].
Response: Comment not incorporated. The hybridization method was reintroduced based on previous public comments. This is an informational General Chapter and there are historical reasons to keep this option.

Introduction
Comment Summary #3: The commenter recommended using the term “parenteral” in the Introduction instead of “parental.”
Response: Comment incorporated.
Comment Summary #4: The commenter stated that the text regarding analytical procedures used to quantify residual DNA describes more than one procedure so the word “procedures” should be used.
Response: Comment incorporated.
Comment Summary #5: The commenter suggested editing the text on process characterization and process related impurities.
Response: Comment incorporated. The text was revised to state, “Process characterization and the theoretical safety concerns associated with process-related impurities…”
Comment Summary #6: The commenter suggested that the text regarding removal of residual DNA from a biopharmaceutical product should be mentioned as under control which is again a critical attribute of the manufacturing process.
Response: Comment incorporated. The text was revised to state, “The ability of a manufacturing process to remove residual DNA from a biopharmaceutical product is an indicator of the quality and consistency of the process and that the process is under control.”
Comment Summary #7: The commenter suggested an alternative text to better describe the safety concerns associated with residual DNA.
Response: Comment incorporated. The referenced text was replaced with “For continuous cell lines, the potential risk of residual DNA arises from both of its biological activities, namely infectivity and oncogenicity. Infectivity could be due to the presence of an infectious viral genome in the cellular DNA of the cell substrate. The oncogenicity activity of residual DNA could arise through its capacity to induce a normal cell to become transformed, which may lead to tumorigenicity.”
Comment Summary #8: The commenter suggested that the section on residual DNA content in biopharmaceutical processes be reorganized for clarity and to reduce duplication of content.
Response: Comment partially incorporated. The following text was added, “Residual DNA content, up to 10 ng of residual DNA per parenteral dose, may be considered for DNA originating from mammalian cell cultures but the acceptable residual DNA content..”

Sample Pretreatment

Comment Summary #9: The commenter suggested clarifying the text regarding detection of specified DNA content in a sample within the range of the analytical procedure.

Response: Comment not incorporated. The purpose is not to detect the DNA but to quantitate the DNA.

Comment Summary #10: The commenter suggested deleting the text on the use of protein reagents and the use of a chemical dissociation reagent.

Response: Comment not incorporated. The Expert Committee determined that the proposed edits would not be beneficial.

Comment Summary #11: The commenter suggested an edit to the text on materials used to pretreat samples.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be beneficial.

Comment Summary #12: The commenter suggested edits to the text on the addition of target DNA-spiked samples

Response: Comment not incorporated. The Expert Committee determined that the proposed edits would not be beneficial.

Comment Summary #13: The commenter suggested rephrasing the text on target DNA-spiked sample and the use of the internal positive control (IPC).

Response: Comment not incorporated. The IPC is used to determine the amplification efficiency. Spiking with target DNA is done to control the extraction efficiency.

Comment Summary #14: The commenter suggested including text stating that the spiked target DNA or the internal positive control (IPC) should have a recovery of 50-150%.

Response: Comment not incorporated. It is not acceptable to have an amplification efficiency of 50% - 150% as determined by the IPC (see response to comment #13 for further information regarding the differences between these 2 controls).

Comment Summary #15: The commenter suggested modifying the text on achieving a recovery acceptance criterion of 50%–150% (where impractical due to sample characteristics) by the use of a correction factor when using an IPC for recovery assessment.

Response: Comment not incorporated. The IPC is used to determine the amplification efficiency. This correction should only be done with the target DNA spike used for extraction efficiency.

Hybridization Based Residual DNA Assay

Comment Summary #16: The commenter suggested an edit to the sentence regarding the labeled probe.

Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be beneficial.

Comment Summary #17: The commenter suggested adding a sentence, “The level of hybridization can be measured using a phosphor-imaging system.”

Response: Comment incorporated.

Comment Summary #18: The commenter suggested deleting the term “phosphor- or” in the sentence regarding detection of fluorescently-labeled probes.

Response: Comment incorporated.
Comment Summary #19: The commenter suggested edits to the text regarding measuring the intensity of the spots following hybridization.
Response: Comment not incorporated. The Expert Committee determined that the proposed edits would not be beneficial.

DNA-Binding Protein Based Residual DNA Assay
Comment Summary #20: The commenter suggested a clarifying edit to the first step (that the DNA to be denatured is from the test sample).
Response: Comment not incorporated. All DNA needs to be denatured, not just the test sample (e.g., the standard calf thymus DNA too).
Comment Summary #21: The commenter suggested edits to state that the DNA-binding protein is nonspecific.
Response: Comment not incorporated. The lack of specificity of this assay is already mentioned numerous times in the General Chapter.
Comment Summary #22: The commenter suggested adding text stating that the amount of complex bound to the membrane is actually directly proportional to the amount of DNA in the test sample to Step number 2.
Response: Comment not incorporated. Step number 2 explains the mechanics of the assay, not the interpretation. The proposed addition may also be confusing, because the instrument uses a power function for the curve fit and the response is not directly proportional.

Polymerase Chain Reaction Techniques
Comment Summary #23: The commenter suggested that section should include a description of newer PCR-based technologies (e.g. digital PCR) and that these new methods should also meet the performance characteristics described in *USP-NF*.
Response: Comment not incorporated. The Expert Committee did not agree that digital PCR is mature enough for inclusion at this time. This is an informational General Chapter and users are able to use alternative methods if demonstrated suitable to regulators.
Comment Summary #24: The commenter suggested an edit to delete the term “fast sample” and include the terms “high” throughput “testing.”
Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be beneficial.
Comment Summary #25: The commenter suggested an edit to the text regarding quantifying the amount of a nucleic acid target sequence.
Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be beneficial.
Comment Summary #26: The commenter suggested the following edits “During the amplification reaction, a thermostable DNA polymerase initiates DNA synthesis where the DNA primer binds to the single-stranded sample…”
Response: Comment incorporated.

Alternative Detection Strategies
Comment Summary #27: The commenter stated that many of the technical approaches and details described in this subsection may not be important to include.
Response: Comment not incorporated. The Expert Committee agreed that they were valuable to add to this informational General Chapter.
Comment Summary #28: The commenter suggested an edit to the subsection title.
Response: Comment not incorporated. This is a sub-heading under a larger heading already titled *Polymerase Chain Reaction Techniques*.
Comment Summary #29: The commenter requested an edit to the sentence regarding running a melting curve at the end of the PCR run based on the principle that every product has a distinct strand dissociation temperature, which is dependent on length and base content of the amplicon.
Response: Comment not incorporated. The Expert Committee determined that the additional details were not necessary.
Comment Summary #30: The commenter requested edits to clarify how the probe unfolds and hybridizes to the target and its subsequent fluorescence.
Response: Comment not incorporated. The concept is provided in a brief bullet manner. The additional proposed detail is correct, but not needed to describe the concept.
Comment Summary #31: The commenter requested and edit to the first sentence of bullet 3: "A variation on the second example described above uses a …"
Response: Comment incorporated.

Quantitative Multiplex PCR-Based Residual DNA Assay
Comment Summary #32: The commenter requested adding the underlined text: "One of the applications of this technique is a duplex qPCR, where the introduction of an exogenous DNA, called IPC (Internal Positive Control, see Sample Pretreatment above), enhances confidence…"
Response: Comment incorporated.

Residual DNA Testing Points to Consider
Comment Summary #33: The commenter suggested an edit to the sentence regarding developing a residual DNA assay and considering the expected characteristics of the residual DNA (e.g., fragments length).
Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be beneficial.
Comment Summary #34: The commenter suggested edits to the two sentences beginning "DNA-binding protein assays and qPCR give quantitative results.."
Response: Comment not incorporated. The Expert Committee determined that the proposed edit would not be beneficial.
Comment Summary #35: The commenter suggested an edit "'…to design the assay with a spike-recovery control with an acceptance criterion…"
Response: Comment incorporated.
Comment Summary #36: The commenter suggested that an internal control may also be desirable to use for spike and recovery.
Response: Comment not incorporated. An IPC is not an acceptable spike control.

Comment Summary #37: The commenter suggested changing the word “Qualified” to “Quantified” when discussing the preparation and qualification of in-house controls.
Response: Comment not incorporated. The term ‘qualified” was intended in this case.
Comment Summary #38: The commenter suggested adding that controls may also be provided in commercially available kits.
Response: Comment not incorporated. A commercial host cell DNA is also prepared and qualified by UV spectroscopy.
Comment Summary #39: The commenter suggested adding text that it may be advantageous to use a biological safety cabinet to minimize sample contamination.
Response: Comment not incorporated. A biological safety cabinet can offer an advantage, but the technique of the analyst is of greater consideration and cannot compensate for poor analyst technique.
Comment Summary #40: The commenter suggested the following edits to clarify the text: “Biopharmaceutical manufacturing processes may typically include operations that shear DNA into smaller fragments,…”
Response: Comment incorporated.
Comment Summary #41: The commenter suggested the clarifying edit: “…the levels of residual DNA in any bioprocess remain a key quality attribute and provides valuable characterization of the manufacturing process.”
Response: Comment incorporated.

General Chapter/Sections: General Chapter <1228.3> Depyrogenation by Filtration/Multiple Sections
Expert Committee: General Chapters—Microbiology
No. of Commenters: 1

Comment Summary #1: The commenter recommended for the sake of consistency that the definition of endotoxin be removed from this General Chapter, because it is included in the overarching chapter of the series <1228> Depyrogenation.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended adding discussion on the use of naturally occurring endotoxins during validation of depyrogenation.
Response: Comment not incorporated. This is already discussed in detail in the overarching chapter of the series <1228> Depyrogenation.

General Chapter/Sections: General Chapter <1228.5> Endotoxin Indicators for Depyrogenation/Multiple Sections
Expert Committee: General Chapters—Microbiology
No. of Commenters: 2
Comment Summary #1: The commenter recommended indicating that the surface of the material used as an indicator for a physical depyrogenation process such as dry heat should have similar heating characteristics as the materials being processed.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended clarifying that the naturally occurring endotoxin may be isolated using a well-documented method and include a reference publication that provides details of the method.

Response: Comment incorporated.
Comment Summary #3: The commenter recommended that the use of higher or lower concentrations of LPS or endotoxin (than 1000 Endotoxin Units) as challenge dose may be justified based on historical data on the endotoxin content of the material.
Response: Comment incorporated
Comment Summary #4: The commenter recommended that test sensitivity be also considered to demonstrate the required log reduction of the depyrogenation process.
Response: Comment incorporated.

General Chapter/Sections: General Chapter <1229.13> Sterilization-in-Place/Multiple Sections
Expert Committee: General Chapters—Microbiology
No. of Commenters: 2
Comment Summary #1: The commenter recommended adding details on considerations regarding the use of moist heat for Sterilization-in-place (SIP).
Response: Comment not incorporated. The absence of details is intentional as the requested change would have added details that were incomplete.
Comment Summary #2: The commenter suggested adding text that removals of residual water subsequent to the sterilization phase is recommended.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested clarifying that sterilization agent removal must include consideration of the potential effects of residual sterilant on the materials to be processed.
Response: Comment incorporated.
Comment Summary #4: The commenter recommended including a reference to the ISO document on SIP.
Response: Comment incorporated.

General Chapter/Section(s): <1231> Water for Pharmaceutical Purposes/Multiple Sections
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 9
General
Comment Summary #1: The commenter requested replacing all images with others that are more clear and legible.
Response: Comment incorporated.

Table of Contents
Expert Committee-initiated Change #1: The title of the section “User Requirements and Design Qualification, URS, FAT, SAT” was changed to "User Requirements Specification and Design Qualification" to align with a comment from a user incorporated in section 4.2.2 of the General Chapter.

2. Source Water Considerations
Comment Summary #2: The commenter requested aligning the numbering scheme with the content of the document, because there are some differences.

Response: Comment incorporated.
Comment Summary #3: The commenter suggested adding guidance by defining suggested frequency in the following sentence, “Water being withdrawn from a nonregulated supply should be sampled and tested appropriately at a suitable frequency that …”
Response: Comment not incorporated. The frequency depends on the stability of the attributes over time, as explained in the contextual text.
Comment Summary #4: The commenter suggested adding clarification on “water for indirect product contact” in the following sentence, “It is the responsibility of the users of any source water to ensure that the water used in the production of drug substances (API), as well as water for indirect drug product contact …”
Response: Comment not incorporated. The text is clear regarding water for cleaning or rinsing.

3. Water Used for Pharmaceutical Manufacturing and Testing Purposes
Comment Summary #5: The commenter suggested adding anti-scalant/dispersants used for scale control upstream of Reverse Osmosis, acid/caustics used for pH adjustments in Reverse Osmosis, and additional examples of common chemical additions to the pretreatment process of a water system mentioned in other sections, to the examples of “no added substances” requirement.
Response: Comment not incorporated. The text provides typical examples and it is not intended to be an exhaustive list.

3.1.4. Pure Steam
Comment Summary #6: The commenter recommended to use the terms “non-condensable gasses”, “superheat,” and “dryness” in the following examples taken from EN285 for clarity: “Other steam attributes not detailed in the monograph, particularly the presence of even small quantities of noncondensable gases or the existence of a superheated or dry state, may also be important for applications such as sterilization.”
Response: Comment not incorporated. The current terms are correct and used consistently across the revision to General Chapter <1231>.

3.3.9. Filtered Water
Comment Summary #7: The commenter recommended being consistent in the document with the references to 0.22 µm and 0.2 µm filters.
Response: Comment incorporated. Both sizes are described.

3.3.10. High-Purity Water
Comment Summary #8: The commenter requested changing the word “high” to “low” in the following sentence: “Therefore, if the analytical use requires that water conductivity remains as high as possible or the bicarbonate/carbon dioxide levels be as low as possible, the water should be protected from atmospheric exposure" because the water should be protected to prevent the conductivity from increasing.
Response: Comment incorporated.
Comment Summary #9: The commenter requested clarifying the wording of this section, because the two alternative procedures to obtain High-Purity Water should be

together. It could be prepared either by deionizing previously distilled water and then filtering it through a 0.45-µm rated membrane or by “Purified Water” if filtered by 0.22-µm and meets or exceeds the conductivity specifications.
Response: Comment not incorporated. The information is correct and available in the same section with additional considerations.

4.2. Validation Approach
Comment Summary #10: The commenter suggested modifying the wording in this section and in other applicable locations within the document in terms of high purity water systems which are typically installed and possibly qualified prior to installation of other user equipment (such as washers, solutions tanks etc.), and the acceptability of those water systems should be based on the quality of the water within the generation and distribution system utilizing the procedures and processes applicable to them.
Response: Comment not incorporated. The system boundary definition is described in the section. If the system does not include delivery, then it must be separately validated.

4.2. Validation Approach & 4.3. Operational Use
Comment Summary #11: The commenter suggested aligning these sections and Figure 3 with the widely applied three phase PQ approach (as described in the FDA Guide to Inspections of High Purity Water Systems and other sources, e.g. ISPE Water and Steam System Baseline guide, WHO TRS 970 Annex 2).
Response: Comment not incorporated because there are several validation approach terminologies and concepts. USP is describing the most commonly used.

4.2.2. User Requirements and Design Qualification, URS, FAT, SAT
Comment Summary #12: The commenter suggested changing the title to "User Requirements Specification and design Qualification" because FAT and SAT are not discussed in the subsequent section. Additionally, only limited portions of a pharmaceutical water system can undergo Factory Acceptance Testing (e.g. still, deionizers, etc.).
Response: Comment incorporated.
Comment Summary #13: The commenter suggested expanding the approaches developed because it is confusing to require user requirements to identify design elements. User requirements and design elements are related but different. Typically (e.g. ISPE Baseline Guide, Vol 5 Commissioning and Qualification) this relationship is shown using a V-Model. The more recent ASTM E2500 verification approach maintains this distinction.
Response: Comment not incorporated. There are several approaches available. The Expert Panel recommended one approach to the Expert Committee and clearly explained and developed it.

4.2.5. Performance Qualification
Comment Summary #14: The commenter suggested clarifying that the period of time for the PQ segments (analogous to validation runs on other equipment) should each be of sufficient length to support the intended sanitization frequency (example - 3 weeks when the sanitization frequency is weekly).

Response: Comment not incorporated. The section already states “or sufficient time to generate adequate data to demonstrate…”
Comment Summary #15: The commenter suggested removing the phrase “and this validation phase has been complete” from the sentence "The water may be used for manufacturing at risk, and the associated products may be released only after water quality attributes have been determined to be acceptable and this validation phase has been complete" because manufacturers of LVP’s with parametric release would not be able to sustain a 2-4 week inventory of product to comply with this requirement. Instead, the user suggested including an alternate allowance based on in-house risk based rationale.
Response: Comment not incorporated. This is a non-mandatory General Chapter and users can use different approaches, if sufficiently justified based on their own risk assessment.

5. Design and Operation of Purified Water and Water for Injection Systems
Comment Summary #16: The commenter suggested changing the sentence, “The quality attributes of the two waters differ only in the presence of a bacterial endotoxin requirement for Water for Injection and in their methods of preparation” to “The quality attributes of the two waters differ only in the presence of a bacterial endotoxin requirement for Water for Injection and in their methods of preparation, as well as with bioburden levels” because there are differences also with Bioburden levels.
Response: Comment partially incorporated. The sentence was revised to state, “The quality attributes of the two waters differ in their bioburden expectation, the presence of a bacterial endotoxin requirement for Water for Injection, and in their methods of preparation.”

5.1.6. Deionization
Comment Summary #17: The commenter indicated that the sentence “Deionization (DI) and Continuous Electrodeionization (CEDI) are effective methods of improving the chemical quality attributes of water by removing cations and anions” is too restrictive, and it should be more open to other de-ionization techniques (such as Electrodialysis, Capacitive De-ionization (CDI), etc.)
Response: Comment not incorporated. The text provides examples of effective and typical examples and it is not intended to be an exhaustive list. Users can use different approaches if sufficiently justified.
Comment Summary #18: The commenter suggested changing the words “ion exchange resins” by “ion exchange materials (such as resins or grafted material)” in the following sentence, “The CEDI system uses a combination of ion-exchange resin, selectively permeable membranes, and an electric charge, providing continuous flow (of product and waste concentrate) and continuous regeneration.”
Response: Comment incorporated.

5.1.7. Reverse Osmosis
Comment Summary #19: The commenter suggested changing the sentence, “A second pass of this permeate water through another RO stage usually achieves the necessary permeate purity if other factors such as pH and temperature have been

appropriately adjusted and the ammonia from chloraminated source water has been previously removed" to "A second pass of this permeate water through another RO stage usually achieves the necessary permeate purity if other factors such as pH and temperature have been appropriately adjusted and the ammonia from source water that has been previously treated with chloramines is removed" to eliminate the word "chloraminated."
Response: Comment incorporated.

5.1.8. Ultrafiltration

Comment Summary #20: The commenter indicated that the following statement is incomplete, "Ultrafiltration is a technology that is often used near the end of a pharmaceutical water purification system for removing endotoxins from a water stream," because ultrafiltration can also be used in different stage of the purification process and is not limited to endotoxin removal.
Response: Comment incorporated. The sentence was revised to state, "Ultrafiltration is a technology that is often used near the end of a pharmaceutical water purification system for removing endotoxins from a water stream though upstream uses are possible."

5.1.13. Distribution Systems

Comment Summary #21: The commenter requested introducing the history around dead legs.
Response: Comment not incorporated. A general description is adequate. This section is not intended to be a design manual.
Comment Summary #22: The commenter requested introducing a diagram showing the piping, valve, and diameters to clearly demonstrate the design of the system.
Response: Comment not incorporated. A general description is adequate. This section is not intended to be a design manual. There are other source for design information (ISPE Guidance is available).
Comment Summary #23: The commenter requested using "continuously sanitizing" (as used in the section on Chemical Sanitization) instead of "self-sanitizing" in the following sentence: "In systems that operate at self-sanitizing temperatures, precautions should be taken to avoid cool points where biofilm development could occur."
Response: Comment not incorporated. The temperature of sanitization was intended.

5.3. Sanitization

Expert Committee-initiated Change #2: The sentence, "Systems can be sanitized using either thermal or chemical means" was changed to "Systems can be sanitized using either thermal or (photo-) chemical means" to consider UV Sanitization.

5.3.1. Thermal Sanitization

Comment Summary #24: The commenter requested clarifying the term "significantly" in the sentence, "The use of thermal methods at temperatures significantly above 80° is contraindicated, because it does not add to microbial control of the system or reduction of biofilm."

Response: Comment incorporated. The sentence was revised to state, “The use of thermal methods at temperatures above 80° is contraindicated because it does not add to microbial control of the system or reduction of biofilm.”

5.3.2. Chemical Sanitization

Comment Summary #25: The commenter suggested adding Sodium Hydroxide to the sentence, “These methods typically use oxidizing agents such as ozone, hydrogen peroxide, peracetic acid, or combinations thereof.”
Response: Comment not incorporated. The list is not precluding Sodium Hydroxide and it is not intended to be an exhaustive list.

5.3.3. UV Sanitization

Comment Summary #26: The commenter suggested clarifying whether UV technology is considered a sanitization technique or not.
Response: Comment not incorporated. The current text is clear in considering UV as a continuously sanitization technique.

6.4.4. Water for Injection Distribution System Sampling

Expert Committee-initiated Change #3: The sentence “In general, water sampling for microbial and bacterial endotoxin testing is expected to occur daily somewhere in the system, with each outlet being sampled NLT weekly” was changed to “In general, water sampling for microbial and bacterial endotoxin testing is expected to occur daily somewhere in the system, with each outlet being sampled periodically, based on a risk assessment, to characterize the quality of the water” to include distribution systems maintained above 65°.

8.1.2.1. Gram-positive bacteria

Expert Committee-initiated Change #4: The term “Gram positives” was changed to “Gram-positive bacteria”, a more proper terminology.

8.1.2.2. Gram-negative bacteria

Expert Committee-initiated Change #5: The term “Gram negatives” was changed to “Gram-negative bacteria”, a more proper terminology.

8.1.3. Fungi

Expert Committee-initiated Change #6: The sentence “Mold spores are easily spread through air and materials, and could contaminate grab water samples” was changed to “Mold spores are easily spread through air and materials, and could contaminate water samples” because the term grab sampling should be reserved for taking a sample directly from a bulk material not collecting a sample from a point-of-use.

8.3.1. Exogenous Contamination

Comment Summary #27: The commenter requested clarifying that unless a trend is observed it might not be necessary to trigger investigation and remediation for the isolation of no-aquatic microorganisms in the following sentence “The detection of non-

aquatic microorganisms may be an indication of sampling or testing contamination or a system component failure, which should trigger investigation and remediation."
Response: Comment not incorporated. The users need to investigate where the non-aquatic microorganisms come from and remediate it. The text is appropriate. If non-water isolates are detected, such as from sampling contamination, then that also must be determined and fixed.

8.5. Test Methods

Comment Summary #28: The commenter suggested providing guidance on an acceptable way to do periodic reassessment, for example, to perform the assessment during trending, because this section states that the user is to perform method validation studies to demonstrate the suitability of the test parameters for bioburden recovery and that it is typically done before or during system validation. This section also states the chosen method should be reassessed periodically, as the microbiome of a new system establishes a steady state (over time).
Response: Comment not incorporated. This General Chapter is not intended to be a complete guidance.

8.5.3. Suggested Classical Culture Methods

Comment Summary #29: The commenter recommended that *Table* 2 provide examples of objectionable organisms and clarify if the water system isolates for growth promotion of media is for both non-sterile and sterile applications.
Response: Comment not incorporated. It is the responsibility of the manufacturer to define what is objectionable and to assure that the test method can recover this organism.
Comment Summary #30: The commenter suggested adding other internationally recognized designations for species of bacteria, besides the American Type Culture Collection (ATCC), which is essentially a commercial entity. There are other "brands" of these bacterial strains available globally via various national culture collections, for example, the World Data Center for Microorganisms that operates under the auspices of the World Federation for Culture Collections (http://refs.wdcm.org/home.htm). This latter approach has been adopted by the International Standards Organization.

Response: Comment not incorporated. Use of alternate strains is covered in *General Notices* under section 6.30. In the General Chapters <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests, <62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms, and <71> Sterility Tests USP has stated that the usage of non-ATCC, but equivalent strains, is permissible

8.5.4. Microbial Identification

Expert Committee-initiated Change #7: The sentence "For more information, see <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use,* <1113> *Microbial Characterization, Identification, and Strain Typing* and <1117> *Microbiological*

Best Laboratory Practices" were added for additional references on objectionable microorganisms, which are tangential to water monitoring.
Comment Summary #31: The commenter suggested clarifying that water system isolates may be incorporated into a company culture collection for use in tests such as antimicrobial effectiveness test, microbial method validation/suitability testing, and media growth promotion.
Response: Comment incorporated.

8.5.5. Rapid Microbiological Methods
Comment Summary #32: The commenter suggested clarifying this section, because of the contradiction that starts by saying the methods provide greater precision and ends by saying there can be instruments sensitivity limitations. The throughput limitation mentioned here depends on several factors specific to each user. This paragraph should focus on the performances of the methods and the work that has been done by USP to push for rapid methods (for example the new General Chapter <1223> Validation of Alternative Microbiological Methods).
Response: Comment incorporated.
Comment Summary #33: The commenter suggested clarifying the section, because when using a method that might destroy the cells, the user can keep a part of the water sample (or a second sample) to redo the testing with the traditional methods in case of contamination. The rapidity of the methods allows the pharmaceutical company to put in place the required actions when a contamination is detected while waiting for the traditional methods results and identification.
Response: Comment incorporated.

9.4. Defining Alert and Actions Levels and Specifications
Comment Summary #34: The commenter requested clarifying the alert and action limits approach when the system consistently shows zero results and clarifying if the intent of this section is to include an objectionable organism assessment.
Response: Comment not incorporated. Section 9.4.3. already describes low level accounts. Manufacturers should use a suitable approach for determining objectionable organisms, as discussed in the USP microbiological General Chapters.

9.4.5. Source Water Control
Comment Summary #35: The commenter suggested replacing the 500 cfu/mL limit with a risk based approach for achieving the appropriate final treated water quality. If a system is properly designed, feed water exceeding 500 cfu/mL can be treated with no effect on the final treated water quality.
Response: Comment not incorporated. The 500 cfu/mL is an action level not a specification.

General Chapter/Section(s):	<2040> Disintegration and Dissolution of Dietary Supplements/Rupture Test for Soft Shell Capsules**.**
Expert Committee:	General Chapters—Dosage Forms
No. of Commenters:	1

Comment Summary: The commenter requested that the current *Rupture Test for Soft Shell Capsule*s be revised, because some DS soft capsule products are unable to comply with rupture test for soft shell capsules under accelerated storage conditions.
Response: Comment not incorporated. The comment was beyond the scope of the proposed revision. USP general chapters and monographs are not intended to be used for compliance under experimental accelerated storage conditions.

Monographs

Monograph/Section(s): Acetaminophen Suppositories/Impurities
Expert Committee: Chemical Medicines Monographs 6
Expert Committee-initiated change #1: The Expert Committee decided to include the Standard solution preparation in the test for 4-Aminophenol in Acetaminophen-Containing Drug Products <227> 4-Aminophenol in Acetaminophen-Containing Drug Products, <227> because the Standard solution described in the General Chapter, is not suitable for accurate quantitation of 4-aminophenol.

Monograph/Section(s): Acetazolamide Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the title of the monograph to indicate that it is a solution if the formulation results in a solution, because the formulation may form a solution when using the tablets or the bulk powder.
Response: Comment not incorporated. The Expert Committee confirmed that acetazolamide is very slightly soluble in water; however, because the *Vehicle* is composed mostly of water, but includes other ingredients, acetazolamide will not form a solution at a concentration of 25 mg/mL.
Comment Summary #2: The commenter suggested that the storage condition of a cold place be revised to indicate storage in a refrigerator to prevent storage in freezer conditions.
Response: Comments incorporated.

Monograph/Section(s): Allopurinol Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter suggested revising the formula to make it clear that 2 g of allopurinol is used (e.g. allopurinol tablets equivalent to 2 g of allopurinol).
Response: Comment incorporated.
Comment Summary #2: The commenter noted that the labeling requirements are not consistent in the compounding monographs and suggested removing the statements to keep out of reach of children and to label with the strength of allopurinol.
Response: Comment incorporated.

Monograph/Section(s): Amiodarone Hydrochloride Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 600 mg of amiodarone hydrochloride is used (e.g. amiodarone hydrochloride tablets equivalent to 600 mg amiodarone hydrochloride).
Response: Comment incorporated

Monograph/Section(s): Amitraz Concentrate for Dip/Identification
Expert Committee(s): Chemical Medicines Monographs 3
Expert Committee-initiated Change #1: The revision proposed under *Identification* was cancelled pending additional supporting data.

Monograph/Section(s): Amlodipine Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter suggested revising the formula to make it clear that 100 mg of amlodipine is used (e.g. amlodipine besylate tablets equivalent to 100 mg amlodipine).
Response: Comment incorporated

Monograph/Sections: Aripiprazole/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the acceptance criteria for aripiprazole related compound G, aripiprazole related compound F, and aripiprazole 4,4' dimer.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Monograph/Section(s): Atenolol Compounded Oral Solution/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter noted that the labeling requirements are not consistent in the compounding monographs and suggested removing the statements to keep out of reach of children and to label with the nominal concentration of atenolol.
Response: Comment incorporated.
Expert Committee-initiated Change #1: The Expert Committee removed the percentage concentration from the *Definitions* section and maintained concentration expression in mg/mL.

Monograph/Section(s): Atenolol Compounded Oral Solution/Labeling
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter noted that the labeling requirements are not consistent in the compounding monographs and suggested removing the statements to keep out of reach of children and to label with the nominal concentration of atenolol.
Response: Comment incorporated.

Monograph/Section(s): Azathioprine Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Baclofen Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Benzalkonium Chloride Solution/*Alcohol Content (if added)*
Expert Committee: Excipient Monographs 1
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the GC column thickness from "1.4-μm layer" to "1.8-μm layer" with supporting data.
Response: Comment incorporated.

Monograph/Section(s): Bethanechol Chloride Compounded Oral Solution/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Bethanechol Chloride Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of “a cold place” be revised to indicate “storage in a refrigerator” to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section: Bismuth Subsalicylate Oral Suspension/Heavy Metals
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1
Comment Summary #1: The commenter requested including a test for lead with a limit of NMT 0.10 µg/g.
Response: Comment not incorporated. The Expert Committee will consider future revisions if needed.

Monograph/Section(s): Calcium Propionate/Identification
Expert Committee: Monographs—Excipients 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended the addition of an identification test for the propionate ion or a test which indicates the anion is a monocarboxylic acid.
Response: Comment not incorporated. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section(s): Captopril Compounded Oral Solution/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of “a cold place” be revised to indicate “storage in a refrigerator” to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Captopril Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of “a cold place” be revised to indicate “storage in a refrigerator” to prevent storage in freezer conditions.
Response: Comments incorporated.

Monograph/Section(s): Cetirizine Hydrochloride Orally Disintegrating Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested decreasing the concentration of sodium 1-decanesulfonate in the mobile phase used in the *Assay* and *Organic Impurities* tests due to difficulty in preparing the buffer at the specified concentration.
Response: Comment not incorporated. The mobile phase in the monograph is consistent with the sponsor's validation data.
Comment Summary #2: The commenter requested that sodium 1-decanesulfonate be replaced with a less costly ion-pairing agent in the *Assay* and *Organic Impurities* tests.
Response: Comment not incorporated. The mobile phase in the monograph is consistent with the validation data.
Comment Summary #3: The commenter recommended removal of the system suitability solution from the *Assay* as resolution can be determined on each sample solution injection.
Response: Comment not incorporated. The system suitability requirements for the assay are consistent with the validation data.
Comment Summary #4: The commenter recommends that the resolution requirement between cetirizine and meclizine related compound A in the *Assay* be changed from NLT 1.5 to NLT7.
Response: Comment not incorporated. A resolution of NLT 1.5 is consistent with the robustness validation data.
Comment Summary #5: The commenter recommends that in the *Assay* and *Organic Impurities* tests the resolution criterion be determined using the more appropriate critical pair of cetirizine and cetirizine *N*-oxide instead of cetirizine and meclizine related Compound A.
Response: Comment not incorporated. The system suitability for the assay is consistent with the validation data.
Comment Summary #6: The commenter recommended that in the *Organic Impurities* test the relative retention times listed in *Table* 2 be used to identify the Cetirizine degradation products instead of a resolution solution prepared using multiple reference standards.
Response: Comment not incorporated. The Expert Committee determined that the organic impurities procedure is suitable for it intended use.
Comment Summary #7: The commenter recommends using cetirizine hydrochloride as standard and the relative response factors (RRFs) to monitor the degradation products in the *Organic Impurities* test. Relative retention times provided in *Table* 2 can aid in the identification of specified degradation products, in lieu of including each impurity in the Standard solution. This approach would save resources.
Response: Comment not incorporated. The Expert Committee determined that the organic impurities procedure is suitable for its intended use.
Comment Summary #8: The commenter recommended changing the wavelength for monitoring 4-chlorobenzophenone from 260 nm to 230 nm in the *Organic Impurities* test.

Response: Comment not incorporated. The wavelength used to monitor 4-chlorobenzophenone is consistent with the validation data.

Monograph/Section(s): Chloroquine Phosphate Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 1.5 g of chloroquine phosphate is used (e.g. chloroquine phosphate tablets equivalent to 1.5 g of chloroquine phosphate).
Response: Comments incorporated.

Monograph/Section(s): Ciprofloxacin/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2
Comment Summary #1: The commenter recommended harmonizing the amount of ciprofloxacin used for *Standard solution* with the amount used for *Sample solution*, in the *Assay*.
Response: Comment not incorporated. The Expert Committee determined that there is no impact, as the final concentrations of ciprofloxacin in the *Standard solution* and *Sample solution* are the same.
Comment Summary #2: The commenter indicated that a peak at retention time of 13.2 minutes is observed in the blank in the test for *Organic impurities.*
Response: Comment not incorporated. The peak at retention time of 13.2 minutes is due to the switch in the mobile phase composition.
Comment Summary #3: The commenter recommended tightening the acceptance criterion for any individual unspecified impurity in the test for *Organic Impurities* based on the ICH guidelines and the FDA approved limit.
Response: Comment not incorporated. The acceptance criterion for any individual unspecified impurity is consistent with FDA requirements.

Monograph/Section(s): Ciprofloxacin Hydrochloride/Organic Impurities
Expert Committee: Chemical Medicines Monographs1
No. of Commenters: 2
Comment Summary #1: The commenter indicated that a peak at retention time of 13.2 minutes is observed in the blank in the test for *Organic impurities*.
Response: Comment not incorporated. The peak at retention time of 13.2 minutes is due to the switch in the mobile phase composition.
Comment Summary #2: The commenter recommended tightening the acceptance criterion for any individual unspecified impurity in the test for *Organic Impurities* based on the ICH guidelines and the FDA approved limit.
Response: Comment not incorporated. The acceptance criterion for any individual unspecified impurity is consistent with FDA requirements.

Monograph/Section(s): Clonazepam Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Codeine Phosphate Compounded Oral Solution/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Compounding Monographs/General
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter indicated that the labeling requirements are not consistent in all of the compounded preparation monographs.
Response: Comments incorporated. The purpose of the revision proposal is to revise the title of the compounding preparation monographs consistent with the USP Nomenclature Guidelines. The Expert Committee revised the labeling section of the monograph proposals to make them more consistent.
Comment Summary #2: The commenter suggested that storage condition of 2º– 8º should be revised to indicate storage in a refrigerator for consistency.
Response: Comments incorporated.
Comment Summary #3: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comments incorporated.
Comment Summary #4: The commenter noted that several monographs cited the specific source of finished product used to prepare the compounded preparation. The commenter also noted the product cited is not the most economical (e.g. generic, highest strength). The specific sources mentioned in the monographs are sometimes also outdated. The commenter suggested removing the specific source of finished product from the monograph unless there is a good reason to require that only a specific finished product be used.
Response: Comments not incorporated. The specific source of finished product cited in the monograph reflects the specific ingredients used during the method development/validation process and stability study. The beyond-use date in the monograph is specific for the formula provided in the monograph. Although changing the ingredient often may not have an impact on the stability of the preparation, it is not known since the monograph preparation was studied as described in the *Definitions*

section of the monograph. The Expert Committee will consider this comment further and determine whether future revisions are necessary.

Monograph/Section(s): Dapsone Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 200 mg of dapsone is used (e.g. dapsone tablets equivalent to 200 mg of dapsone).
Response: Comments incorporated.
Comment Summary #2: The commenter suggested using 100 mg instead of 25 mg dapsone tablets.
Response: Comments not incorporated. The specific strength of the finished product cited in the monograph reflects the specific ingredients used during the method development/validation process and stability study. The beyond-use date in the monograph is specific for the formula provided in the monograph. Although changing the ingredient often may not have an impact on the stability of the preparation, it is not known since the monograph preparation was studied as described in the *Definitions* section. The Compounding Expert Committee will consider proposing future revisions to the compounding general chapters and/or the *General Notices* to allow compounders the flexibility to interchange of finished products in the monograph.

Monograph/Section(s): Desloratadine/Multiple Sections
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 4
Comment Summary #1: The commenter requested modifications to *Organic Impurities Procedure 1* and *Organic Impurities Procedure 2* to improve resolution, sensitivity and retention time stability.
Response: Comment not incorporated. The Expert Committee determined that the methods are suitable for their intended use.
Comment Summary #2: The commenter indicated that not all of the impurities listed in *Table 3, Organic Impurities, Procedure 2* are available in the USP catalog.
Response: Comment not incorporated. The impurities needed to perform the method are available for purchase through USP.
Comment Summary #3: The commenter observed co-elution of impurities when using *Organic Impurities, Procedure 2*.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.
Comment Summary #4: The commenter requested the acceptance criteria for Total impurities be revised to be consistent with regulatory approved limits.
Response: Comment not incorporated. The specified Total impurity limits meet FDA approved specifications.
Comment Summary #5: The commenter requested the instruction for *Organic impurities, Procedure 1* be changed from "…when the impurity profile includes

desloratadine related compound B and fluoroloratadine" to "…when the impurity profile includes desloratadine related compound B or fluoroloratadine."
Response: Comment incorporated.
Comment Summary #6: The commenter requested the instruction for *Organic impurities, Procedure 2* be changed from "…when the impurity profile includes dechlorodesloratadine, desloratadine related compound A and dehydroloratadine" to "…when the impurity profile includes dechlorodesloratadine, desloratadine related compound A or dehydroloratadine."
Response: Comment incorporated.
Comment Summary #7: The commenter requested that the *Loss on Drying* (LOD) test be added to the monograph with a limit of NMT 0.5% as proposed in *PF* 39(2), and leave the definition as on "the dried basis."
Response: Comment not incorporated. The change from LOD test to water determination test was done to make the monograph consistent with the *European Pharmacopoeia* monograph. USP uses both procedures only if the article exists in different hydrated forms or polymorphs; however, in response to this comment, the Expert Committee determined that the definition should be revised from "on the anhydrous" to "on the anhydrous and solvent free basis."

Monograph/Section(s): Desloratadine Orally Disintegrating Tablets/Organic impurities
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1
Comment Summary #1: The commenter requested the units for the concentration for USP Desloratadine RS in the standard solution be changed from µg/mL to mg/mL.
Response: Comment incorporated. For clarity, the concentration of the components of the Standard solution and the nominal concentration of desloratadine in the Sample solution were also changed to mg/mL.

Monograph/Section(s): Desloratadine Tablets/ Organic impurities
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1
Comment Summary #1: The commenter requested the limit for desloratadine related compound F be widened from NMT 0.2% to NMT 0.30%, and the total impurities limit be widened from NMT 0.4% to NMT 0.50% to match FDA approved specifications.
Response: Comment incorporated.

Monograph/Section(s): Diclofenac Sodium/Identification C
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended either retaining the flame test or using an alternative procedure because of the safety concerns related to 10%(W/V) etramethylammonium hydroxide solution used in the preparation of methoxyphenylacetic TS.
Response: Comment incorporated. The Expert Committee decided to retain the flame test and remove the cross reference to General Chapter <191>.

Monograph/Section(s): Diltiazem Hydrochloride Compounded Oral Solution/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comments incorporated.

Monograph/Section(s): Diltiazem Hydrochloride Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comments incorporated.

Monograph/Section(s): Diltiazem Hydrochloride Extended-Release Capsules/Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 3
Comment Summary #1: The commenter requested revising the acceptance criteria for desacetyl diltiazem from NMT 0.5% to NMT 1.5% and the total impurities from NMT1.0% to NMT 2.0% in the test for *Organic impurities* to be consistent with FDA approved product specifications.
Response: Comment incorporated.
Comment Summary #2: The commenter indicated that the sample preparation time for the *Assay* is long.
Response: Comment not incorporated. The proposed procedure is consistent with a validated method. The Expert Committee will consider future revisions upon receiving the supporting data.
Comment Summary #3: The commenter requested revising the diluent used in the sample preparation for *Assay,* because of the potential formation of agglomerates.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receiving the supporting data.
Comment Summary #4: The commenter requested adding glacial acetic acid along with the sodium hydroxide to allow flexibility in adjusting the pH of Solution A under Assay.
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that the chromatographic procedure under *Organic impurities* resulted in a noisy baseline, and that some peaks from the blank are closely eluting either with diltiazem peak or desacetyl diltiazem peak.
Response: Comment not incorporated. The Expert Committee will consider future revisions upon receiving the supporting data.

Comment Summary #6: The commenter indicated that the chromatographic column used in the *Organic impurities* test is deteriorated after every 32 injections.
Response: Comment not incorporated. The Expert Committee will consider future revisions, if needed.

Monograph/Section(s): Dipyridamole Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Dolasetron Mesylate Compounded Oral Solution/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Dolasetron Mesylate Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of a cold place be revised to indicate storage in a refrigerator to prevent storage in freezer conditions.
Response: Comments incorporated.

Monograph/Section(s): Doxapram Hydrochloride/Multiple sections
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated Change #1: The phrase "Meets the requirements" was added to *Identification C* for clarity and consistency with current *USP* style.
Expert Committee-initiated Change #2: The calculation and Table entry related to individual impurities within the test for *Organic Impurities* was updated to consistently cite the phrase "any individual unspecified impurity" for clarity and consistency with current *USP* style.

Monograph/Section(s): Enalapril Maleate Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter recommended omitting the monograph, because there is a FDA-approved Enalapril Maleate Powder for Oral Solution.

Response: Comments not incorporated. The monograph should be maintained in the event of intermittent drug shortages and product availability. A monograph offers consistency in the formulation in the event compounding is needed.
Comment Summary #2: The commenter suggested revising the formula to make it clear that 100 mg of enalapril maleate is used (e.g. enalapril maleate tablets equivalent to 100 mg of enalapril maleate).
Response: Comment incorporated.

Monograph/Section(s): Flecainide Acetate Compounded Oral Suspension/ Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that storage condition of 2º - 8º should be revised to indicate storage in a refrigerator for consistency.
Response: Comment incorporated.

Monograph/Section(s): Flucytosine Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested deleting the terminal zero in the formulation in accord with *General Notices* 10.40.20.
Response: Comment incorporated.

Monograph/Section(s): Ganciclovir Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter noted that ganciclovir capsules are no longer commercially available and suggested modifying the formulation to reflect this change in marketed products.
Response: Comments not incorporated. The specific finished product cited in the monograph reflects the specific ingredients used during the method development/ validation process and stability study. The beyond-use date in the monograph is specific for the formula provided in the monograph. Although changing the ingredient often may not have an impact on the stability of the preparation, it is not known since the monograph preparation was studied as described in the *Definitions* section. The Compounding Expert Committee will consider proposing future revisions to the compounding general chapters and/or the *General Notices* to allow compounders the flexibility to interchange the finished products used in the monograph.
Comment Summary #2: The commenter suggested adding a statement in the monograph to state that ganciclovir must be handled with great care because it is a potent cytotoxic agent and suspected carcinogen.
Response: Comments not incorporated. Handling of hazardous drugs is addressed in General Chapter <800> *Hazardous Drugs—Handling in Healthcare Settings*

Monograph/Section(s): Granisetron Hydrochloride Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that storage condition of 2º - 8º should be revised to indicate storage in a refrigerator for consistency.
Response: Comment incorporated.

Monograph/Section(s): Hydralazine Hydrochloride Compounded Oral Solution/Labeling
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter noted that the labeling requirements express the strength as a percentage and parenthetically (mg/ 5mL) is not consistent with other compounding monographs and should be removed.
Response: Comment incorporated. The labeling requirement for the strength as a percentage is removed from the monograph.

Monograph/Section(s): Hydrochloric Acid Compounded Injection/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter noted that the packaging requirement does not provide information on containers equivalent to polypropylene containers and suggested removing it from the monograph.
Response: Comment incorporated. The *Packaging* requirement was revised to delete the text “or equivalent”.
Comment Summary #2: The commenter indicated that all single-dose products be labeled as such in the *General Notices* and suggested removing the labeling requirement that it does not contain an antimicrobial preservative.
Response: Comment partially incorporated. The Expert Committee determined that it was important to indicate that the preparation is packaged in a single-dose container since the specific tests do not require antimicrobial effective testing.

Monograph/Section(s): Ibuprofen Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 3
Comment Summary #1: The commenter indicated that the system suitability requirements cannot be met in the test for *Organic impurities,* because of the low sensitivity of ibuprofen at 254 nm.
Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is suitable as written based on the supporting data.
Comment Summary #2: The commenter recommended revising the symbol for time from “min” to “minutes” in the *Sample solution* for *Assay*.
Response: Comment not incorporated. The symbol “min” for minute is described in the *General Notices 8.240* and is consistent with the current *USP* style.

Comment Summary #3: The commenter suggested replacing the “flat bed shaker” specified in the *Sample solution* under *Assay* with “mechanical shaker” to allow flexibility.
Response: Comment incorporated.
Comment Summary #4: The commenter requested retaining the acceptance criterion of NMT 0.25% instead of the proposed NMT 0.1% for ibuprofen related compound C in *Organic impurities* to be consistent with the currently marketed drug products.
Response: Comment incorporated.
Comment Summary #5: The commenter requested clarifying ibuprofen related compound J as specified degradation product in the test for *Organic impurities*.
Response: Comment not incorporated. Ibuprofen related compound J is a specified degradation product controlled at the same level as for the unspecified degradation product and is included in the total degradation products.
Comment Summary #6: The commenter indicated that the proposed acceptance criteria for ibuprofen related compound J and the unspecified degradation product exceed the ICH identification threshold and the acceptance criterion for the total degradation products is high in the test for *Organic impurities*.
Response: Comment not incorporated. The proposed acceptance criteria are consistent with the currently marketed drug products.

Monograph/Section(s): Indomethacin Compounded Topical Gel/Labeling
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter suggested deleting the labeling requirement that the preparation should only be used as directed.
Response: Comment incorporated.

Monograph/Section(s): Isradipine Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to clarify that 100 mg of isradipine is used (e.g. isradipine capsules or powder equivalent to 100 mg of isradipine).
Response: Comment incorporated.

Monograph/Section(s): Ketoconazole Compounded Oral Suspension/ Packaging
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: *The* commenter suggested removing “amber” from the *Packaging* requirements, because it is repetitive with the requirement for light-resistant.
Response: Comments incorporated.

Monograph/Section(s): Labetalol Hydrochloride Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comments incorporated.

Monograph/Section(s): Lisinopril/Organic Impurities
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 5
Comment Summary #1: The commenter requested revising the acceptance criteria for N-Alkyl-L-Lysine, Lisinopril epimer, *R,S,S*-Diketopiperazine and *S,S,S*-Diketopiperazine from NMT 0.15% to NMT 0.3% and Lisinopril cyclohexyl analog and *DL*-Homophenylalanine, from NMT 0.15% to NMT 0.30% and the total impurities from NMT0.50% to NMT 0.5% not including Lisinopril epimer in the test for *Organic Impurities* to be consistent with FDA approved specifications.
Response: Comment incorporated.
Comment Summary #2: The commenter requested revising the *Organic Impurities* procedure as it is less sensitive to all specified impurities.
Response: Comment not incorporated. The Expert Committee determined that the proposed procedure can adequately establish the quality of the drug substance.
Comment Summary #3: The commenter requested harmonizing the proposal with the current *European Pharmacopeia (EP)* 8.7 monograph, because the proposal does not include all the impurities listed in the *EP* 8.7 and also the proposed USP impurity limits differ from the corresponding *EP* 8.7 limits.
Response: Comment not incorporated. The proposal is suitable as written and is consistent with FDA approved specifications for the marketed products in the United States.

Monograph/Section(s): Lisinopril Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 100 mg of lisinopril is used (e.g. Lisinopril tablets equivalent to 100 mg of lisinopril).
Response: Comment incorporated.

Monograph/Section(s): Magnesium Aluminum Silicate/Identification test and Viscosity test
Expert Committee: Monographs—Excipients 1
No. of Commenters: 1
Comment Summary #1: The commenter noted that the *Appearance* test is not effective as an identification test except to distinguish the 2 types, IA and IB, which have overlapping viscosity. The commenter recommended including particle size range or

mesh size as a mean to completely differentiate the types of Magnesium Aluminum Silicate that have overlapping viscosity ranges.
Response: Comment not incorporated. For many years, the overlap of Viscosity range and Aluminum/Magnesium ratio numbers for Types IA and IB has occurred. However, it was never seen as an issue to the users of Magnesium Aluminum Silicate (MAS) products. It was because there was a definite and obvious difference in the appearance between the two Type materials. IB is a micronized grade of the IA material. Type IA is either a granulated or flaked form. The differences in appearance are quite obvious to those peering at either Type.

It is not typical for MAS to be characterized by particle size in the dry state. Processing to create a particle size range and subsequent testing to assure the range was achieved is not done. Nor does it need to be done as these materials are for the most part dispersed in water with shear, creating a colloidal suspension. Users of Type IA or IB MAS do so more because of the aspect of the material being micronized or not, not on the viscosity range or Al/Mg ratio or a potential particle size range. The micronized grade, IB, is typically selected over the IA when there is a desire to use MAS dry as in tablets, pressed powder cakes or face masks. To use another form (granule or flake) would introduce particles of a different nature to the other micronized ingredients. The users do not express a requirement that certain particle size ranges be made available – it is micronized or it is not. Introducing "appearance" as a way of further differentiating between Types IA and IB was the correct way to proceed in the presence of overlapping ranges. Because of the obvious appearance differences that exist between Type IA and IB grades, instituting particle size measurements goes beyond the need for a user to be sure the material they are using is micronized or not.
Comment Summary #2: The commenter recommended revising the wording from "Transfer the contents of the blender to a 600-mL beaker, and allow to stand for 5 min" to "Transfer the contents of the blender to a 600-ml beaker, and allow to stand until the sample temperature reaches 33 ± 3º."
Response: Comment not incorporated. Magnesium Aluminum Silicate is thixotropic, the measured viscosity depends on carefully controlling the time period during which the dispersion sits (i.e., the colloidal structure forms). If the monograph requires that the sample stand until its temperature reaches 33 ± 3º then there is no control over how this is done or how long it takes, so the careful energy/time balance that is designed to make the viscosity test reproducible is lost.

Monograph/Section(s): Metolazone Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Metoprolol Tartrate Compounded Oral Solution/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of "a cold place" be revised to indicate "storage in a refrigerator" to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Metronidazole Gel/Assay
Expert Committee: Chemical Medicines Monographs 1
Expert Committee-initiated Change #1: The Expert Committee revised the relative standard deviation system suitability requirement from NMT 1.0% to NMT 2.0%. The Expert Committee determined that NMT 2.0% provides an adequate measurement of system suitability in this procedure.

Monograph/Section(s): Naratriptan Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: Commenter noted that 50 mg of naratriptan is equivalent to 55.43 mg of naratriptan hydrochloride and suggested revising the formulation to reflect the equivalency information to the 2 decimal point.
Response: Comment incorporated.

Monograph/Section(s): Niacin
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1
Comment Summary #1: The commenter suggested that additional information such as absorption maximum at 263 nm and minimum at 239 nm should be added to the acceptance criteria for the Identification B test, which would provide more clarity for the analyst.
Response: Comment not incorporated. The additional information is not necessary because it is not part of the requirements for the acceptance criteria.

Monograph/Section(s): Octreotide Acetate/Identification B
Expert Committee: Biologics Monograph 1—Peptides
No. of Commenters: 1
Comment Summary #1: The commenter requested allowing flexibility to use any validated amino acid analysis method for the drug substance without changing the specifications, and defining the proposed method in the monograph as a representative procedure.
Response: Comment incorporated.

Monograph/Section(s): Ondansetron Compounded Oral Suspension/Labeling
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: Commenter suggested revising the labeling statement to reverse the primary expression of strength in terms of ondansetron.
Response: Comment incorporated.

Monograph/Section(s): Oral Rehydration Salts/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated Change #1: "*Standard preparation 1*" was renamed "*Standard solution 1*" in the *Assay, Citrate* for consistency with the corresponding solution name within General Chapter <345> *Assay for Citric acid/Citrate and Phosphate.*

Monograph/Section(s): Oxymorphone Hydrochloride Extended-Release Tablets/Dissolution
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2
Comment Summary #1: Two commenters requested adding new dissolution tests to accommodate FDA approved specifications.
Response: Comment not incorporated. The Expert Committee will consider inclusion of additional dissolution tests in a future revision upon receipt of supporting data.

Monograph/Section(s): Oxymorphone Hydrochloride Tablets/Dissolution
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter requested adding a new dissolution test to accommodate FDA approved specifications.
Response: Comment not incorporated. The Expert Committee will consider inclusion of an additional dissolution test in a future revision upon receipt of supporting data.

Monograph/Section(s): Pentoxifylline Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 2 g of pentoxyifylline is used (e.g. pentoxifylline extended-release tablets equivalent to 2 g of pentoxifylline).
Response: Comment incorporated.

Monograph/Section(s): Phenobarbital Compounded Oral Suspension/Formula
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter suggested revising the formula to make it clear that 1.2 g of phenobarbital is used (e.g. phenobarbital tablets equivalent to 1.2 g of phenobarbital).

Response: Comment incorporated.
Comment Summary #2: The commenter suggested omitting the monographs, because there is a phenobarbital elixir commercially available.
Response: Comments not incorporated. The commercially available phenobarbital oral solution (elixir) contains between 12% and 15% alcohol, which may be clinically inappropriate for certain patient populations.

Monograph/Section(s): Polyethylene Glycol/Viscosity
Expert Committee: Excipient Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter requested keeping the viscosity reference to Polyethylene Glycol 3350 in the Polyethylene Glycol *NF* monograph, because many manufacturers use this material as an inactive ingredient.
Response: Comment not incorporated. The Expert Committee determined that keeping the viscosity reference was not consistent with FDA approved specifications.

Monograph/Section(s): Polyethylene Glycol 3350/Limit of Ethylene Glycol and Diethylene Glycol
Expert Committee: Excipient Monographs 1
No. of Commenters: 1
Comment Summary #1: The commenter recommended changing the resolution between diethylene glycol and ethylene glycol from “NLT 1.5” to “NLT 0.9” with supporting data.
Response: Comment incorporated.
Comment Summary #2: The commenter recommended revising storage condition and the committee agreed to remove the storage requirement “Store at room temperature,” and replace with the statement “Avoid exposure to excessive heat.”
Response: Comment incorporated.

Monograph/Section(s): Polyvinyl Acetate Dispersion/Multiple Sections
Expert Committee: Excipient Monographs 1
No. of Commenters: 1
Comment Summary #1: The labeling statement indicates that the name and quantities of added surface active agent (SAA) and stabilizer has to be mentioned in the label. In the *Other Components* section, the commenter noted that the test for Stabilizers or Surface Active Agents is to be conducted only when povidone is present in the dispersion. There is no test for SAA or stabilizer when anything other than povidone is used. The commenter recommended that this inconsistency be addressed.
Response: Comment incorporated. The Expert Committee removed the surface active agents and specified povidone and sodium lauryl sulfate as stabilizers in the monograph *Definition*. The Expert Committee removed the surface active agents in the section of *Other Components*. Furthermore, the Expert Committee replaced the labeling requirement with the text of “Label it to indicate the amounts of povidone and sodium lauryl sulfate.”

Monograph/Section(s): Potassium Bromide Compounded Oral Solution, Veterinary/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the monograph to indicate that the expression of strength is based on mg of potassium bromide per mL instead of mg of bromide per mL.
Response: Comment incorporated.

Monograph/Section(s): Progesterone Compounded Vaginal Inserts/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested excluding 100 mg from the range of progesterone specified in the formulation, because there is an FDA approved vaginal insert product containing 100 mg of progesterone.
Response: Comment not incorporated. The Expert Committee determined that there is a risk of confusion by excluding a specific strength from the monograph and there may be clinical justification for compounding the indicated strength such as patient sensitivities to inactive ingredients and potential for drug shortages.
Comment Summary #2: The commenter suggested removing the labeling requirement that the preparation be used only as directed.
Response: Comments incorporated.

Monograph/Section(s): Promethazine Hydrochloride/Organic Impurities
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1
Comment Summary #1: The commenter requested that the test for *Organic Impurities* be replaced with the Related Substances method from the *European Pharmacopeia* (*EP*) to avoid having to run two different methods.
Response: Comment not incorporated. The Expert Committee determined that the method is suitable for its intended use. The *Organic Impurities* method was also proposed in three promethazine drug product monographs (Tablets, Oral Solution, and Injection). Using the current method provides consistency across the *USP* monograph family and the run time is about half of the *EP* method.
Expert Committee-initiated Change #1: The name of USP Promethazine Hydrochloride Related Compound B RS in the *System suitability stock solution* and *System suitability solution* in the *Assay* is changed to USP Promethazine Related Compound B RS to be consistent with the Reference Standard label and other sections of the monograph.

Monograph/Section(s): Promethazine Hydrochloride Tablets/Assay
Expert Committee: Chemical Medicines Monographs 5
Expert Committee-initiated Change #1: The name of USP Promethazine Hydrochloride Related Compound B RS in the *System suitability stock solution* and *System suitability solution* in the *Assay* is changed to USP Promethazine Related

Compound B RS to be consistent with the Reference Standard label and other sections of the monograph.

Monograph/Section(s): Propylthiouracil Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to clarify that 500 mg of propylthiouracil is used (e.g. propylthiouracil tablets equivalent to 500 mg of propylthiouracil).
Response: Comment incorporated.

Monograph/Section(s): Pyrazinamide Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to clarify that 1 g of pyrazinamide is used (e.g. pyrazinamide tablets equivalent to 1 g of pyrazinamide).
Response: Comment incorporated.

Monograph/Section(s): Pyrimethamine Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that storage condition of 2º - 8º should be revised to indicate storage in a refrigerator for consistency.
Response: Comment incorporated.

Monograph/Section(s): Quinidine Sulfate Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of “a cold place” be revised to indicate “storage in a refrigerator” to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Rifabutin Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 3 g of rifabutin is used (e.g. rifabutin tablets equivalent to 3 g of rifabutin).
Response: Comment incorporated.

Monograph/Section(s): Rifampin Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the packaging and storage requirement to replace the term “child-resistant closures” with “tight light-resistant containers.”
Response: Comment incorporated
Comment Summary #2: The commenter suggested eliminating the concentration in the labeling requirement.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested revising the monograph procedures to empty contents of four rifampin 300-mg capsules or eight rifampin 150-mg capsules on to a piece of weighing paper to align with the FDA-approved label for rifampin capsules.
Response: Comments not incorporated. The monograph allows flexibility in using either the capsule or the powder form of rifampin. The package insert instructions for preparation are specific to one commercial product that may not apply to other products. Furthermore, instructions to use and rinse weighing paper may not be practical or appropriate in all circumstances.

Monograph/Section(s): Ropinirole Extended-Release Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenter noted that chemical name and structure for Ropinirole dimer in the test for *Organic Impurities* may not be correct based on literature information.
Response: Comment not incorporated. The chemical name and structure for ropinirole dimer is consistent with the information provided by the sponsor.
Comment Summary #2: Two commenters requested the inclusion of an FDA approved *Dissolution* test.
Response: Comments incorporated. The liquid chromatographic procedure used in Dissolution Test 2 is based on analyses performed with Waters Xterra RP8 brand of L7 column. The typical retention time for ropinirole is about 3.8 min. The liquid chromato-graphic procedure used in *Dissolution Test* 3 is based on analyses performed with Waters Symmetry brand of L1 column. The typical retention time for ropinirole is about 2.7 min.
Comment Summary #3: The commenter indicated that monopropyl ropinirole, ropinirole *N*-hydroxymethyl, ropinirole methylene dimer and propylidine ropinirole in the test for *Organic Impurities* are process impurities. The commenter requested not to include limits for the process impurities.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon the receipt of the supporting data.

Monograph/Section(s): Sildenafil Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 2
Comment Summary #1: The commenter indicated that there are safety issues concerning labeling information for children and recommended omitting the monograph.
Response: Comment not incorporated. The commercially available solid dosage form of the product is not indicated for use in children and the commercially available liquid dosage form may not be the appropriate dose for all children.
Comment Summary #2: The commenter suggested revising the formula to clarify that 250 mg of sildenafil is used (e.g. sildenafil tablets equivalent to 250 mg of sildenafil).
Response: Comment incorporated.
Comment Summary #3: The commenter suggested adding a statement in the labeling section to require a calibrated measuring device.
Response: Comment not incorporated. All oral liquid preparations should be dispensed with an appropriate calibrated measuring device and it would be inappropriate to distinguish this particular preparation from all other formulations requiring a measuring device.
Comment Summary #4: The commenter indicated that the definition should specify the labeled content of sildenafil citrate in terms of sildenafil.
Response: Comment partially incorporated. The preparation is prepared from sildenafil citrate and dosed based on the strength of sildenafil.

Monograph/Section(s): Sodium Bromide Compounded Injection, Veterinary/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: Commenter recommended revising the *Definition* section to reflect the expression of strength on mg sodium bromide per mL instead of mg bromide per mL.
Response: Comment incorporated.

Monograph/Section(s): Sodium Bromide Compounded Oral Solution, Veterinary/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the *Definition* section to reflect the expression of strength on mg sodium bromide per mL instead of mg bromide per mL.
Response: Comment incorporated.

Monograph/Section(s): Sodium Hypochlorite Compounded Topical Solution/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested including a labeling statement to indicate that the product is for external use only.
Response: Comment partially incorporated. The labeling requirement currently contains a provision noting that the preparation is for external use only and to be applied to wounds and burns.
Comment Summary #2: The commenter suggested eliminating the note allowing the use of commercial unscented laundry bleach, because of the potential presence of unacceptable contaminants.
Response: Comment not incorporated. The formula may be used globally and restricting the purity of the starting material may limit the use of this monograph globally.

Monograph/Section(s): Sodium Phenylbutyrate Compounded Oral Suspension/Labeling
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter noted that there is an FDA-approved product that may be mixed with food. The approved product is stable for up to one week at room temperature or refrigerated when mixed with water. The commenter recommended omitting the monograph.
Response: Comment not incorporated. The formulation in the monograph is supported by a stability study. USP does not support compounding a preparation when there is a commercial product available. The monograph is maintained in the event of drug shortages, intermittent drug unavailability, and to support access worldwide.

Monograph/Section(s): Sotalol Hydrochloride Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to clarify that 600 mg of sotalol hydrochloride is used (e.g. Sotalol Hydrochloride tablets equivalent to 600 mg of sotalol hydrochloride).
Response: Comments incorporated.
Comment Summary #2: The commenter noted that the FDA-approved labeling for the commercially available sotalol hydrochloride tablets includes directions on how to extemporaneously prepare an oral liquid formulation and that there is a commercially available sotalol hydrochloride solution. The commenter recommended revising the monograph to be consistent with the FDA approved labeling for the commercially available tablets.
Response: Comment not incorporated. The labeling instructions may be specific to one commercial product that may not apply to other manufactured products. USP does not support compounding preparation when there is a commercial product available. The

monograph is maintained in the event of drug shortages, intermittent drug unavailability, and to support access worldwide.

Monograph/Section(s): Sprionolactone and Hydrochlorothiazide/Formula Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to clarify that 500 mg of spironolactone and 500 mg of hydrochlorothiazide are used (e.g. Spironolactone and Hydrochlorothiazide tablets equivalent to 500 mg of spironolactone and 500 mg of hydrochlorothiazide).
Response: Comment incorporated.

Monograph/Section(s): Sulfamethoxazole and Trimethoprim Oral Suspension/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1
Expert Committee-initiated Change #1: Because of challenges encountered while evaluating *USP Sulfanilic Acid RS* and *USP Sulfanilamide RS* for quantitative use in the *Organic Impurities* procedure, the *Standard stock solution A* and *Standard solution* sections were revised to remove the reference to USP Sulfanilic acid RS and USP Sulfanilamide RS. Relative response factors are included in *Table* 2 for the calculation of sulfanilic acid and sulfanilamide. USP Sulfamethoxazole RS, which is used in the analysis, was included in these solutions. The calculations section in the test for Organic Impurities and the *USP Reference Standards* <11> section were also updated to reflect these changes.
Expert Committee-initiated Change #2: The Expert Committee revised the System suitability solution in the test for *Organic Impurities* to remove the use of USP Sulfanilic acid RS and USP Sulfanilamide RS. The relative retention times listed in *Table* 2 for these two impurities are sufficient for peak identification. The System suitability requirement was also updated to reflect these changes.
Expert Committee-initiated Change #3: The Expert Committee corrected the preparation of Standard stock solution B in the test for Organic Impurities to include USP Trimethoprim RS.
Expert Committee-initiated Change #4: The Expert Committee corrected the chemical name of USP Diaveridine RS from 5-[(3,4-Dimethoxyphenyl)methyl]-2,4-pyrimidinediamine to 5-(3,4-Dimethoxybenzyl)pyrimidine-2,4-diamine in *USP Reference Standards* <11> section.

Monograph/Section(s): Sumatriptan Compounded Oral Suspension/Labeling
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: Commenter suggested revising the labeling section to remove the requirement for labeling the strength of sumatriptan.
Response: Comment incorporated.

Monograph/Section(s): Tacrolimus/Multiple Sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 3
Comment Summary #1: The commenter recommended incorporating the acceptance criteria for Tacrolimus open ring and Tacrolimus 19-epimer in the test for *Organic impurities*.
Response: Comment not incorporated. Based on the information that tacrolimus 19-epimer and tacrolimus open ring are formed in the *Sample solution* in the presence of water, the Expert Committee determined that these limits are not suitable for inclusion in the public standard. Manufacturers are not precluded from having internal limits for these impurities.
Comment Summary #2: The commenter recommended retaining the use of low-actinic glassware for the preparation and storage of solutions for the *Assay* and *Organic Impurities* procedures.
Response: Comment not incorporated. The statement added to "Protect solutions containing tacrolimus from light" provides flexibility and does not preclude the use of low-actinic glassware.
Comment Summary #3: The commenter recommended removing Tacrolimus 8-propyl analog from USP Tacrolimus System Suitability Mixture RS because the peak can be identified from the *Peak identification solution 2* in the test for *Organic impurities, Procedure 2.*
Response: Comment not incorporated. USP Tacrolimus System Suitability Mixture RS is not manufactured by mixing the individual components. It is not possible to remove specific compounds from the mixture.
Comment Summary #4: The commenter indicated that changing the diluent in the *Assay* and *Organic impurities, Procedure 2 to* acetonitrile decreases sensitivity and does not improve the procedures. They requested to keep the existing *Diluent* and solution equilibration time.
Response: Comment incorporated. The revisions proposed under *Assay* and *Organic impurities, Procedure 2* to replace the *Diluent* with acetonitrile *and to delete the* solution equilibration time are cancelled. Manufactures are not precluded from using alternative procedures and should refer to *General Notices 6.30. Alternative and Harmonized Methods and Procedures.*
Comment Summary #5: The commenter requested adding the note "if present" in the impurities table for Ascomycin 19-epimer and Desmethyl tacrolimus in *Organic impurities, Procedure 2.*
Response: Comment incorporated.

Monograph/Section(s): Tacrolimus Capsules/Dissolution
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 1
Comment Summary #1: The commenter requested including FDA approved parameters and tolerances as *Dissolution Test 5*.
Response: Comment incorporated

Monograph/Section(s): Tacrolimus Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 50 mg of tacrolimus is used (e.g. Tacrolimus capsules equivalent to 50 mg of tacrolimus).
Response: Comment incorporated.
Comment Summary #2: The commenter noted that the manufacturer information given for the starting tacrolimus ingredient needs to be updated. The commenter suggested clarifying whether a different manufactured capsule may be substituted since the monograph contains a note that tacrolimus powder is not interchangeable.
Response: Comment not incorporated. The statement indicating that tacrolimus powder is not to be used is based on concerns of particle size. The stability study was conducted on the specific type of capsules specified in the monograph, which was the only product available at the time. Any changes to the starting material may not support the beyond-use date established in the monograph.

Monograph/Section(s): Temozolomide Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to clarify that 1 g of temozolomide is used (e.g. Temozolomide capsules equivalent to 1 g of temozolomide).
Response: Comment incorporated.

Monograph/Section(s): Terbinafine Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the *Definition* reflect the amount of terbinafine hydrochloride equivalent to terbinafine.
Response: Comment not incorporated. The preparation is dosed based on the terbinafine content and should be labeled in terms of terbinafine.

Monograph/Section(s): Terbutaline Sulfate Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested adding a note in the *Definition* to not use the preparation if it is discolored.
Response: Comment not incorporated. The note is present in the Terbinafine Sulfate Injection monograph; however, the same discoloration is not known to occur in the compounded preparation.

Monograph/Section(s): Tetracycline Hydrochloride Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested adding the molecular formula for tetracycline in the *Definition* section of the monograph.
Response: Comment incorporated

Monograph/Section(s): Tiagabine Hydrochloride Compounded Oral Suspension/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that storage condition of 2º - 8º should be revised to indicate storage in a refrigerator for consistency.
Response: Comment incorporated.

Monograph/Section(s): Tramadol Hydrochloride and Acetaminophen Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 750 mg of tramadol hydrochloride and 6500 mg of acetaminophen are used (e.g. Tramadol Hydrochloride and Acetaminophen tablets equivalent to 750 mg of tramadol hydrochloride and 6500 mg of acetaminophen).
Response: Comment incorporated.

Monograph/Section(s): Tramadol Hydrochloride Compounded Oral Suspension/Definition
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 500 mg of tramadol hydrochloride is used (e.g. Tramadol Hydrochloride tablets equivalent to 500 mg of tramadol hydrochloride).
Response: Comment incorporated.

Monograph/Section(s): Trihexyphenidyl Hydrochloride Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated Change #1: The amount of trihexyphenidyl hydrochloride and the size of the volumetric flask used in the *Sample solution* were updated for consistency with the sponsor's submission.

Monograph/Section(s): Ursodiol Compounded Oral Suspension/Definition

Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 5 g of ursodiol is used (e.g. Ursodiol tablets equivalent to 5 g of ursodiol).
Response: Comments incorporated.

Monograph/Section(s): Valacyclovir Compounded Oral Suspension/Multiple Sections
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested revising the formula to make it clear that 5g of valacyclovir is used (e.g. Valacyclovir tablets equivalent to 5 g of valacyclovir).
Response: Comment incorporated.
Comment Summary #2: The commenter noted a correction to the molecular formula of valacyclovir in the *Assay* section of the monograph.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested revising the compounding procedures to reflect the directions in the FDA-approved labeling.
Response: Comments not incorporated. The labeling instructions for preparation may be specific to one commercial product that may not apply to other products. Furthermore, the monograph preparation is supported by a stability study to establish a *Beyond-Use Date*.

Monograph/Section(s): Verapamil Hydrochloride Compounded Oral Solution/Storage
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter suggested that the storage condition of a cold place be revised to indicate storage in a refrigerator to prevent storage in freezer conditions.
Response: Comment incorporated.

Monograph/Section(s): Verapamil Hydrochloride Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1
Comment Summary #1: The commenter noted that there were two compounded preparation monographs for a verapamil hydrochloride oral dosage form and suggested eliminating the monograph for Verapamil Hydrochloride Oral Suspension. The commenter indicated that suspendability and bioavailability may be an issue with the oral suspension formulation.
Response: Comment not incorporated. The monograph for Verapamil Hydrochloride Oral Suspension allows the use of tablets in addition to the bulk ingredient. Limiting the formulation only to oral solution limits the starting material to the bulk ingredient which may not always be available.

Monograph/Section(s): Zolmitriptan Orally Disintegrating Tablets/Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter requested the inclusion of a special holder in the *Disintegration* test.
Response: Comment not incorporated. The Expert Committee determined that a reference to a special holder is not needed within the public standard.
Comment Summary #2: The commenter requested to add an analytical procedure based on UV to the *Dissolution* test.
Response: Comment incorporated.
Comment Summary #3: The commenter requested the widening of the limit of zolmitriptan related compound E from 0.5% to NMT 0.6% to be consistent with FDA approved specifications.
Response: Comment incorporated.