



Commentary

USP 42–NF 37, First Supplement

February 1, 2019

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 re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status without re-publication in *PF*, a summary of comments received and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of USP.org 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 Product–Product Quality Tests](#)

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[<701> Disintegration](#)

[<729> Globule Size Distribution in Lipid Injectable Emulsions](#)

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Monographs

[Acetazolamide](#)

[Amantadine Hydrochloride](#)

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[Azelastine Hydrochloride Ophthalmic Solution](#)

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[Clindamycin Hydrochloride Compounded Oral Solution](#)

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[Cyclophosphamide for Injection](#)

[Desvenlafaxine](#)

[Desvenlafaxine Fumarate](#)

[Desvenlafaxine Succinate](#)

[Dexamethasone](#)

[Dextrose](#)

[Diclofenac Sodium Topical Solution](#)

[Ephedrine Hydrochloride Ergocalciferol Capsules](#)

[Estriol Compounded Vaginal Cream](#)

[Ethambutol Hydrochloride](#)

[Famciclovir Tablets](#)

[Fluvoxamine Maleate Tablets](#)

[Hydromorphone Hydrochloride](#)

[Itraconazole Capsules](#)

[Leucovorin Calcium](#)

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[Lovastatin Tablets](#)

[Maleic Acid](#)

[Naltrexone Hydrochloride](#)

[Naproxen Compounded Oral Suspension](#)

[Olanzapine and Fluoxetine Capsules](#)

[Oxycodone Hydrochloride](#)

[Paroxetine Hydrochloride](#)

[Pyridostigmine Bromide](#)

[Spironolactone](#)

[Star Anise Oil](#)

[Succinylcholine Chloride](#)
[Sulfamethoxazole](#)
[Tiagabine Hydrochloride](#)
[Tranexamic Acid Tablets](#)
[Vitamin A Capsules](#)
[Vitamin A Oral Liquid Preparation](#)
[Vitamin A Tablets](#)
[Vitamin E Capsules](#)
[Xylometazoline Hydrochloride](#)
[Xylometazoline Hydrochloride Nasal Solution](#)
[Zolmitriptan](#)

No comments were received for the following proposals:

General Chapters

<644> Conductivity of Solutions

Monographs

Amcinonide
Amiloride Hydrochloride and Hydrochlorothiazide Tablets
Aminobenzoate Potassium for Oral Solution
Aminoglutethimide
Aminoglutethimide Tablets
Aminosalicylate Sodium
Aminosalicylate Sodium Tablets
Aminosalicylic Acid Tablets
Astaxanthin Esters
Azithromycin for Injection
Cefazolin Ophthalmic Solution
Chlorhexidine Gluconate Topical Gel
Cocaine and Tetracaine Hydrochlorides and Epinephrine Topical Solution
Corticotropin for Injection
Corticotropin Injection

Fluvastatin Tablets
Gingko Capsules
Gingko Tablets
Glycopyrrolate Tablets
Inamrinone Injection
Lamotrigine Tablets for Oral Suspension
Loracarbef Capsules
Loracarbef for Oral Suspension
Manganese Sulfate Injection
Mephenytoin
Mephenytoin Tablets
Meprednisone
Meprobamate Oral Suspension
Mesoridazine Besylate
Mesoridazine Besylate Injection
Mesoridazine Besylate Oral Solution

Mesoridazine Besylate Tablets
Methacycline Hydrochloride Capsules
Methanamine Mandelate Delayed-Release Tablets
Methanamine Mandelate Oral Solution
Methanamine Mandelate Suspension
Methdilazine Hydrochloride
Methdilazine Hydrochloride Oral Solution
Methdilazine Hydrochloride Tablets
Methenamine Oral Solution
Methotrexate for Injection
Methyldopa and Chlorothiazide Tablets
Methyldopa Oral Suspension
Methylene Blue Injection, Veterinary
Methylprednisolone Acetate Cream
Methylsergide Maleate Tablets
Metyrapone Tablets
Mezlocillin for Injection
Mezlocillin Sodium
Miconazole Injection
Morcizine Hydrochloride Tablets
Morrhuate Sodium Injection
Nafcillin Sodium Capsules
Nafcillin Sodium for Oral Solution
Nafcillin Sodium Tablets
Naldixic Acid
Naldixic Acid Oral Suspension
Naldixic Acid Tablets
Naltrexone Hydrochloride Tablets
Netilmicin Sulfate
Netilmicin Sulfate Injection
Norfloxacin
Norfloxacin Ophthalmic Solution
Norfloxacin Tablets
Octylamine
Omeprazole Oral Suspension
Oxacillin Sodium Capsules
Oxacillin Sodium for Oral Solution
Oxaliplatin Injection
Oxazepam Tablets
Pantaprazole Oral Suspension
Phenylephrine Hydrochloride Injection
Phenylephrine Hydrochloride Nasal Solution
Phenylephrine Hydrochloride Ophthalmic Solution
Phytonadione Compounded Oral Suspension
Probucol
Probucol Tablets
Prochlorperazine Maleate Tablets
Repository Corticotropin Injection
Selemectin
Sisomicin Sulfate
Sisomicin Sulfate Injection

Stavudine for Oral Solution
Triamterene and Hydrochlorothiazide Capsules
Tryptamine Hydrochloride
Vitamin A
Vitamin E
Vitamin E Preparation

General Chapters

General Chapter/Section(s): <2> Oral Drug Products—Product Quality Tests / Multiple Sections
Expert Committee (EC[s]): General Chapters—Dosage Forms
No. of Commenters: 1

INTRODUCTION / Drug Product Quality Tests and Performance Tests

Comment Summary #1: The commenter suggested retaining the list of drug product quality tests to assess attributes, but deleting the parentheticals “(universal tests)” and “(specific tests),” because the first sentence in the next section titled “Product Quality Tests for Oral Drug Products” introduces the concept of universal tests and specific tests, and the following information clearly describes which tests fall into each category.

Response: Comment incorporated.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Universal Tests for Oral Drug Products

Comment Summary #2: The commenter recommended including “microbiological examination” in the list of tests that should be applied to all oral dosage forms, because it is commonly included in the specifications of orally administered products.

Response: Comment not incorporated. USP is aligned with International Conference on Harmonisation (ICH) Q6A *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*, which does not include microbiological testing as a universal test.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Tablets / DISINTEGRATION

Expert Committee-Initiated Change #1: In the first sentence “Disintegration is an essential attribute of oral solids, except for those intended to be chewed before being swallowed and for delayed- or extended-release products”, the words “to be chewed before being swallowed and” were removed to align the chapter with the proposed General Chapter <1711> *Oral Solid Dosage Forms—Dissolution Testing* published in *PF 44(5)* [Sep.–Oct. 2018] and the U.S. Food and Drug Administration (FDA) Guidance titled, “Quality Attribute Considerations for Chewable Tablets-Guidance for Industry,” published in August 2018.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Uncoated Tablets

Comment Summary #3: The commenter recommended deleting the reference to “disintegrating tablets” in the sentence listing uncoated tablets, because it is not a recognized USP dosage form.

Response: Comment incorporated.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Uncoated Tablets / CHEWABLE TABLETS

Expert Committee-Initiated Change #2: The text “Chewable tablets are not required to comply with the disintegration test. Chewable tablets (intact) should undergo dissolution testing, as a product performance test (if cited in the monograph), because they might be swallowed without proper chewing by a patient. In general, the dissolution test conditions for chewable tablets should be the same as for nonchewable tablets of the same active ingredient or moiety” was changed to “Chewable tablets (intact) should undergo dissolution and disintegration testing, as a product performance test (if cited in the monograph), because the tablets might be swallowed without proper chewing by a patient. In general, the dissolution and disintegration test conditions for chewable tablets should be the same as for nonchewable tablets of the same active ingredient or moiety” to align the chapter with the proposed General Chapter <1711> *Oral Solid Dosage Forms—Dissolution Testing* published in *PF 44(5)* and the FDA Guidance titled, “Quality Attribute Considerations for Chewable Tablets-Guidance for Industry,” published in August 2018.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Capsules

Comment Summary #4: The commenter suggested not deleting the last sentence of the section, “Modified-release capsules include but are not limited to: delayed-release capsules and extended-release capsules”, because it is not clear the reason for the removal and it adds valuable information.

Response: Comment partially incorporated. The sentence was edited to be aligned with General Chapter <1151> and moved to the previous paragraph for a better flow of the information.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Capsules / UNIFORMITY OF DOSAGE UNITS

Expert Committee-Initiated Change #3: A new section titled, “UNIFORMITY OF DOSAGE UNITS,” (same as *per Specific Tests for Tablets*) was introduced for completeness and consistency.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Capsules / Disintegration

Comment Summary #5: The commenter recommended revising the first sentence of the section, “for capsules, proceed as directed in *Disintegration* <701> *Soft Gelatin Capsules*”, to read “for capsules, proceed as directed in <701> if a disintegration test is required” to clarify that a disintegration test is not required if a dissolution test is included in the drug product specification.

Response: Comment incorporated.

Comment Summary #6: The commenter recommended retaining the original sentence, “There are no additional specific quality tests for extended-release capsules and delayed-release capsules”, because it is not clear why the extended release capsules are deleted.

Response: Comment partially incorporated. The sentence was changed to read “There are no additional specific quality tests for modified-release capsules” to align with General Chapter <1151>.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Granules

Comment Summary #7: The commenter suggested revising the final sentence from “On the basis of the nature of the article and scientific criteria, additional tests may apply, including powder fineness and others” to “On the basis of the nature of the article and scientific criteria, additional tests may apply, including powder fineness and content uniformity per USP <905> if granules are packaged in single unit containers”, because granules are commonly packaged in single unit containers.

Response: Comment incorporated.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Powders

Comment Summary #8: The commenter requested the removal of the sentence “Oral powders should indicate: ‘For Oral Use Only.’” because USP is trying to have all labeling requirements currently in USP General Notices and General Chapters relocated to General Chapter <7> *Labeling*. This sentence describes a labeling requirement and as such it should appear in <7>.

Response: Comment not incorporated. There are official monographs using this statement. In the future, all the labeling requirements under <7> could cover these cases, but in the meantime, the Chapter will retain this sentence.

Comment Summary #9: The commenter recommended revising the second sentence, “Tests that are considered specific to the type of powders include: Minimum Fill (755) and volatile content (see (731) and (921))”, to read “Tests that are considered specific to the type of powders include: Minimum Fill (755) for products packaged in multiple-dose containers; Content Uniformity <905> for products packaged in single-unit containers; and volatile content (see (731) and (921))” because powders are often packaged in single dose containers.

Response: Comment incorporated.

PRODUCT QUALITY TESTS FOR ORAL DRUG PRODUCTS / Specific Tests for Liquids

Comment Summary #10: The commenter recommended adding tests for preservative content and antimicrobial effectiveness. Preservatives are often included in oral liquids, and General Chapter <51> *Antimicrobial Effectiveness Testing* requires testing for antimicrobial effectiveness if preservatives are included in oral liquids.

Response: Comment partially incorporated. “Preservative content” was added. “Antimicrobial effectiveness” is performed during development. Once it has been established, only “preservative content” is performed for release.

General Chapter/Section(s): <41> Balances /Repeatability
Expert Committee(s): General Chapters–Chemical Analysis
No. of Commenters: 3

Comment Summary #1: The commenter recommended not progressing with the addition of a footnote to the *REPEATABILITY* section. The footnote is out of context in <41> and would be more appropriate in General Chapter <1251> *Weighing on an Analytical Balance*.

Response: Comment not incorporated. The EC finds the information in the footnote to add value to the content of <41>.

Comment Summary #2: The commenter suggested that the footnote added to the *REPEATABILITY* section of the chapter incorrectly presents the minimum weight calculation as an equation whereas the relationship is an inequality.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested that the content of the footnote could be included in the main text of the *REPEATABILITY* section.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested deleting the last sentence of the last paragraph of the *REPEATABILITY* section because it is redundant.

Response: Comment incorporated.

General Chapter/Section(s): <64> Probiotic Tests / Multiple Sections
Expert Committee: General Chapters–Dietary Supplements
No. of Commenters: 4

General

Comment Summary #1: The commenter suggested referring to General Chapter <1113> *Microbial Characterization, Identification, and Strain Typing*. In general, techniques such as 16S rRNA base sequencing are excellent for identification of bacterial species but not the separation of species to strains. Strain typing may be achieved with pulsed field gel electrophoresis, restrictive fragment length polymorphism, or multi locus analysis.

Response: Comment not incorporated. While polymerase chain reaction (PCR) may not be applicable in all cases, it has been validated for numerous strains. Monograph sponsors are free to submit other validated methods for strain identification. Future revisions to this chapter will be considered upon the receipt of the necessary supporting data for other methods.

Comment Summary #2: The commenter suggested that despite differences of opinion in the technical literature on the predictiveness of in vitro functional tests for efficacy of probiotics, there is strong evidence that probiotic strains that score well on these tests will persist in the human lower intestine. Contrary to the positions taken by some members of the Probiotics Expert Panel, the inclusion of these tests in General Chapter <64> will be helpful in strain selection during development and will not mean that the tests will be routinely included in individual probiotic monographs.

Response: Comment not incorporated. Functional tests are not required in the probiotic specifications by current good manufacturing practice (cGMP) and thus are not part of the monograph requirements. Functional tests may be included in the manufacturer's generally recognized as safe (GRAS) dossier for probiotics, which – where available – is evaluated by the USP Dietary Supplements Admission Evaluation Joint Standards-Setting Subcommittee.

INTRODUCTION

Comment Summary #3: The commenter asked whether the bacterial survival rate is systematically evaluated before use of the dried biomass.

Response: Comment not incorporated. Tests to determine the number of living bacteria are described in the *ENUMERATION FOR NON-SPORE-FORMING BACTERIA STRAINS* subsection.

IDENTIFICATION

Comment Summary #4. The commenter highlighted that PCR is currently tied to a specific technology and are not widely used globally. Additionally, consumer sector microbiology laboratories are not equipped to run this specific technology. A suggestion would be to have a provision of using alternate methods for more flexibility.

Response: Comment not incorporated. As cited in *General Notices 6.30. Alternative and Harmonized Methods and Procedures*, any validated method that has been shown to be equivalent to the monograph method may be used.

Comment Summary #5: The commenter asked why temperature units are not mentioned throughout the chapter.

Response: Comment not incorporated. Per *General Notices 8.180. Temperatures*, temperatures are expressed in centigrade unless otherwise indicated.

EC Initiated Change #1: In order to provide other options for DNA polymerases, 5PRIME HotMasterMix DNA Polymerase (Quantabio VWR catalog #:10847-804) has also been included in the chapter as a high fidelity source.

ENUMERATION

Comment Summary #6: The commenter indicated that the storage temperature of broth and agar at 4°C is too specific. If refrigeration is needed, the storage range would be between 2°C

and 8°C. Suggest using language similar to General Chapter <71> *Sterility Tests*: “Store at a temperature between 2°C and 8°C in a sterile well-closed container unless it is intended for immediate use. Do not use the medium for a longer storage period than has been validated.”

Response: Comment incorporated.

Comment Summary #7: The commenter indicated that the tempering temperature is too specific. Suggest using language similar to General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*: “Not more than 45°C.”

Response: Comment incorporated.

Comment Summary #8: The commenter indicated that the incubation time is too specific. Unless there is a specific requirement to use 72 hours, suggest the following range: *3-5 Days in anaerobic conditions supplemented with 5% CO₂*.

Response: Comment partially incorporated; does not include the requirement of supplementation with 5% CO₂.

Comment Summary #9: The commenter indicated that reagents are tied to specific companies (*Table 1* and *Table 2*). As a rule, USP chapters do not endorse or require using specific companies. Suggestion is to reword to make this section more general for application in testing labs globally for ease of execution.

Response: Comment not incorporated. Commercial sources are also provided in other USP general chapters and monographs to facilitate the acquisition of materials and reagents to users.

EC Initiated Change #2: In the *Lactobacilli MRS* agar preparation procedure, the word “broth” was replaced with “agar media”.

CONTAMINANTS

Comment Summary #10: The commenter indicated that although it is more appropriate to cite General Chapters <2021> *Microbial Enumeration Tests—Nutritional and Dietary Supplements* and <2022> *Microbiological Procedures for Absence of Specified Microorganisms—Nutritional and Dietary Supplements* than General Chapters <61> and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*, the tests may be unsuitable for some less fastidious probiotic species that may grow on standard microbiological culture media without the inclusion of antibiotic like vancomycin to suppress the probiotic.

Response: Comment not incorporated. The tests proposed in <2021> and <2022> are considered suitable in cGMP for controlling contaminants in probiotics. However, future revisions to this chapter will be considered upon the receipt of the necessary supporting data for other methods.

Comment Summary #11: The commenter highlighted that *Pseudomonas aeruginosa* is not considered a foodborne pathogen and should not be listed for risk assessment.

Response: Comment not incorporated. It is still important to include *Pseudomonas aeruginosa* in the list of contaminants for probiotics.

Comment Summary #12: The commenter suggested that the statements on risk assessment programs such as hazard analysis and critical control points (HACCP) seem to belong more in an informational chapter rather than a general chapter as they are broad and do not provide specific direction.

Response: Comment not incorporated. It was considered important to leave this statement in the chapter.

Comment Summary #13: The commenter asked what method/differentiative media is recommended to be used for *Listeria monocytogenes* and *Cronobacter sakazakii*.

Response: Comment not incorporated. There are official methods available for *Listeria monocytogenes* and *Cronobacter sakazakii*, and it is under the criteria of the user to determine the appropriate method/media.

Comment Summary #14: The commenter recommended adding a section detailing method suitability.

Response: Comment not incorporated. Future revisions to this chapter will be considered upon the receipt of the necessary supporting data for other methods.

Comment Summary #15: The commenter indicated that in *Table 3*, the test objects should not be determined according to the “Product Strain.”

Response: Comment incorporated. The title in first column was changed from “Probiotic Strain” to “Probiotic Classification.”

Comment Summary #16: The commenter highlighted that in *Table 3*, for probiotic strain belonging to spore-forming bacteria, total yeasts and molds count (TYMC) is needed, but the test listed in the second line seems to be wrong or duplicated

Response: Comment incorporated. The duplicate line for *Total yeasts and molds* belonged to *Non-spore-forming bacteria* and was moved to this classification.

Comment Summary #17: The commenter asked if probiotics belonging to “yeasts and molds” will be adopted in USP monographs in the future.

Response: Comment not incorporated. The panel cannot predict the development of future probiotics monographs belonging to yeast and molds at this moment.

Comment Summary #18: The commenter provided the following insight about contaminants in probiotics. For the test methods listed in <2021>and <2022>, a considerable portion of the medium systems is the same as <61> and <62>. However, the most significant difference between probiotics and other drugs is that the former contains a large number of live bacteria. Therefore, ordinary mediums (such as Soybean-Casein Digest Agar, Fluid Soybean-Casein Digest Medium, and Nutrient Agar) often do not inhibit the growth of probiotics strains well. When evaluating the results of *Total aerobic microbial count (TAMC)/TYMC/Non-lactic acid bacteria* (“Non-pathogenic Microbes / Fungi Count” in the *Chinese Pharmacopoeia [ChP]*), sometimes it may be very difficult to verify the recovery rate for the methods. The growth of a large number of probiotics does inhibit the recovery of a small amount of contaminating bacteria, and the method used to eliminate the interference of probiotics will also eliminate these contaminating bacteria, which is the biggest contradiction.

Response: Comment not incorporated. The tests proposed in <2021> and <2022> are considered suitable in cGMP for controlling contaminants in probiotics. Other methods may be considered in future revisions of this chapter.

General Chapter/Section(s): <701> Disintegration

Expert Committee(s): General Chapters–Dosage Forms

No. of Commenters: 2

Comment Summary #1: The commenter requested that the *PROCEDURE FOR DELAYED-RELEASE TABLETS AND CAPSULES* retain the use of simulated gastric fluid and simulated intestinal fluid along with the proposed 0.1M hydrochloric acid and pH 6.8 phosphate buffer to allow continuity for laboratories who have been using these media proposed for deletion.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested that providing a separate, unique procedure for sublingual tablets and buccal tablets will allow flexibility in recognition that disintegration of these products may be too rapid for testing according to the *PROCEDURE FOR UNCOATED AND PLAIN-COATED TABLETS*.

Response: Comment not incorporated. Accommodation of special testing requirements such as for the time limit and testing conditions is provided within the individual drug product monograph.

Comment Summary #3: The commenter requested that the *Procedure and Criteria for Effervescent Tablets for Oral Solution* and the *Procedure and Criteria for Effervescent Granules* indicate that alternative information may be presented in the individual drug product monograph.

Response: Comment incorporated.

General Chapter/Sections: <729> Globule Size Distribution In Lipid Injectable Emulsions

Expert Committee(s): General Chapters–Dosage Forms

No. of Commenters: 1

METHOD I—LIGHT-SCATTERING METHOD

Comment Summary #1: The commenter suggested changing the header to align in structure with Method II.

Response: Comment incorporated.

METHOD II—MEASUREMENT OF LARGE GLOBULE CONTENT BY LIGHT OBSCURATION OR EXTINCTION METHOD

Comment Summary #2: The commenter recommended adding language that would allow degassing or sonicating the water sample, similar to Method I.

Response: Comment incorporated.

General Chapter/Section(s): <1057> Biotechnology-Derived Articles—Total Protein Assay

Expert Committee: General Chapters–Biological Analysis Expert Committee

No. of Commenters: 3

Comment Summary # 1: The commenter recommended adding for each method a list of known interfering substances and their interfering threshold to aid in method selection.

Response: Comment not incorporated. It is difficult to anticipate all potential interfering substances, and non-interference should be confirmed during the verification study.

Comment Summary # 2: The commenter recommended adding a method comparison table to aid in the selection of the most suitable methods.

Response: Comment not incorporated. The selection of the method by any user is impacted by a number of user defined factors including complexity of sample, accuracy required, etc. A comparative table would be difficult to create to cover the many factors that may affect the method choice.

Comment Summary # 3: The commenter recommended replacing in the *INTRODUCTION* the phrase “accuracy/variability” with “accuracy and precision”.

Response: Comment incorporated.

Comment Summary # 4: The commenter recommended clarifying how certain factors such as analyst contact, sample availability, and analysis time can negatively impact the quality of test results when a robust test method is established.

Response: Comment not incorporated. The Expert Committee noted that the laboratories should be evaluating these parameters during method validation.

Comment Summary # 5: The commenter recommended clarifying the definition of a complex sample.

Response: Comment not incorporated. The definition of a complex sample varies widely and users are free to define in their own way and use the best practices recommended in <1057> to build a suitable method.

Comment Summary # 6: The commenter recommended adding a reference to chapters on amino acid analysis because these methods can be used for total protein measurements.

Response: Comment not incorporated. The EC determined that the reference was not needed since USP’s two chapters containing amino acid analysis guidance for protein measurements are easy to find by their titles: General Chapters <1052> *Biotechnology-Derived Articles—Amino Acid Analysis* and <507> *Protein Determination Procedures*.

Comment Summary # 7: The commenter recommended adding “if relevant” to the requirement to perform the extraction procedure on blank samples.

Response: Comment not incorporated. The extraction of a blank sample should always be performed unless it is verified and justified that the extraction procedure does not have any impact on the data.

Comment Summary # 8: The commenter recommended revising the suggested protein concentration range and adding more information about the spectrophotometer’s dynamic range.

Response: Comment not incorporated. The range is defined by the instrument specifications and can vary with the instrument used and the impact of the particular blank for that sample, which may consume a large portion of the dynamic range.

Comment Summary # 9: The commenter recommended providing more information about the choice of reference material used in the bicinchoninic acid (BCA) assay *Method 4* section.

Response: Comment not incorporated. The text is clear as written.

Comment Summary # 10: The commenter recommended adding a gravimetric method as a suitable approach to ensure accuracy for high concentration protein preparations.

Response: Comment not incorporated. <1057> is an informational chapter, and specifying which methods to be used is not necessary. Methods and their alternatives can be assessed and justified by individual users.

General Chapter/Section(s): <1151> Pharmaceutical Dosage Forms / Multiple Sections

Expert Committee(s): General Chapters–Dosage Forms

No. of Commenters: 1

General Considerations:

Comment Summary #1: The commenter suggested that sentence one of paragraph two should be reworded, by replacing the words “drug product” with “medicine,” to indicate that placebos as well as drug products are administered using dosage forms.

Response: Comment incorporated. The EC added placebo as a class of materials administered in dosage forms.

Comment Summary #2: The commenter suggested clarifying sentences six and seven of paragraph two to make clear that the new list of official dosage forms comprises terms used in official article titles, while the *GLOSSARY* includes other terms in addition to these preferred terms.

Response: Comment incorporated.

Comment Summary #3: The commenter requested not including General Chapter <771> *Ophthalmic Products—Quality Tests* in the *Route of Administration* subsection because ophthalmic products are included among mucosal products as evidenced by text in General Chapter <4> *Mucosal Drug Products—Product Quality Tests*.

Response: Comment incorporated.

Dosage Forms

Comment Summary #4: The commenter requested retention under *Foams* of two sentences marked for deletion. The sentences are: “Foams are primarily intended for application to the skin or mucous membranes. Foams can be formulated to quickly break down into liquid or to remain as foam to ensure prolonged contact.”

Response: Comment not incorporated. The EC finds that information should not be included in <1151> if it can be found in other general chapters. After the proposed General Chapter <607> *Pharmaceutical Foams* becomes official, reference to it will be made in <1151>.

Comment Summary #5: The commenter requested clarification under *Gels* that the list of possible components expressly includes dietary supplements or drug substances.

Response: Comment incorporated.

Comment Summary #6: The commenter requested moving paragraph two under *Implants* to reside under *Suspensions*. This paragraph describes a product that is injected and thus would be referred to as an injectable suspension.

Response: Comment incorporated.

Comment Summary #7: The commenter requested deletion of paragraph five under *Implants* because it is redundant, having been addressed in paragraph one.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested that for clarity, under *Pellets*, paragraph two could present the therapeutic functions of oral pellets as a list.

Response: Comment incorporated.

Glossary

Comment Summary #9: The commenter suggested replacing the word “canister” with “container” in recognition that non-pressurized foams do not need to be stored in a canister.

Response: Comment incorporated.

Comment Summary #10: The commenter requested reordering the “Injectable suspension, extended-release” entry to “Extended-release injectable suspension” to clarify the appropriate form for titling such an article, i.e., [DRUG] Extended-release injectable suspension.

Response: Comment incorporated.

Comment Summary #11: The commenter suggested an alternative definition for “Liposomes.”

Response: Comment not incorporated. Revising the GLOSSARY definition of “Liposomes” will be considered for future revision.

Comment Summary #12: The commenter requested several changes to the entry for “Pellets,” addressing aspects of pellets used in veterinary medicine.

Response: Comment incorporated.

Monographs

Monograph/Section: Acetazolamide / Organic Impurities

Expert Committee: Chemical Medicines Monographs 3

No. of Commenters: 1

Comment Summary #1: The commenter requested clarification for not including a specified impurity, 5-Amino-1,3,4- thiadiazole-2-thiol, with the impurities listed in *Table 1*.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting documents.

Monograph/Section(s): Amantadine Hydrochloride / Multiple sections

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 2

Comment Summary #1: The commenter commented that adamantane is listed as a potential impurity in the manufacturer’s technical package and is not valid to use it as an internal standard in the *ASSAY* and the test for *ORGANIC IMPURITIES*.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section(s): Amantadine Hydrochloride Capsules / Multiple Sections

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 2

Comment summary #1: The commenter suggested revising pore size of the filter used in the Sample stock solution preparation in the ASSAY from 0.45 µm to 0.7 µm, to allow for filtration without excessive backpressure.

Response: Comment incorporated. The pore size of the filter is removed to provide flexibility.

Comment Summary #2: The commenter commented that adamantane is listed as a potential impurity in the manufacturer's technical package and is not valid to use it as an internal standard in the test for *ORGANIC IMPURITIES*.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #3: The commenter recommended reducing the injection volume from 2 µL to 1.5 µL in the test for *ORGANIC IMPURITIES* to diminish the risk of backflash in the gas chromatography (GC) injection port.

Response: Comment not incorporated. The EC determined that a change to injection volume is allowed by the General Chapter <621> *Chromatography*.

Monograph/Section(s): Amantadine Hydrochloride Oral Solution / Organic impurities

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 1

Comment Summary #1: The commenter commented that the *Acceptance criteria* for any individual unspecified impurity is different from what has been approved by the FDA.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #1: The commenter recommended revising the term "Any individual unspecified impurity" with "Any unspecified degradation product" to be consistent with ICH Q3B, *Impurities in New Drug Products*, terminology.

Response: Comment not incorporated. The EC determined that the terminology is consistent with other amantadine family of monographs.

Monograph/Section: Amcinonide Ointment / Identification

Expert Committee: Chemical Medicines Monographs 5

No. of Commenters: 1

Comment Summary #1: The commenter recommended adding a second orthogonal identification test.

Response: Comment not incorporated. The EC will consider a future revision upon receipt of the supporting data.

Monograph/Sections: Azelastine Hydrochloride Ophthalmic Solution / Organic Impurities

Expert Committee: Chemical Medicines Monographs 5

No. of Commenters: 2

Comment Summary #1: The commenter requested revising the acceptance criterion of the total degradation products from not more than (NMT) 1.4% to NMT 1.5% to be consistent with the approved specification.

Response: Comment incorporated.

Comment Summary #2: The commenter requested revising the acceptance criterion of OSMOLALITY AND OSMOLARITY from 271-312 mOsmol/kg to 265-375 mOsmol/kg to be consistent with the approved specification.

Response: Comment incorporated.

Monograph/Sections: Benazepril Hydrochloride Tablets / USP Reference Standards <11>

Expert Committee: Chemical Medicines Monographs 2

Expert Committee-initiated Change #1: The EC decided to retain the chemical information for USP Benazepril Related Compound B in *USP REFERENCE STANDARDS <11>* section to be consistent with the chemical name on the current USP reference standard label.

Expert Committee-initiated Change #2: The EC included the chemical name for USP Benazepril Related Compound C, (3S)-3-[[[(1S)-1-Carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine]-1-acetic acid, in *USP REFERENCE STANDARDS <11>* section to be consistent with the chemical name on the current reference standard label.

Monograph/Sections: Benzphetamine Hydrochloride / Multiple Sections

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 2

Comment Summary #1: The commenter indicated that the run times for *ASSAY* and *ORGANIC IMPURITIES* are too long and recommended developing more efficient methods.

Response: Comment not incorporated. The EC determined the proposed methods are suitable for intended use.

Comment Summary #2: The commenter indicated that benzphetamine related compound E and benzphetamine related compound F appear to be process specific and may not be likely impurities in other processes.

Response: Comment not incorporated. The proposed specifications for benzphetamine related compound E and benzphetamine related compound F are consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon receipt of necessary supporting data.

Comment Summary #3*: The commenter indicated that the *Acceptance criteria* for *ASSAY*, total impurities, any other individual impurity, and methamphetamine hydrochloride are not consistent with the FDA-approved limits.

Response: Comment not incorporated. The *Acceptance criteria* are consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon receipt of necessary supporting data.

Expert Committee-Initiated Change #1: The Expert Committee revised the preparation of *System suitability solution* in *ORGANIC IMPURITIES* to clarify that the "USP Benzphetamine Hydrochloride RS" is used instead of "Benzphetamine Hydrochloride."

Monograph/Sections: Benzphetamine Hydrochloride Tablets / Organic Impurities

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the *Acceptance criteria* for benzphetamine related compound E and any unspecified impurity are not consistent with the FDA-approved limits.

Response: Comment not incorporated. The *Acceptance criteria* are consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon receipt of necessary supporting data.

Comment Summary #2: The commenter recommended adding a footnote to indicate that the methamphetamine hydrochloride impurity needs to be controlled only if present.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of necessary supporting data.

Monograph/Section(s): Cholecalciferol Capsules / Labeling
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2

Comment Summary #1: The commenter recommended that the monograph provides the option for strength to be expressed in terms of International Units, in parentheses, after the declaration of the amount of cholecalciferol in mcg.

Response: Comment incorporated.

Comment Summary #2: The commenter proposed introducing a footnote with the relationship of the USP Units or International Units to mass when labeling provides the option to label dose in terms of units in addition to the required labeling in mass.

Response: Comment incorporated.

Monograph/Section(s): Clindamycin Hydrochloride Compounded Oral Solution
Expert Committee(s): Compounding
No. of Commenters: 1

Comment Summary #1: The commenter noted that the compounded preparation monograph might encourage compounding of the drug when an FDA-approved product may meet patients' medical needs.

Response: Comment not incorporated. The EC does not encourage compounding where there is a suitable commercially available product. However, as the commenter mentioned, there may be situations where there is a specific medical need or a drug shortage, and the preparation may need to be compounded.

Comment Summary #2: The commenter noted that the labeling section states: "Label it to indicate that it is to be well-shaken before use..." The commenter suggested deleting this section because the formulation is a solution that does not need to be shaken.

Response: Comment not incorporated. The formulation does need to be shaken before use because it is compounded in a thixotropic vehicle that settles into gel on standing and needs to be shaken before administration.

Monograph/Section(s): Cyanocobalamin Chewable Gels / Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1

Comment Summary: The commenter suggested increasing the *Acceptance criteria* for the upper limits from NMT 150% (NMT 160% for US) to 155% (NMT 165% for US) due to possible variations in the process, assay, and stability values.

Response: Comment incorporated

Monograph/Section: Cyclophosphamide for Injection / Organic Impurities:
Procedure for the Lyophilized Formulation

No. of Commenters: 1

Comment Summary #1: The commenter recommended clarifying the peaks used for the *Resolution* requirement.

Response: Comment incorporated. The peaks listed for resolution requirement is changed from "between any pair of adjacent Reference Standard peaks" to "between Cyclophosphamide Related Compound A and Cyclophosphamide Related Compound D".

Monograph/Sections: Desvenlafaxine / Multiple Sections
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested revising the second chemical name in the chemical information section to remove the word "hydrogen."

Response: Comment incorporated.

Comment Summary #2: The commenter requested the addition of a temperature requirement in the *PACKAGING AND STORAGE* section.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Sections: Desvenlafaxine Fumarate / Multiple Sections

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter requested the addition of a temperature requirement in the *PACKAGING AND STORAGE* section.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Expert Committee-initiated Change #1: The second chemical name in the chemical information section of the monograph was updated for consistency with the Desvenlafaxine and Desvenlafaxine Succinate monographs.

Expert Committee-initiated Change #2: The *Note* in the *ASSAY* section was corrected to reference the relative retention times instead of relative response times.

Expert Committee-initiated Change #3: For consistency with the Desvenlafaxine Succinate monograph and for clarity that the drug substance is calculated on the anhydrous basis, the molecular formulas for desvenlafaxine fumarate in the *Definition* and *ASSAY* sections, and the calculations in the *ASSAY* section, were updated to remove the reference to the monohydrate form.

Monograph/Sections: Desvenlafaxine Succinate / Multiple Sections

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 2

Comment Summary #1: The commenter requested revising the second chemical name in the chemical information section to remove the word “hydrogen” because it seems to imply that the compound is a derivative of hydrogen and that naming the compound as a cyclohexanol derivative is sufficient.

Response: Comment not incorporated. The proposed text is appropriate for use in the public standard.

Comment Summary #2: The commenters requested revising the *Acceptance criteria* in the test for the *RESIDUE ON IGNITION* from NMT 0.10% to NMT 0.1% for consistency with what has been approved.

Response: Comment incorporated.

Comment Summary #3: The commenters requested revising the *Acceptance criteria* for total Impurities in the test for the *ORGANIC IMPURITIES* from NMT 0.50% to NMT 1.0% for consistency with what has been approved.

Response: Comment incorporated.

Comment Summary #4: The commenters requested revising the *Acceptance criteria* in the test for the *OPTICAL ROTATION* or removing the test for consistency with what has been approved.

Response: Comment incorporated.

Comment Summary #5: The commenters requested revising the *Acceptance criteria* in the test for the *WATER DETERMINATION* to be consistent with what has been approved.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Comment Summary #6: The commenter requested the addition of a temperature requirement in the *PACKAGING AND STORAGE* section.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Sections: Dexamethasone / Multiple Sections

Expert Committee: Chemical Medicines Monographs 5

No. of Commenters: 1

Comment Summary #1: The commenter requested the replacement of the proposed ASSAY and ORGANIC IMPURITIES tests with the procedure used in the ORGANIC IMPURITIES test in the corresponding European Pharmacopeia monograph.

Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Comment Summary #2: The commenter requested changing the solvent from dioxane to ethanol in the OPTICAL ROTATION test.

Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Dextrose / Identification

Expert Committee(s): Excipients Monographs 2

No. of Commenters: 3

Comment Summary #1: The commenter requested the reason and additional information about including a drying step in the infrared (IR) test for Identification (ID).

Response: The Expert Committee responded that this revision was based on the queries from several stakeholders who observed that the IR spectrum of the hydrate form has slight difference from the anhydrous form, which is the form of the current USP Dextrose RS. After the studies by applying different drying conditions to the Dextrose samples prior to the IR test, the results demonstrated that the currently proposed drying condition is the best one.

Comment Summary #2: The commenter recommended using the drying condition on the USP Dextrose RS label (105° under vacuum for at 16 hours) instead of the proposed drying condition (70° under vacuum for at least two hours).

Response: Comment not incorporated. According to the study results from different drying conditions, the current proposed drying condition is the best suitable one. Some stakeholders reported that they observed discoloration of Dextrose monohydrate sample after drying under 105°. After the monograph revision becomes official, the USP Dextrose RS label will reflect the proposed drying condition in the monograph.

Comment Summary #3: The commenter recommended not specifying <197K> for the ID test because they have been using the <197A> for the IR test. In addition, they suggested not adding a drying procedure prior to performing the IR test because they observed no impact on the identification of dextrose monohydrate.

Response: Comment not incorporated. The EC recommended keeping the proposal of <197K> because queries were received to specify the IR test method in the monograph. In addition, no data was available to support the use of <197A> in USP currently. However, since <197A> is mentioned as an alternative method according to <197>, the commenter can still use <197A> for IR if equivalency is demonstrated. The drying procedure was included based on the same response to the Commenter #1.

Monograph/Section(s): Diclofenac Sodium Topical Solution / Multiple Sections

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the *CONTENT OF DIMETHYL SULFOXIDE* and the *CONTENT OF ETHANOL* tests from the monograph because contents of these co-solvents are formulation specific and may vary for different products.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended revising the acceptance criterion for the pH test to be consistent with the FDA-approved limit.

Response: Comment incorporated. The EC revised the *Acceptance criteria* for pH determination from 8.5–10.0 to 8.0-10.0.

Comment Summary #3: The commenter requested revising the *Acceptance criteria* for the *CONTENT OF DIMETHYL SULFOXIDE* test from 41.0%–48.0% to 41.0%–50.0%.

Response: Comment not incorporated. The EC deleted the *CONTENT OF DIMETHYL SULFOXIDE* test from the monograph.

Monograph/Section: Ephedrine Hydrochloride/Packaging and Storage
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1
Comment Summary #1: The commenter recommended including a temperature requirement to the Packaging and Storage section of the monograph
Response: Comment incorporated.

Monograph/Section(s): Ergocalciferol Capsules / Labeling
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2
Comment Summary #1: The commenter recommended that the monograph provide the option for strength to be expressed in terms of International Units, in parentheses, after the declaration of the amount of ergocalciferol in mcg.
Response: Comment incorporated.
Comment Summary #2: The commenter proposed introducing a footnote with the relationship of the USP Units or International Units to mass when labeling provides the option to label dose in terms of units in addition to the required labeling in mass
Response: Comment incorporated.

Monograph/Section(s): Estriol Compounded Vaginal Cream
Expert Committee(s): Compounding
No. of Commenters: 1
Comment Summary #1: The commenter noted that the preparation may present particular safety risks given that FDA has not approved any drug containing estriol and FDA-approved estrogen products are labeled with a boxed warning related to health risks.
Response: Comment not incorporated. The EC recognizes that there may be safety risks associated with certain compounded preparations, especially when quality standards are not met. Estriol and other estrogens are commonly used to prepare compounded preparations for patients as evidenced by the literature available. The EC developed the monograph based on a stability-indicating assay and performed stability testing to ensure that if the preparation is compounded as described, the specified beyond use date (BUD) would apply. Additionally, USP has a drug substance monograph for estriol.

Monograph/Section(s): Ethambutol Hydrochloride / Multiple sections
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2

Comment summary #1: The commenter noted that it may be difficult for some of the approved applicants to meet the tighter limit for total impurities and individual specified limit for ethambutol related compound A and ethambutol related compound B.

Response: Comment not incorporated. The EC determined that the proposed limits are consistent with sponsor's FDA approval and will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment summary #2: The commenter recommended naming all ethambutol and ethambutol related compounds as derivatives of the same core structure in order to be consistent.

Response: Comment incorporated. The chemical name for ethambutol hydrochloride in the DEFINITION is updated to include azanediyldibutanol derivative.

Comment summary #3: The commenter recommended including a temperature requirement under the *PACKAGING AND STORAGE* section.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment summary #4: The commenter requested updating the equilibration step in *Table 1* from 45 minutes to 50 minutes in the test for *ORGANIC IMPURITIES* to be consistent with their validation data.

Response: Comment incorporated.

EC initiated change #1: The EC updated the chemical information for USP Ethambutol Related Compound A RS and USP Ethambutol Related Compound B RS to include the salt form in the *USP REFERENCE STANDARDS <11>* section.

Monograph/Section(s): Famciclovir Tablets / Multiple sections

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 2

Comment summary #1: The commenter suggested removing the term "if necessary" in the sample preparation in *DISSOLUTION Test 1* as dilution is mandatory to keep the sample solution equivalent to the standard solution.

Response: Comment incorporated.

Comment summary #2: The commenter suggested removing the *Peak identification solution* as peaks can be identified by the relative retention time in the test for *ORGANIC IMPURITIES*.

Response: Comment not incorporated. The EC determined that the *Peak identification solution* will be useful for manufacturers, and there are no compendial requirements for this solution.

Comment summary #3: The commenter suggested removing the *System suitability solution* and *Resolution* requirement as the impurities are not monitored in the test for *ORGANIC IMPURITIES*.

Response: Comment not incorporated. The EC determined that the *System suitability* requirement is needed to ensure separation of impurities.

Comment summary #4: The commenter requested updating the parameters and tolerances in the *DISSOLUTION* test to accommodate FDA-approved specifications for their product.

Response: Comment incorporated. The EC decided to add a new *DISSOLUTION Test 3* at the ballot.

Monograph/Sections: Fluvoxamine Maleate Tablets / Identification

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter suggested the addition of infrared absorption as an additional identification test.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Fluvoxamine Maleate Tablets / Organic Impurities

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 2

Comment Summary #1: The commenter requested to tightening the *Acceptance criteria* for succinic fluvoxamine.

Response: Comment not incorporated. The proposed limit for succinic fluvoxamine is consistent with the acceptance criteria in the sponsor's FDA-approved application. The EC will consider future revisions upon receipt of supporting data.

Comment Summary #2: The commenter noted that the impurity profile is different from the FDA-approved application.

Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Comment Summary #3: The commenter requested correcting the name of aminoethyl fluvoxamine.

Response: Comment incorporated.

Comment Summary #4: The commenter requested that *ORGANIC IMPURITIES Procedure 1* and *ORGANIC IMPURITIES Procedure 2* be replaced with a single procedure, specific for all impurities.

Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Monograph/Section: Hydromorphone Hydrochloride / Organic Impurities

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criterion for individual unspecified impurity in *Procedure 1* from 0.1% to 0.10% to be consistent with that in *Procedure 2* and the ICH recommended limit.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of necessary supporting data.

Expert Committee-Initiated Change #1: The EC revised the chemical information for USP Hydromorphone Related Compound A in *USP REFERENCE STANDARDS <11>*, reflecting the perchlorate salt form of the USP Hydromorphone Related Compound A RS.

Monograph/Section(s): Itraconazole Capsules / Multiple sections

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 3

Comment Summary #1: The commenter recommended including a dissolution test for all FDA-approved manufacturers.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Comment Summary #2: The commenter noted that the acceptance criterion for total impurities is different from what has been approved by the FDA in the test for *ORGANIC IMPURITIES*.

Response: Comment incorporated. The acceptance criterion for total impurities is revised from NMT 1.0% to NMT 1.50%.

Comment summary #3: The commenter suggested changing the detector wavelength from 225 nm to 260 nm in the *ASSAY* and the test for *ORGANIC IMPURITIES* as some excipients/placebos interfere at 225 nm in the formulation.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Comment summary #4: The commenter noted that the DISSOLUTION test parameters and tolerances are different from what was proposed.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section: Leucovorin Calcium / Multiple Sections

Experts Committee: Chemical Medicines Monographs 3

No. of Commenters: 4

Comment Summary #1: The commenters requested revising the limits for several impurities in the test for *ORGANIC IMPURITIES* to be consistent with the FDA-approved specifications.

Response: Comment incorporated. The *Acceptance criteria* for the following impurities are changed as below:

Impurity Name	Acceptance Criteria, NMT (%)
5-Formyl-5,6,7,8-tetrahydropteroic acid	0.5
4-Aminobenzoylglutamic acid	1.5
10-Formyldihydrofolic acid	1.0
5,10-Diformyltetrahydrofolic acid	1.5
7,8-Dihydrofolic acid	0.5
10-Formylfolic acid	0.5
Folic acid	1.5
5-(γ -Folinoyl)tetrahydrofolate	0.3
Individual unspecified Impurity	0.3
Total Impurities	2.5

Comment Summary #2: The commenter recommended revising the *ASSAY* procedure to use a single high performance liquid chromatography (HPLC) procedure for *ASSAY* and *ORGANIC IMPURITIES*.

Response: Comment not incorporated. The EC determined that the *ASSAY* procedure is suitable as a public standard.

Comment Summary #3: The commenters requested adding a second organic impurities procedure for their product with a different impurity profile.

Response: Comment not incorporated. The EC determined that the proposed procedure is suitable for the intended use.

Comment Summary #4: The commenters recommend adding a note to the test for *LIMIT OF 5-(γ -FOLINOYL)TETRAHYDROFOLATE* to indicate that this test is only required when 5-(γ -folinoyl)tetrahydrofolate is identified as a specified impurity in the drug substance impurity profile.

Response: Comment incorporated. A *Note* is added to indicate that 5-(γ -folinoyl)tetrahydrofolate is tested only when it is present in the manufacturing process.

Monograph/Section: Leucovorin Calcium for Injection / Multiple Sections

Expert Committee: Chemical Medicines Monographs 3

No. of Commenters: 3

Comment Summary #1: The commenters requested revising the limits for several impurities in the test for *ORGANIC IMPURITIES* to be consistent with the FDA-approved specifications.

Response: Comment incorporated. The *Acceptance criteria* for the following impurities are changed as below:

Impurity Name	Acceptance Criteria, NMT (%)
5-Formyl-5,6,7,8-tetrahydropteroic acid	2.0
4-Aminobenzoylglutamic acid	2.0
10-Formyldihydrofolic acid	2.0
5,10-Diformyltetrahydrofolic acid	2.0
7,8-Dihydrofolic acid	2.0
10-Formylfolic acid	2.0
Folic acid	2.0
Individual unspecified Impurity	0.5
Total Impurities	2.5

Comment Summary #2: The commenters recommended replacing the ultraviolet (UV) with an IR test for *IDENTIFICATION*.

Response: Comment not incorporated. The EC may consider a revision in the future upon receipt of supporting documents.

Comment Summary #3: The commenter requested revising the acceptance criterion for *BACTERIAL ENDOTOXINS TEST* <85> to be consistent with the approved specification.

Response: Comment incorporated. The numerical limit is changed to “Meet the requirements,” calculated according to General Chapter <85> *Bacterial Endotoxins Test*.

Comment Summary #4: The commenter recommended tightening the pH limits from 6.5–8.5 to 7.0–8.5.

Response: Comment not incorporated. The pH limit in monograph is consistent with the FDA-approved acceptance criteria. The EC may consider a future revision upon receipt of supporting documents.

Expert Committee-initiated Change #1: The USP Endotoxin RS is deleted from USP REFERENCE STANDARDS <11> according to *General Announcement* “USP Monographs Will No Longer Cite Reference Standards Required by a General Chapter as of *USP 41–NF 36*”.

Monograph/Sections: Lovastatin Tablets / Organic Impurities

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 4

Comment Summary #1: The commenter recommended revising the *Acceptance criteria* for lovastatin acid and total degradation products in *Table 1* to be consistent with the FDA-approved limits.

Response: Comment incorporated. The EC revised the *Acceptance criteria* for lovastatin acid from NMT 0.75% to NMT 0.85% and total degradation products from NMT 1.0% to NMT 2.5%.

Comment Summary #2: The commenter recommended revising the *Acceptance criteria* for total degradation products in *Table 1* from NMT 1.0% to NMT 2.0% to be consistent with the FDA-approved limit.

Response: Comment not incorporated. The EC revised the *Acceptance criteria* for total degradation products in *Table 1* from NMT 1.0% to NMT 2.5%.

Monograph/Section(s): Maleic Acid/Multiple Sections

Expert Committee(s): Excipients Monographs 1

Expert Committee-initiated Change #1: Add a sentence after *Table 1* that directs the users to re-equilibrate the system after it returned to original conditions.

Expert Committee-initiated Change #2: Add a *Labeling* section that provides labeling requirements for Maleic Acid used in injectable dosage forms.

Monograph/Section: Naltrexone Hydrochloride / Packaging and Storage
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1*: The commenter recommended adding a temperature requirement to the PACKAGING AND STORAGE section.
Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Naproxen Compounded Oral Suspension
Expert Committee(s): Compounding
No. of Commenters: 1
Comment Summary #1: The commenter noted that the compounded preparation monograph is essentially a copy of an FDA-approved product and such preparation should not be compounded unless the patient has a specific medical need.
Response: Comment not incorporated. The EC does not encourage compounding where there is a suitable commercially available product. However, as the commenter mentioned, there may be situations where there is a specific medical need or drug shortages where the preparation may need to be compounded.

Monograph/Sections: Olanzapine and Fluoxetine Capsules
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter suggested the addition of infrared absorption as an additional identification test.
Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Monograph/Section: Oxycodone Hydrochloride / Organic Impurities
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1
Comment Summary #1: The commenter requested correcting the chemical name for noroxycodone hydrochloride impurity in *Table 3*.
Response: Comment incorporated. The EC revised the chemical name to 4,5 α -Epoxy-14-hydroxy-3-methoxymorphinan-6-one hydrochloride.
Expert Committee-Initiated Change #1: The EC revised footnote c in *Table 3* to include the salt form "hydrochloride" in the chemical name.

Monograph/Sections: Paroxetine Hydrochloride / Limit of Paroxetine Related Compound C
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1
Comment Summary #1: The commenter indicated the specified column with 5- μ m particle size is not available and should be replaced with a 10- μ m column.
Response: Comment incorporated.

Monograph/Sections: Pyridostigmine Bromide / Packaging and Storage
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 1

Comment Summary #1: The commenter requested the inclusion of a temperature requirement in the *PACKAGING AND STORAGE* section.

Response: Comment not incorporated. The EC will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Spironolactone / Multiple Sections
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the *Acceptance criteria* for the spironolactone related compound A, spironolactone related compound B, spironolactone related compound D, and the spironolactone epimer as they are not consistent with the FDA-approved limits.

Response: Comment not incorporated. The *Acceptance criteria* are consistent with the sponsor's FDA-approved application. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #2: The commenter requested including an additional chemical name in accordance with the current USP naming convention, under the chemical information of the drug substance.

Response: Comment incorporated. The EC included the chemical name, (2'R)-7 α -(Acetylthio)-3',4'-dihydro-5'H-spiro[androst-4-ene-17,2'-furan]-3,5'-dione.

Comment Summary #3: The commenter requested harmonizing the preparation of *System suitability solution* and the *Suitability requirements* with the Spironolactone monograph in European Pharmacopoeia.

Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section(s): Star Anise Oil/ Identification
Expert Committee(s): Excipients Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended adding a second *Identification* test based on IR-spectrometry to distinguish Star Anise Oil from Anise Oil.

Response: Comment not incorporated. The comparison of IR spectra of Star Anise Oil and Anise Oil showed that they were identical and therefore cannot be used for distinguishing Star Anise Oil from Anise Oil

Expert Committee-initiated Change #1: In the *Chromatographic similarity* section of the *Chromatographic Identity* test, add a *Note* that directs the users to check similarity between the chromatogram of the *Standard* and the reference chromatogram provided with the lot of USP Star Anise Oil RS being used.

Monograph/Sections: Succinylcholine Chloride / Packaging and Storage
Expert Committee: Chemical Medicines Monographs 5
No. of Commenters: 1

Comment Summary #1: The commenter requested the inclusion of a temperature requirement.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section(s): Sulfamethoxazole / Organic impurities
Expert Committee: Chemical Medicines Monographs 1
No. of Commenters: 2

Comment summary #1: The commenter suggested removing the *Peak identification solution* as peaks can be identified by the relative retention time.

Response: Comment not incorporated. The EC determined that the *Peak identification solution* will be useful for users and there are no requirements for this solution.

Comment summary #2: The commenter suggested that the *Acceptance criteria* for all impurities, including that of total impurities, are different from those that have been approved by the FDA.

Response: Comment not incorporated. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Sections: Tiagabine Hydrochloride / Organic Impurities

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter requested to revise the limit for desmethyl tiagabine impurity to be consistent with the approved specification.

Response: Comment not incorporated. The proposed limit for desmethyl tiagabine is consistent with the acceptance criteria in the sponsor's FDA-approved application. The EC will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Tranexamic Acid Tablets / Multiple Sections

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the *ASSAY Acceptance criteria* to be consistent with the FDA-approved limits.

Response: Comment incorporated. The *ASSAY Acceptance criteria* are revised from 95.0%–105.0% to 90.0%–110.0%.

Comment Summary #2: The commenter requested revising the *ASSAY Acceptance criteria* from 95.0%–105.0% to 90.0%–110.0% to be consistent with the FDA-approved limits.

Response: Comment incorporated.

Comment Summary #3: The commenter recommended adding a dissolution test to be consistent with the commenter's FDA-approved drug product.

Response: Comment not incorporated. The EC included the proposed new dissolution test via a separate revision proposal.

Monographs/Section(s): Vitamin A Capsules / Labeling

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 1

Comment Summary: The commenter recommended following the comments provided on the Ergocalciferol and Cholecalciferol monographs.

Response: Comments incorporated.

Monographs/Section(s): Vitamin A Oral Liquid Preparation / Labeling

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 1

Comment Summary: The commenter recommended following the comments provided on the Ergocalciferol and Cholecalciferol monographs.

Response: Comments incorporated.

Monographs/Section(s): Vitamin A Tablets / Labeling
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary: The commenter recommended following the comments provided on the Ergocalciferol and Cholecalciferol monographs.
Response: Comments incorporated.

Monographs/Section(s): Vitamin E Capsules / Labeling
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1
Comment Summary: The commenter recommended following the comments provided on the Ergocalciferol and Cholecalciferol monographs.
Response: Comments incorporated.

Monograph/Sections: Xylometazoline Hydrochloride / Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated change #1: In the test for *ORGANIC IMPURITIES*, included relative response factor (RRF) value of 1.0 for any unspecified impurity because the calculation formula includes RRF value. Replace “Disregard any impurity peak less than 0.03%” with “The reporting threshold is 0.03%” to make it consistent with the current USP style.

Monograph/Sections: Xylometazoline Hydrochloride Nasal Solution / Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
Expert Committee-initiated change #1: In the test for *ORGANIC IMPURITIES*, included RRF value of 1.0 for any unspecified impurity because the calculation formula includes RRF value. Replace “Disregard any impurity peak less than 0.03%” with “The reporting threshold is 0.03%” to make it consistent with the current USP style.

Monograph/Sections: Zolmitriptan / Organic Impurities
Expert Committee: Chemical Medicines Monographs 4
No. of Commenters: 3
Comment Summary #1: The commenter indicated the limit of related compound G is different from the approved limits.
Response: Comment not incorporated because the limits are consistent with the FDA-approved specifications for several approved applicants.
Comment Summary #2: The commenter indicated that their drug substance has one additional process impurity and requested the revision of the monograph
Response: Comment not incorporated because introduction of the new impurity will require additional supporting data and evaluation. The EC may consider a future revision and when all the supporting data are available.
Comment Summary #3: The commenter requested that USP harmonize the monograph *IMPURITIES* procedures with European Pharmacopoeia.
Response: Comment not incorporated because this would require additional validation data. The EC may consider a future revision and when the necessary supporting data is available.