



Commentary

USP 41–NF 36, First Supplement

February 1, 2018

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:

[<741> Melting Range or Temperature](#)

[<123> Glucagon Bioidentity Tests](#)

[<198> Nuclear Magnetic Resonance Spectroscopy Identity Testing of Bacterial Polysaccharides Used In Vaccine Manufacture](#)

[<1151> Pharmaceutical Dosage Forms](#)

[<1231> Water for Pharmaceutical Purposes](#)

Monographs:

[Acamprosate Calcium](#)

[Acetaminophen Oral Suspension](#)

[Acetaminophen Tablets](#)

[Amitriptyline Hydrochloride](#)

[Amlodipine and Atorvastatin Tablets](#)

[Ascorbic Acid Chewable Gels](#)

[Azithromycin Tablets](#)

[Baclofen Tablets](#)

[Benzethonium Chloride](#)

[Brimonidine Tartrate](#)

[Calcium Citrate Malate](#)

[Carbidopa and Levodopa Extended-Release Tablets](#)

[Cholecalciferol Chewable Gels](#)

[Cholecalciferol Tablets](#)

[Clarithromycin](#)

[Coffee Fruit Dry Extract](#)

[Coix Seed](#)

[Coix Seed Powder](#)

[Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution](#)

[Flax Seed Oil](#)

[Glyceryl Tricaprylate](#)

[Glycine](#)

[Levocarnitine](#)

[Lidocaine](#)

[Methotrexate Injection](#)

[Miconazole Nitrate](#)

[Minocycline Hydrochloride](#)

[Nicotine Transdermal System c](#)

[Omega-3-Acid Ethyl Esters Capsules](#)

[Pantoprazole Sodium](#)

[Pentazocine](#)

[Pralidoxime Chloride](#)

[Pralidoxime Chloride for Injection](#)

[Prasugrel Hydrochloride](#)

[Pravastatin Sodium](#)

[Raltegravir Chewable Tablets](#)

[Raltegravir Tablets](#)

[Rizatriptan Benzoate Orally Disintegrating Tablets](#)

[Rosuvastatin Calcium](#)
[Rosuvastatin Tablets](#)
[Sodium Fluoride and Acidulated Phosphate Topical Solution](#)
[Sodium Fluoride Oral Solution](#)
[Somatropin](#)
[Sumatriptan Nasal Spray](#)
[Taurine](#)
[Tranexamic Acid Injection](#)
[Tranycypromine Tablets](#)
[Triamterene](#)
[Valerian Root Dry Extract Capsules](#)
[Valerian Root Powder Capsules](#)

No comments were received for the following proposals:

General Chapters:

<724> Drug Release

<2040> Disintegration and Dissolution of Dietary Supplements

Monographs:

Amitriptyline Hydrochloride Injection
Amoxicillin
Anthrax Vaccine Adsorbed
Aztreonam
BCG Vaccine
Carprofen
Chymotrypsin
Chymotrypsin for Ophthalmic Solution
Colchicine
Cortisone Acetate Injectable Suspension
Cyclopentolate Hydrochloride
Dexamethasone Sodium Phosphate inhalation Aerosol
Doxycycline Hyclate Capsules
Doxycycline Hyclate Tablets
Estradiol Benzoate
Hydrocortisone Acetate Ophthalmic Ointment
Hydroxyzine Pamoate Oral Suspension
Isopropyl Isostearate
Lidocaine Hydrochloride Oral Topical Solution
Lidocaine Hydrochloride Topical Solution
Mebendazole Tablets
Meloxicam Oral Suspension
Menaquinone-4
Metaproterenol Sulfate Inhalation Aerosol
Methylcobalamin
Methylcobalamin Tablets
Miconazole Nitrate Topical Powder
Norelgestromin
Octinoxate

Octisalate
Octocrylene
Omega-3 Acids Ethyl Esters
Perphenazine Injection
Perphenazine Oral Solution
Perphenazine Syrup
Pilocarpine Hydrochloride Tablets
Polydextrose
Scopolamine Hydrobromide
Squalane
Terbutaline Sulfate Inhalation Aerosol
Tetracycline
Tetrahydrozoline Hydrochloride Ophthalmic Solution
Tiamulin
Tiamulin Fumarate
Tocainide Hydrochloride
Tocainide Hydrochloride Tablets
Trazadone Hydrochloride Tablets
Verapamil Hydrochloride Extended-Release Tablets
Xylazine

General Chapters

General Chapter/Sections: <741> Melting Range or Temperature/Multiple Sections
Expert Committee: General Chapters—Physical Analysis
No. of Commenters: 3

General

Comment Summary #1: The commenter suggested harmonizing the content wording and organizational layout of this General Chapter with both the World Health Organization (WHO) and the *European Pharmacopeia* to avoid confusion across global organizations.

Response: Comment not incorporated. This chapter is not in the current harmonization work plan.

Comment Summary #2: The commenter recommended that all procedures be written in a consistent way regardless of whether the initial temperature is 5° or 10° below the expected melting point.

Response: Comment not incorporated. There are additional instructions for each class of substance or apparatus beyond the temperature.

Introduction

Comment Summary #3: The commenter requested clarifying the definitions to improve the terminology for single data point reporting and decomposition and to align with the WHO and *European Pharmacopeia* definitions.

Response: Comment partially incorporated. The definitions in the *Introduction* were revised but not completely aligned with the referenced pharmacopeias.

Comment Summary #4: The commenter suggested changing the definitions of melting range, melting temperature, and melting point from “first detectable liquid phase is detected...” to “first detectable change of phase or liquid phase is observed....”

Response: Comment incorporated.

Comment Summary #5: The commenter suggested changing “the sample size, the particle size, the efficiency of the heat diffusion...” to “the sample size, the particle size, the efficiency of heat diffusion within the sample....”

Response: Comment incorporated.

Comment Summary #6: The commenter suggested adding allowances for single data point reporting, regardless of whether the beginning or the end is obscured.

Response: Comment not incorporated. If decomposition obscures at the beginning of melt, the substance has changed and a melting point is no longer a valid measurement.

Comment Summary #7: The commenter suggested clarifying the sample preparation by adding the following: “tap the bottom of the capillary on a hard surface so that the materials pack well into the capillary and perform the melting determination....”

Response: Comment partially incorporated. The current and proposed text in the *Introduction* is only relevant for Class I and Ia, and it should apply to both apparatuses and also to the various classes of materials being tested. The *Introduction* was edited accordingly. In addition, a detailed description of sample preparation is provided later under *Procedures* for Class I, Apparatus I, and this section contains the requirement for tapping the capillary on a hard surface, which does not apply or is different for Classes Ib, II, and III.

Comment Summary #8: The commenter recommended clarifying that there is a thermal lag between the liquid and the sample when a different ramp rate is employed.

Response: Comment incorporated.

Comment Summary #9: The commenter proposed adding wording to clarify that the melting point standards are allowed to be used for instrument calibration.

Response: Comment incorporated. The following sentence was added: “The USP Melting Point Standards are intended to check the accuracy of the device and may be suitable to calibrate.”

Apparatus

Comment Summary #10: The commenter suggested clarifying the usage of cameras or other computerized equipment by changing the wording from “with advantages in terms of accuracy, sensitivity, or precision...” to “to improve accuracy, sensitivity, or precision....”

Response: Comment incorporated.

Procedure for Class I, Apparatus I

Comment Summary #11: The commenter suggested changing the text describing the different sample size due to instrument design from “alternative sample sizes may be instructed...” to “alternative sample sizes may be used as instructed....”

Response: Comment incorporated.

Comment Summary #12: The commenter suggested changing the ramp rate language in the procedure from “sufficiently to cause the temperature to rise at a rate of about 3°/min. When the temperature is about 3° below the lower limit of the expected melting

range, reduce the heating so that the temperature rises at a rate of about 1°/min...” to “sufficiently to achieve the ramp rate of about 3°/min. When the temperature is about 3° below the lower limit of the expected melting range, reduce the heating so that the ramp rate of about 1°/min is achieved....”

Response: Comment incorporated.

Expert Committee-Initiated Change #1: The height of the column in the bottom of the tube was changed from “3 mm high” to “a nominal height of 3 mm high.”

Expert Committee-Initiated Change #2: The phrase “(melting point)” was added to clarify a single data point reporting when melting occurs with decomposition.

Procedure for Class Ib, Apparatus I

Comment Summary #13: The commenter suggested changing the wording regarding the charge of the capillary tube from “Without previous powdering, charge the cooled material...” to “Without powdering, charge the cooled material....”

Response: Comment incorporated.

Procedure for Class I, Apparatus II

Comment Summary #14: The commenter recommended adding a brief description of approaches broadly used by the automated system to clarify the concept of currently referred alteration in detector value.

Response: Comment incorporated. The following general sentence was added under *Apparatus II*: “Some approaches broadly used by automated systems employ optical methods such as light absorption or bulk reflection.”

Expert Committee-Initiated Change #3: The phrase “(melting point)” was added to clarify a single data point reporting when melting occurs with decomposition.

Procedure for Class Ia, Apparatus II

Expert Committee-Initiated Change #4: The phrase “(melting point)” was added to clarify a single data point reporting when melting occurs with decomposition.

Procedure for Class III

Comment Summary #15: The commenter suggested changing the wording on sample preparation from “Melt a quantity of the test substance slowly, while stirring, until it reaches a temperature of 90°–92°...” to “While stirring, melt a quantity of the test substance slowly until it reaches a temperature of 90°–92°....”

Response: Comment incorporated.

General Chapter/Sections: <123> Glucagon Bioidentity Tests/Multiple Sections

Expert Committee: Biologics 1—Peptides

No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the text to allow more flexibility in the execution of the method.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended revising the instructions due to changes in the cyclic AMP (cAMP) kit components following publication in *Pharmacopeial Forum (PF)*.

Response: Comment incorporated. The preparation of the Donor Biotin-cAMP Beads was added to the reagent section, and the item number was updated in the footnote.

Comment Summary #3: The commenter recommended removing the absolute temperature requirement for Medium A since warming to ambient temperature is sufficient.

Response: Comment incorporated. The text was revised by replacing “37° Medium A” with “warmed Medium A”.

Comment Summary #4: The commenter recommended revising the volume of Medium A to be added to the trypsinized cells by replacing “about 2x” with a “minimum of 2x.”

Response: Comment incorporated.

Comment Summary #5: Three commenters recommended revising the text to clarify how many replicates of the test samples needed and how they are used to calculate the final potency results.

Response: Comments incorporated.

Comment Summary #6: The commenter recommended clarifying the events that define the 40-minute interval during which the cells must be loaded into the wells.

Response: Comment incorporated.

Comment Summary #7: The commenter recommended allowing diluents other than *Water for Injection* to reconstitute the *USP Glucagon Reference Standard solution* and the *Sample solution*.

Response: Comment incorporated. A note was added to the text to allow this flexibility.

Comment Summary #8: The commenter recommended revising the text to allow more flexibility in the preparation of the *Standard solution* series (R8-R2) and the *Sample solutions* series A8–A2 and B8–B2 to accommodate slight differences in responses among different products.

Response: Comment incorporated. A note was added in the *Standard solution* section to state that “alternative suitable concentrations can be similarly prepared if necessary and validated.” In the *Sample solution* section the word “described” was replaced with “suggested.”

Comment Summary #9: The commenters recommended clarifying the detection mode used in the method.

Response: Comment not incorporated. The detection mode is luminescence. The donor beads are excited at 680 nm, generating singlet oxygen. If acceptor beads are nearby, it will result in emission in the indicated wavelength range.

Comment Summary #10: The commenter recommended revising the *Table 2* legend to have the same number of independent dilution series prepared and plated for Samples A (A2-A8) and B (B2-B8) and the standard (R2-R8).

Response: Comment partially incorporated. The method was validated as written, but the language was made more flexible by removing the word “independent” from the text describing the standard solution series preparation.

Comment Summary #11: The commenter recommended revising the plate layout in *Table 2* to allow other suitable plate maps.

Response: Comment not incorporated. The layout of the plate was validated as written and found to be critical to reduce plate effects.

Comment Summary #12: The commenter recommended clarifying the requirements for the cAMP controls C9, C6, C4, and C1 (E12-H12) in the plate layout in *Table 2*.

Response: Comment not incorporated. The controls are required to assure system suitability of the cAMP kit performance.

Comment Summary #13: The commenter recommended clarifying whether the blank wells that do not contain glucagon sample or standard are filled with medium.

Response: Comment incorporated. The text and *Table 2* legend were edited to clarify that 30 μ l of Medium B is added to the wells that do not contain glucagon sample or standard.

Comment Summary #14: The commenter indicated that column 12 in the plate layout in *Table 2* should contain the cAMP standards C3-C8, which are added to the separate plate described in *Table 3*.

Response: Comment not incorporated. The plate layout was validated as such and cannot be modified. Per *USP* General Notices 6.30, alternative methods can be used if validated and if the results are equivalent or better than the compendial method.

Comment Summary #15: The commenter recommended clarifying the system suitability requirement that the *Sample Solutions* and *Standard Solutions* must be within the linear range of the *cAMP standard curve*.

Response: Comment incorporated. The text was revised to clarify that the lower asymptote of the 4-parameter logistic standard curves, generated from *Sample solutions* A2–A8 and B2–B8 and *Standard solutions* R1–R8, must be above the lower limit (defined as C3) of the linear range of the *cAMP standard solutions*. In addition, a note was added to clarify that the upper asymptotes of the 4-parameter logistic standard curves, generated from *Sample solutions* A2–A8 and B2–B8 and *Standard solutions* R1–R8, should be approximately equal to or less than the C8 response of the *cAMP standard solutions* and within the linear range of the instrument used.

Comment Summary #16: The commenter recommended deleting the EC_{50} value as a data acceptance criterion from the method.

Response: Comment incorporated.

Comment Summary #17: The commenter recommended deleting the requirements for linearity and slope from the *Calculations* sections since a 4-parameter logistic fit is used to fit the data.

Response: Comment partially incorporated. The wording “Parallel-curve analysis” and “4-parameter logistic fit” was added for clarity. The requirement for the slope statistical test was maintained while the requirement for linearity was removed to avoid confusion and because linearity is already assessed within the parallelism exercise.

Comment Summary #18: The commenter requested that other approaches for calculating a final potency value for a test sample be allowed rather than the combination of Independent Assays provided in General Chapter <111> *Design and Analysis of Biological Assays*, in alignment with other chapters on bioassay (e.g., General Chapter <1034> *Analysis of Biological Assays*).

Response: Comment not incorporated. *USP* General Chapters numbered above 1000 are not required. In addition, General Chapter <111> was recently revised to include the same combination of independent assay options found in General Chapter <1034>.

Expert Committee-initiated Change #1: In the cell culture preparation section, the Glucagon Receptor Cell Line will no longer be provided as a USP RS but is available from American Type Culture Collection (ATCC) for compendial purposes; therefore, “USP” and “RS” were removed here and in the RS section, and a footnote was added to direct stakeholders to ATCC.

Expert Committee-initiated Change #2: In the *cAMP Standard solutions* section, a note was added to ensure that the *Standard solutions*, *cAMP Standard solutions*, and *Assay solutions* responses were within the linear range of the instrument: “[NOTE- To conform to the linear range of the instrument being used, analysts may find it necessary to adjust by dilution each of the Standard solutions, cAMP standard solutions, and Assay solutions. Alternative suitable concentrations can be similarly prepared if necessary and validated.]”

Expert Committee-initiated Change #3: Footnotes 9-13 were revised to reduce duplication and to correct one PerkinElmer catalog number.

General Chapter/Sections: <198> Nuclear Magnetic Resonance Spectroscopy
Identity Testing of Bacterial Polysaccharides Used in
Vaccine Manufacture/Multiple Sections
Expert Committee: General Chapters—Biological Analysis
No. of Commenters: 1

2.2 Reagents for Vaccine Polysaccharide Sample Solutions

Comment Summary #1: The commenter suggested specifying the units associated with the percentages of the chemical shift reference compounds, as different solutions are commercially available in (w/w) or (w/v).

Response: Comment incorporated. The text “(w/v)” has been added after “0.1%-0.01%” to clarify the unit associated with the percentages.

2.9 System Suitability

Comment Summary #2: The commenter suggested that the text on using NLT 64 scans should be changed to a NLT S/N ratio instead.

Response: Comment not incorporated. For a test to “pass” requires that a certain S/N is achieved for specified peaks; hence, S/N cannot be used to define experimental conditions. It is a test to screen out low-sensitivity systems. Use of a higher sensitivity system can require fewer scans, and this change can be validated and used per *General Notices* section 6.30.

Comment Summary #3: The commenter recommended using a recycle delay of 15 s instead of 30 s, with all other parameters remaining the same, in the system suitability procedure. This would reduce the experiment time by a factor of 2 (keeping the same S/N ratio), and also be suitable for quantitative measurements.

Response: Comment not incorporated. The purpose of the system suitability test is to mimic the assays used for “real” samples. In some cases, these tests will be used to quantify acetate anion. The T1 of acetate is what defines the recycle time in this test, not that of the system suitability standard. On that basis, 30 s has been found to be appropriate.

Expert Committee-initiated Change #1: The text “(or three distinctive resonances in polysaccharides with monosaccharide or disaccharide repeat units)” was added to *NMR Spectrum of the Test Sample* in Section 2.5 because some polysaccharides may have smaller repeating units and may not be able to meet the “at least five resonances” requirement.

Monograph/Sections: <1151> Pharmaceutical Dosage Forms/
Multiple Sections
Expert Committees: General Chapters–Dosage Forms
No. of Commenters: 5

General Considerations

Comment Summary #1: The commenter requested that under *Release Profile*, the discussion of modified release should clearly indicate that this term is not used in official article titles. Only three of the four profiles (immediate-release, delayed-release, and extended-release) are used in official article titles.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested including the expression “long-acting” under the list of other expressions that are not used in official article titles.

Response: Comment incorporated.

Dosage Forms

Comment Summary #3: The commenter requested, under the discussion of chewable gels within *Gels*, adding “or dietary supplements” to the contents whose taste might be masked by the addition of flavors and sweeteners.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested rewording the last paragraph in the section on preparation of gels to clarify the molding of chewable gels.

Response: Comment incorporated.

Comment Summary #5: The commenter suggested including artificial sweeteners on the list of ingredients for chewable gels.

Response: Comment not incorporated. “Sweetener” is a general term that includes the possibility that artificial materials are used.

Comment Summary #6: The commenter suggested modifying the preparation section under *Lozenges* to reflect the similarity to the preparation of chewable gels.

Response: Comment not incorporated. This change will be considered for the next revision of the chapter.

Comment Summary #7: The commenter requested that the wording under *Lozenges* be changed from “naming pharmacopeial articles” to “official article titles” to indicate the appropriate naming conventions for the terms cough drops, pastilles, and troches.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested that the wording under *Powders* be changed from “can” to “may” in the following sentence: “The particle size of powders delivered to the lung or nose can influence where the powder is deposited.”

Response: Comment not incorporated. The use of the word “may” implies “may not.” The Committee disagrees with the implication that particle size may not influence deposition in the lung or nose.

Comment Summary #9: The commenter suggested that the wording under *Powders* be changed from “can” to “may” in the following sentence: “Particle size can influence the mixing, segregation, and aggregation of the particles...”

Response: Comment incorporated.

Comment Summary #10: Under *Suspensions*, the commenter suggested cross referencing *Powders* in the following statement: “Some suspensions are prepared and ready for use, and others are prepared as solid mixtures intended for reconstitutions with an appropriate vehicle just before use.”

Response: Comment not incorporated. This addition will be considered in the next revision proposal.

Glossary

Comment Summary #11: The commenter requested changing the last sentence under *Delayed-release* to “is used in official article titles” for consistency throughout the chapter.

Response: Comment incorporated.

Comment Summary #12: The commenter suggested the addition of “repeat-action” and “long-acting” to the list of terms that are not used in official article titles.

Response: Comment incorporated.

General Chapter/Sections:	<1231> Water for Pharmaceutical Purposes/ Multiple Sections
Expert Committee:	General Chapters—Chemical Analysis
No. of Commenters:	5

General

Comment Summary #1: The commenter suggested refocusing the chapter to strongly support the use of inline chemical and microbiological monitoring as more reliable and timely than laboratory-based testing. The commenter recommended referencing the American Public Health Association (APHA)/American Water Works Association (AWWA) standard methods and sample storage instead of *USP <61> Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and *<62> Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*, which are not designed to test pharmaceutical grade water.

Response: Comment not incorporated. This general information chapter covers current practices and provides references for some methods that are used as a basis.

3.3.1. Drinking Water/Figure 2a

Comment Summary #2: The commenter suggested redesigning Figure 2a to consider the use of *Purified Water* for the final steps of active pharmaceutical ingredient (API) manufacture if the API is intended to be used for parenteral drugs.

Response: Comment not incorporated. There are many potential scenarios in which water purity other than *Purified Water* might be appropriate for parenteral APIs. Further

processing of an API or its precursors in which the water was used might reduce or eliminate endotoxins and remove other chemical impurities in the water from the finished API. Also, very low API doses may make the levels of endotoxins and other impurities in the water inconsequential in the dosage form.

5.1.9. Microbial-Retentive Filtration

Comment Summary #3: The commenter recommended rewording this section because *Brevundimonas diminuta* is typically used for filter validation studies. It is unclear which other challenge organisms should be used, and their use is not consistent with studies typically performed by filter manufacturers or with current regulatory review policies.

Response: Comment partially incorporated. Names of specific microorganisms have been removed because this section describes the filtration phenomenon and does not describe validation studies.

Comment Summary #4: The commenter suggested removing the notion of membrane filters to be used in water systems. Membrane filters could mask design deficiencies or even lead to water contamination due to microorganisms growing on the membrane surface.

Response: Comment incorporated. Additionally, this concern is clarified in the final paragraph of the same section.

Comment Summary #5: The commenter suggested deleting paragraphs 1 to 4 and 6 of this section because it is commonly accepted that 0.1 µm rated filters intended to improve the water quality as built-in units have no effect.

Response: Comment not incorporated. This concern is addressed in the same section, which uses the clarifying wording “in some situations,” and this is an informational chapter intended to provide guidance.

6.1. Purposes and Procedures

Comment Summary #6: The commenter requested deleting the following text: “However, depending on the use of the data [process control (PC) or QC sampling)], inline/online testing may not be suitable, making the offline testing of grab samples the only suitable approach” because all data gathered during the water system operation are relevant for assessing system performance. Also, online results may be used as “QC” results if records are reviewed by Quality.

Response: Comment incorporated. Additional changes were made for consistency.

6.1.1. PC Sampling

Comment Summary #7: The commenter requested adding the verb “is” between “it” and “drawn” to correct the sentence.

Response: Comment incorporated.

6.2.2. Microbial Attributes

Comment Summary #8: The commenter suggested deleting the second paragraph of this section because “QC release testing” is not possible for water distributed in pipes. The water is already used when testing results are available.

Response: Comment not incorporated because microbiological tests are not as uniform as total organic carbon (TOC)/Conductivity tests. In the last revision, this section was clarified to better define online vs. offline testing in the *PC Sampling* and *QC Sampling* sections.

7.1. Chemical Tests for Bulk Waters

Expert Committee-Initiated Change #1: For accuracy and clarity, the following text was added to the description of the contributing ion column in *Table 1*: “individual (H^+ , OH^- , HCO_3^-) and group (Cl^- , $+Na^+$, $+NH_4^+$) of....”

7.4. Elemental Impurities in Pharmaceutical Water

Comment Summary #9: The commenter recommended adding “for Large-Volume Parenterals (LVP)” to maintain consistency and improve clarity.

Response: Comment partially incorporated. Large-Volume Parenterals were not included because the proposed text applies to all parenterals. Changes were made to be inclusive for all parenteral doses.

8.1. Microorganism Types

Comment Summary #10: The commenter recommended providing additional explanation for several statements in this section. For example, the reference to the nutritional requirements of different types of microorganisms should state what those requirements are and why they are not met by pharmaceutical grade water.

Response: Comment not incorporated. This section is only a general discussion on micro evaluation and not a referee procedure. It has been written for broader stakeholders that might not be familiar with micro (e.g., engineers and chemists).

8.1.1. Archaeans

Comment Summary #11: The commenter recommended adding the nutritional requirements for *Archaeans*.

Response: Comment not incorporated. The chapter provides a general description of the growth environment for this type of organism at an appropriate level of detail.

8.1.2. Bacteria

Comment Summary #12: The commenter recommended clarifying that bacteria are important as a source of potential human infection and have the ability to grow to high numbers in low-nutrient environments.

Response: Comment partially incorporated. Information regarding pathogenicity was added.

8.1.2.1. Gram-positive Bacteria

Comment Summary #13: The commenter requested deleting the description of *Bacilli* as contaminants because they are common soil and air components.

Response: Comment incorporated.

8.1.2.2. Gram-negative Bacteria

Comment Summary #14: The commenter requested clarifying the impact and relevance of endotoxins due to their metabolic versatility and ability to cause human infection, grow in water, and withstand preservative systems.

Response: Comment partially incorporated. Some aspects are already covered in other sections.

8.1.2.3. Mycoplasma

Comment Summary #15: The commenter suggested clarifying that plant Mycoplasma are common. They result in turbidity in plant-derived peptones in media fills, and some genera of mycoplasma, e.g., *Acholeplasma*, do not require sterols for growth in culture.

Response: Comment incorporated.

8.1.3. Fungi

Comment Summary #16: The commenter suggested clarifying that the prevalence of yeast in products suggests that they are not non-aqueous.

Response: Comment incorporated. Additional changes were made for consistency and clarity.

8.1.4. Viruses

Comment Summary #17: The commenter suggested clarifying that bacteriophages are more widespread than pathogenic viruses and may exchange genetic material with bacteria.

Response: Comment not incorporated. While these statements are true, they are not applicable to water systems.

Expert Committee-Initiated Change #2: It was clarified that it is unlikely that “human pathogenic” viruses will be present or will proliferate in pharmaceutical-grade waters.

8.1.5. Thermophiles

Comment Summary #18: The commenter recommended adding some nutritional/environmental examples clarifying why the thermophiles are not a concern for pharmaceutical grade water. A relevant reference was suggested.

Response: Comment partially incorporated. The reference to the article was not included due to USP policies.

8.2. Biofilm Formation in Water Systems

Comment Summary #19: The commenter suggested clarifying how to detect and mitigate biofilms.

Response: Comment not incorporated. This information is described in other sections of this General Chapter. This section is about understanding biofilm formation.

8.2.1. Biofilm-Forming Bacteria in Water Systems

Comment Summary #20: The commenter suggested omitting the term “pseudomonads.” Taxonomic revisions using nucleic acid hybridization and more recent ribosomal ribonucleic acid (rRNA) base sequencing have separated the genera

Burkholderia, *Ralstonia*, *Comamonas*, *Acidovorax*, *Defia*, *Hydrogenophagas*, *Brevundimobas*, *Stenotropomonas*, and *Xantomonas* from *Pseudomonas*.

Response: Comment not incorporated. The current term is accurate because these organisms (pseudomonads) share physiological and morphological characteristics. A clarification was added to indicate that these genera are members of the family of *Pseudomonadaceae*.

Comment Summary #21: The commenter suggested deleting *Methylobacterium* from the list of common microorganisms recovered from water system samples because this slow-growing species will probably not be recovered using the incubation time recommended in *Table 3*.

Response: Comment not incorporated. This is a general list of biofilm forming bacteria, and there is no expectation for recovery.

8.2.2. Non-Biofilm-Forming Bacteria in Water Systems

Comment Summary #22: The commenter suggested modifying the title of the subsection because enteric Gram-negative bacteria such as the members of the genera *Escherichia*, *Salmonella*, *Shigella*, *Serratia*, *Proteus*, *Enterobacter*, and *Klebsiella* are capable of forming biofilms in clinical situations that require richer nutrient levels than those found in water systems. Only *Escherichia*, *Salmonella*, and *Enterobacter* are used as indicator organisms.

Response: Comment partially incorporated. Some changes were incorporated for clarity and accuracy.

8.3. Microorganism Sources

Comment Summary #23: The commenter recommended deleting or shortening these sections because the division between exogenous and endogenous contamination is not particularly useful to the stakeholder.

Response: Comment not incorporated. This section provides practical information about potential sources of contamination.

Comment Summary #24: The commenter recommended clarifying the exogenous/endogenous classification because Environmental Protection Agency (EPA) Water Standards do not require an absolute absence of *E. coli*, but rather a limit on the frequency of isolation depending on the number of customers served by the water authority.

Response: Comment not incorporated. The absence of fecal coliforms is required, but a percentage of non-*E. coli* coliforms is permitted.

8.4. Endotoxin

Comment Summary #25: The commenter recommended revising the proposed definition of “Endotoxin” because the phrase “natural endotoxin complex” is not supported by current peer-reviewed scientific literature.

Response: Comment incorporated. Changes were made to be more general in describing endotoxins.

8.4.1. Sources

Comment Summary #26: The commenter suggested deleting the additional description of endotoxins in this section.

Response: Comment incorporated. The additional description was moved to the *Definition* section.

Expert Committee-Initiated Change #3: It was clarified that endotoxins may be introduced from the source water or may be released from cell surfaces of bacteria “in water systems biofilms” instead of bacteria “that colonize the water system.”

8.4.2. Removal and Control

Comment Summary #27: The commenter suggested incorporating distillation as a removal process.

Response: Comment incorporated.

8.5. Test Methods

Comment Summary #28: The commenter recommended eliminating the references to *USP* general chapters <61> and <62> as water testing methods. A standard method is preferred, and the literature suggests that spread plates should be incubated at 28°C for at least 5 days given the highest counts.

Response: Comment not incorporated. This section contains a general discussion about test method selection.

Comment Summary #29: The commenter suggested deleting the following sentence: “In general, users should select the method that recovers the highest planktonic microbial counts in the shortest time, thus allowing for timely investigations and remediation.” This requirement is difficult to achieve because the highest count may only be obtained with longer incubation periods (especially for water microorganisms).

Response: Comment not incorporated. The description in the section is aligned with current practices within the pharmaceutical water community.

Comment Summary #30: The commenter suggested deleting the following sentence: “In addition, the chosen method should be reassessed periodically, as the microbiome of a new water system gradually establishes a steady state relative to the system’s routine maintenance, use, and sanitization procedures.” This requirement for periodic re-evaluation of the test method for water testing is unnecessary.

Response: Comment incorporated.

Comment Summary #31: The commenter suggested clarifying that steady-state conditions take years to achieve and most bacteria found in water systems are in biofilms.

Response: Comment not incorporated. Biofilms are adapted to environmental/engineering/nutrient changes in water systems, but planktonic microbes could be significant.

8.5.1. Microbial Enumeration Considerations

Comment Summary #32: The commenter suggested deleting the following sentence: “However, from a PC perspective, this limitation is acceptable because it is the relative changes in the trends for water sample microbial counts that indicate the state of PC.”

This statement contradicts the extensive validation activity described previously in this section.

Response: Comment not incorporated. This is an informative general discussion.

Comment Summary #33: The commenter recommended clarifying that a sample from a point-of-use is not a grab sample, which is from a bulk material.

Response: Comment incorporated.

8.5.2. The Classical Cultural Approach

Comment Summary #34: The commenter suggested aligning this section with *Ph.Eur.*, *Japanese Pharmacopeia*, and Standard Methods for the Examination of Water and Wastewater and using only the one test method that best fits (e.g., R2A agar, minimum 5-day incubation, 30-35°C). The commenter suggested adding a footnote explaining that other methods may be used if more appropriate.

Response: Comment not incorporated. The intention of this chapter is not to be prescriptive, and currently it provides flexibility.

Comment Summary #35: The commenter suggested incorporating the APHA/AWWA standard methods for consistency and practicality. It is unrealistic for the average QC microbiologist to work through all the options in <1231> and select the best approach for their manufacturing site. Plate Count Agar is not a high-nutrient medium compared to soybean-casein digest agar (high) and R2A agar (low).

Response: Comment not incorporated. General information chapter <1231> provides more flexibility to users while selecting appropriate media. Its current text is high-level and appropriate for most stakeholders.

Comment Summary #36: The commenter recommended referencing the APHA/AWWA standard methods and sample storage, as the *USP* does not currently provide a suitable water testing method.

Response: Comment not incorporated. The use of alternative methods has been addressed previously based on public comments, and the current content provides flexibility.

8.5.2.1. Growth media

Comment Summary #37: The commenter suggested deleting the following sentence because it is not supported by literature and contradicts standard procedures and other pharmacopeias: “The use of R2A may not be the best choice for high-purity water systems. Even though high-purity water creates an oligotrophic environment, it has been shown empirically that in many high-purity compendial waters, the microbial count disparity between low- and high-nutrient media is dramatically less to nil, compared to potable water.”

Response: Comment not incorporated. The current content is not prescriptive, and there are documented experiences showing that oligotrophic microorganisms in pharmaceutical grade water could grow well on high-nutrient media.

Comment Summary #38: The commenter recommended providing evidence for the statement that R2A agar may not be the best choice for high-purity water systems because the stakeholders need a standard method for monitoring water.

Response: Comment not incorporated. Every water system is potentially different, and flexibility needs to be provided.

Expert Committee-Initiated Change #4: For clarity and consistency, the text regarding medium that has been demonstrated “as acceptable through comparative media analysis is recommended” was replaced with “through validation studies, to be the most optimal for the microbiome in a particular water system is essential.”

8.5.2.2. Incubation conditions

Comment Summary #39: The commenter suggested deleting the phrase comparing proposed incubation conditions that recover higher microbial counts “than classical compendial methods” because *USP* General Chapter <61> is not a compendial method for water testing.

Response: Comment not incorporated. *USP* General Chapter <61>, as well as test methods in other compendia such as “Standard Methods,” can be used as test parameter starting points for adapted use for *Purified Water* or *Water for Injection* with appropriate qualification of natural flora recovery efficacy.

8.5.2.3. Selection of method conditions

Expert Committee-Initiated Change #5: Some text originally located under 8.5.2.2. *Incubation Conditions* was moved to a new section titled 8.5.2.3. *Selection of method conditions* because it is not related to incubation. Additionally, the following sentence was added at the end of the new section for clarity: “The selection of method parameters should provide conditions that adequately recover microorganisms from the water system including those that are objectionable for the intended water use.”

8.5.3. Suggested Classical Cultural Methods/Table 3

Comment Summary #40: The commenter suggested replacing “Plate Count Agar” (PCA) with “R2A media” because R2A has been demonstrated to recover a much higher quantity of microorganisms than PCA (refer to the Reasoner et al. studies that led to the revision of the U.S. EPA Drinking Water Regulations). PCA is not the medium recommended in ISO 6222:1999, and the use of PCA favors the recovery of secondary contaminations during sampling as opposed to planktonic bacteria that are adapted to low-nutrient environments (which are recovered using R2A agar).

Response: Comment not incorporated. For the purpose of simplicity, *USP* cannot describe multiple media. The comments are accurate, but *USP* is retaining its historical method, which is similar to Japanese regulations for Drinking Water.

Comment Summary #41: The commenter recommended the following changes: replace the pour plate sample size of 1.0 mL with 1 mL, use PCA or R2A agar for the APHA/AWWA 9215 Heterotrophic Plate Count, adjust the sample size of 100 mL for purified water that has an action level of 100 CFU/mL, use a 0.45-micron porosity to yield the highest count and largest colony sizes, increase the incubation times, and reduce the incubation temperatures.

Response: Comment not incorporated. The pharmaceutical and microbiological community is aligned with the current official approach, and the chapter is not prescriptive.

Comment Summary #42: The commenter recommended stating that *Methylobacterium extorquens* are prepared cultures from commercial sources because

P. aeruginosa and *B. subtilis* as growth-promoting bacteria are rarely isolated from pharmaceutical grade water.

Response: Comment not incorporated. The current official approach is a current practice aligned with *Ph.Eur.* The chapter is not prescriptive.

Expert Committee-Initiated Change #6: The introduction to *Table 3* was replaced with the following sentence: “Example methods are presented in *Table 3*.” This change was made to emphasize that the chapter is not prescriptive and the table contains only examples of suggested classical cultural methods.

8.5.4. Microbial Identification

Comment Summary #43: The commenter suggested deleting “identify” from the stated needs because identifying without selecting would imply the need to identify all colonies detected on growth medium.

Response: Comment not incorporated. Identification of all colonies detected on growth medium is the intention of the sentence.

Comment Summary #44: The commenter suggested clarifying the definition of an objectionable microorganism because 21 CFR 211.113 defines objectionable microorganisms in terms of non-sterile drug products and not water.

Response: Comment not incorporated. Microorganisms may be objectionable for the type of water used to manufacture non-sterile products.

8.5.5. Rapid Microbiological Methods

Comment Summary #45: The commenter suggested providing additional guidance on this topic, including more technical details considering the description of the clear limitations of the classical test.

Response: Comment not incorporated. This is not a comprehensive General Chapter, but rather an introduction to the topic. This General Chapter refers to <1223> *Validation of Alternative Microbiological Methods* for further information on validation of rapid microbiological methods (RMM).

Comment Summary #46: The commenter suggested adding laser-induced autofluorescent particulate monitoring to the list of RMMs.

Response: Comment not incorporated. The list only provides examples as per <1223>.

Expert Committee-Initiated Change #7: One of the four categories of RMM was updated from “Artifact-Based” to “Metabolite-Based” for accuracy.

9.2. Examples of Critical Parameter Measurements

Comment Summary #47: The commenter suggested incorporating particulate matter routinely monitored in a water system as a critical measurement.

Response: Comment not incorporated. Particulate matter is not an attribute in pharmaceutical water systems.

9.3. Purpose of the Measurements

Comment Summary #48: The commenter suggested clarifying that processes have a natural variation, and that a monitoring program should demonstrate that a water system is in state of statistical control and detect a loss of control.

Response: Comment not incorporated. This general information chapter comprises a general discussion.

9.4. Defining Alert and Action Levels and Specifications

Comment Summary #49: The commenter recommended stating that Alert and Action Levels should be statistically based using historic monitoring data, e.g., a non-parametric confidence interval set at 95% for alert and 99% for action levels.

Response: Comment not incorporated. This general informational chapter provides high-level discussion and not specific statistical strategies.

Comment Summary #50: The commenter recommended clarifying that action levels for pharmaceutical grade water used in manufacturing as feed water, pharmaceutical ingredients, and cleaning materials are typically set for monitoring purposes at 500 cfu/mL for potable water, 100 cfu/mL for USP purified water, and 10 cfu/100 mL for USP water for injection. Alert or warning levels are typically determined from the statistical evaluation of the historic water monitoring data, and excursions may be identified using Western Electric trend rules or constructing a CUM-SUM control chart.

Response: Comment not incorporated. The described 3-tier approach is generally accepted, and specific statistical strategies are not provided in this chapter.

9.4.4. Specifications

Comment Summary #51: The commenter suggested clarifying the term “unbiased microbial monitoring” because Purified Water systems produce water for multiple uses and thus the specifications are usually driven by ingredient use. Cultural methods are highly selective for bacteria that grow on microbiological growth media under the incubation conditions employed.

Response: Comment incorporated.

9.4.5. Source Water Control

Comment Summary #52: The commenter suggested clarifying that the heterotrophic count of 500 cfu/mL is a measure of residual chlorine levels, limited biofilm formation, and good water circulation and should not be used as a potable water specification. Notification of boil alerts and routine review of quarterly water test report from water authorities should be recommended.

Response: Comment not incorporated. The count of 500 cfu/mL is not a specification; it is an action level with the appropriate response/reaction described.

Monographs

Monograph/Sections: Acamprosate Calcium/Multiple Sections

Expert Committee: Chemical Medicines 4

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the acceptance criterion for acetic acid from *Table 1* of the test for *Organic Impurities* because it already has an acceptance criterion of 5000 ppm (0.50%) in General Chapter <467> *Residual Solvents*.

Response: Comment incorporated.

Comment Summary #2: The commenter requested adding a storage temperature requirement.

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

EC-initiated change #1: In the test for *Organic Impurities*, the relative retention time for acetic acid was moved from *Table 1* into the *System suitability* section.

Monograph/Sections: Acetaminophen Tablets/Multiple sections

Expert Committee: Chemical Medicines 6

No. of Commenters: 3

Comment Summary #1: The commenter requested not replacing the General Chapter <227> test with the *Organic Impurities* test for monitoring 4-Aminophenol in acetaminophen-containing products because the impurity is already being monitored by the procedure outlined in the General Chapter.

Response: Comment not incorporated. The Expert Committee determined that the proposed *Organic Impurities* procedure and the acceptance criteria adequately monitors the drug product quality, as it not only monitors 4-aminophenol but also monitors other impurities and includes acceptance criteria for unspecified and total impurities.

Comment Summary #2: The commenter requested that sample preparation in the Assay be revised in support of a uniform and consistent sample preparation method by crushing and/or grinding the film-coated and chewable tablets.

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure allows for the whole tablet to be dissolved without crushing/grinding and does not have any inconsistencies in sample preparation.

Comment Summary #3: The commenter indicated that the chromatographic conditions for *Organic Impurities* are not aligned with Assay conditions, requiring the implementation of two different chromatographic procedures, and *Dissolution* continues to use a stand-alone spectrophotometric method.

Response: Comment not incorporated. The Expert Committee determined that the proposed revisions to the monograph are suitable for the intended purpose.

Monograph/Sections: Acetaminophen Oral Suspension/Multiple Sections

Expert Committee: Chemical Medicines 6

No. of Commenters: 2

Comment Summary #1: The commenter indicated that the previously validated Assay method developed in collaboration with multiple manufacturers was not fully considered for an official status.

Response: Comment not incorporated. The Expert Committee determined that the proposed Assay procedure is fully validated and is suitable for its intended purpose.

Comment Summary #2: The commenter stated that the proposed *Organic Impurities* procedure replaces a previously modernized organic impurity method described in General Chapter <227> and includes an additional specified impurity that is either adequately described or recognized as a key degradant.

Response: Comment not incorporated. The Expert Committee determined that the proposed *Organic Impurities* procedure and the acceptance criteria adequately monitors the drug product quality, as it monitors 4-aminophenol along with other impurities and includes acceptance criteria for unspecified and total impurities.

Comment Summary #3: The commenter stated the proposed changes are not in line with the USP monograph modernization strategy.

Response: Comment not incorporated. The Expert Committee determined that the proposal is consistent with USP's approach to include unspecified and total impurities into the monograph.

Monograph/Sections : Amitriptyline Hydrochloride/ Packaging and Storage

Expert Committee: Chemical Medicines 4

No. of Commenters: 1

Comment Summary #1: The commenter requested adding a storage temperature requirement.

Response: Comment not incorporated. The Expert Committee will consider revising this monograph in the future upon receipt of the necessary supporting data.

Monograph/Sections: Amlodipine and Atorvastatin Tablets/Organic Impurities

Expert Committee: Chemical Medicines 2

No. of Commenters: 1

Comment Summary #1: The commenter requested widening the disregard limits from <0.5% to <1.0% based on the International Conference on Harmonization (ICH) guidelines.

Response: Comment not incorporated. The Expert Committee decided to remove the disregard limit from the monograph to allow individual manufacturers to meet the disregard requirements in accordance with their FDA-approved applications.

Monograph/Sections: Ascorbic Acid Chewable Gels/Multiple Sections

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 3

Comment Summary #1: The commenter suggested increasing or eliminating the acceptance criteria for the upper limit in the *Definition*. It was proposed that product manufacturers could establish a suitable upper limit based on safety and stability studies conducted for the particular formulation.

Response: Comment not incorporated. The Expert Committee agreed that there is no adequate justification to consider additional changes to the proposed upper limit of NMT 150% of the labeled amount of ascorbic acid.

Comment Summary #2: The commenter proposed increasing the acceptance criteria for the pH value since product pH is highly dependent on the formulation and may be above the recommended value of NMT 3.7.

Response: Comment incorporated. The Expert Committee agreed to set the pH value at NMT 4.5.

Comment Summary #3: The commenter suggested removing the Water Activity acceptance criteria from the monographs. Although Water Activity is used to control product microbial contamination, specific microbial testing and microbial specifications are also listed in the monograph.

Response: Comment not incorporated. Water Activity is an important parameter for the quality of chewable gel products.

Comment Summary #4: The commenter suggested revising the *Packaging and Storage* section to remove the phrase, “protect from moisture,” and to add the phrase, “protect from heat.”

Response: Comment incorporated.

Monograph/Section: Azithromycin Tablets/Organic Impurities

Expert Committee: Chemical Medicines 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended including a note about the stability of Diluent A in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph.

Comment Summary #2: The commenter recommended tightening the pH range of the Buffer preparation in the test for *Organic Impurities*.

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

Comment Summary #3: The commenter requested revising the relative response factor values for Azithromycin N-oxide and 3'-(N,N-Didemethyl) Azithromycin impurities in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee will consider a future revision to the monograph.

Comment Summary #4: The commenter requested including the 3'-N-demethylazithromycin impurity in the system suitability solution for identification purposes.

Response: Comment not incorporated. The Expert Committee agreed that impurity identification by relative retention time is acceptable.

Monograph/Sections: Baclofen Tablets/ Assay and Organic Impurities

Expert Committee: Chemical Medicine 4

No. of Commenters: 1

Comment Summary #1: The commenter requested their methods for *Assay and Organic Impurities* be added as alternative methods to the proposed procedures.

Response: Comment not incorporated. The proposed *Assay and Organic impurities* methods are suitable for their intended use. The commenter may use alternative methods as described in *General Notices* Section 6.30, “Alternative and Harmonized Methods and Procedures”.

Monograph/Sections: Benzethonium Chloride/Organic Impurities

Expert Committee: Chemical Medicines 6

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the percent relative standard deviation requirement from NMT 1.0% to NMT 5.0% based on the 1 ug/mL *Standard solution*.

Response: Comment incorporated.

Monograph/Section: Brimonidine Tartrate/Organic impurities
Expert Committee: Chemical Medicines 3
No. of Commenters: 2

Comment Summary #1: The commenter recommended including relative response factors in *Table 1* and the calculations in the test for *Organic Impurities*.

Response: Comment not incorporated. The determination of organic impurities is consistent with the approved method.

Comment Summary #2: The commenter recommended revising the acceptance criteria for several organic impurities and total impurities to be consistent with FDA-approved limits.

Response: Comment incorporated. The tartrate and all specified impurities except for desbromobrimonidine have been deleted from *Table 1*. The following acceptance criteria have been changed to be consistent with FDA-approved limits: the limit of desbromobrimonidine was changed from NMT 0.10% to NMT 0.1%; the limit for any unspecified impurity was changed from NMT 0.10% to NMT 0.1%; and the limit for total impurities was changed from NMT 0.2% to NMT 0.3%.

Expert Committee-initiated Change #1: A note to disregard tartrate at a relative retention time of 0.09 was added to the test for *Organic Impurities*.

Expert Committee-initiated Change #2: A note was added to the test for *Organic Impurities* to indicate the relative retention times for brimonidine-related compound E and brimonidine, which are used to determine the resolution.

Expert Committee-initiated Change #3: The statement “Disregard any impurity peak less than 0.05%” was replaced with “The reporting threshold is 0.05%” in the test for *Organic Impurities*, to be consistent with current *USP* style.

Monograph/Sections: Calcium Citrate Malate/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements

Expert Committee-initiated Change #1: The acceptance criteria for individual contents of citrate and malate were replaced with the acceptance criteria for the sum of citrate and malate contents in the test for *Content of Citrate, Malate and Fumarate*.

Expert Committee-initiated Change #2: All the calculations in the *Assay* for calcium and in the test for *Content of Citrate, Malate and Fumarate* were changed from “on the as is basis” to “on the dried basis.”

Monograph/Sections : Carbidopa and Levodopa Extended-Release Tablets/
Organic Impurities

Expert Committee: Chemical Medicines 4

Expert Committee-initiated Change #1: In the test for *Organic Impurities*, the statements “for peaks associated with carbidopa, disregard peaks less than 0.05% of carbidopa from the *Sample solution*” and “for peaks associated with levodopa, disregard peaks less than 0.05% of levodopa from the *Sample solution*” were replaced with “the

reporting threshold is 0.05%, relative to the related drug substance” to be consistent with ICH Q3B terminology.

Monograph/Sections: Cholecalciferol Chewable Gels/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 3

Comment Summary #1: The commenter suggested increasing or eliminating the acceptance criteria for the upper limit in the *Definition*. It was proposed that product manufacturers could establish a suitable upper limit based on safety and stability studies conducted for the particular formulation.

Response: Comment not incorporated. The Expert Committee concluded that there is no adequate justification to consider additional changes to the proposed upper limit of NMT 140% (NMT 150% for dietary supplements) of the labeled amount of cholecalciferol.

Comment Summary #2: The commenter proposed increasing the acceptance criteria for the pH value since the product pH is highly dependent on the formulation and may be above the recommended value of NMT 3.6.

Response: Comment incorporated. The Expert Committee agreed to set the pH value at NMT 4.5.

Comment Summary #3: The commenter suggested removing the Water Activity acceptance criteria from the monographs. Although Water Activity is used to control product microbial contamination, specific microbial testing and microbial specifications are also listed in the monograph.

Response: Comment not incorporated. Water Activity is an important parameter for the quality of chewable gel products.

Comment Summary #4: The commenter suggested revising the *Packaging and Storage* section to remove the phrase, “protect from moisture,” and to add the phrase, “protect from heat.”

Response: Comment incorporated.

Monograph/Sections: Cholecalciferol Tablets/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2

Comment Summary #1: The commenter suggested increasing the acceptance criteria for the upper limit in the *Definition* due to product stability and overage issues.

Response: Comment incorporated. The Expert Committee agreed to increase the upper limit from NMT 110% to NMT 115%, which allows dietary supplement product manufacturers to increase the upper limit acceptance criteria to NMT 125% of the labeled amount of cholecalciferol.

Comment Summary #2: The commenter indicated that the manufacturer of the Poroshell 120 SB-AQ, 4.6-mm × 15-cm; 2.7- μ m column used for the *Assay* procedure did not confirm that the column has L56 packing, which is indicated in the monograph proposal.

Response: Comment incorporated. Based on the additional information received from the column manufacturer, the poroshell 120b SB-AQ column packing was corrected on L96.

Monograph/Section: Clarithromycin/Organic Impurities

Expert Committee: Chemical Medicines 1

Expert Committee-initiated Change #1: The text “See Table 2” was deleted from the test for *Organic Impurities* under the Acceptance Criteria section as an editorial correction.

Monograph/Sections: Coffee Fruit Dry Extract/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 3

Comment Summary #1: The commenter indicated the possibility of confusion by using 3-/4-/5-/mono-/di- substituted quinic acids for the names of caffeoylquinic acids in the Coffee Fruit Dry Extract monograph due to the evolving ring numbering using International Union of Pure and Applied Chemistry (IUPAC) nomenclature.

Response: Comment incorporated. The changes to the text are summarized as follows:

- a. Use the common names chlorogenic acid, neochlorogenic acid, cryptochlorogenic acid, isochlorogenic acid A, isochlorogenic acid B, and isochlorogenic acid C for the caffeoylquinic acids in the monograph.
- b. Include graphic conformational structures of the caffeoylquinic acids in the monograph.
- c. To address the nomenclature confusion, include a note stating, “These compounds are often referred in the literature as 3-/4-/5-/mono-/di- substituted quinic acids. Due to the confusion in historic and evolving IUPAC ring numbering, that nomenclature is not used in this pharmacopeia. Instead, the compounds are described by their conformational structures in the table above.”

Comment Summary #2: The commenter indicated that USP Lab test results showed that the high-performance liquid chromatography (HPLC) chromatograms displayed an additional peak after 5-*O*-feruloylquinic acid, while the sponsor’s HPLC chromatogram only displayed one peak, which should be a co-elution of 5-*O*-feruloylquinic acid with another constituent due to the low resolution of the column.

Response: Comment incorporated. A sentence was added after 5-*O*-feruloylquinic acid stating, “which typically co-elutes with another constituent and sometimes can be resolved into two peaks.”

Comment Summary #3: The commenter recommended corrected the conversion factors for isochlorogenic acid B, isochlorogenic acid A, and isochlorogenic acid C to 0.84, 0.80, and 0.80, respectively, based on USP lab test results.

Response: Comment incorporated. The conversion factors were revised from 0.92, 0.77, and 0.77 to 0.84, 0.80, and 0.80, respectively.

Monograph/Sections: Coix Seed/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 3
Comment Summary #1: The commenter indicated that ID B refers to *Standard solution A* and *Standard solution B* as defined in the test for *Content of Triglycerides*. The *Standard solutions* in the test for *Content of Triglycerides* are defined as 1-6.
Response: Comment incorporated. The monographs were modified to make the terms consistent.
Comment Summary #2: The commenter recommended referring to the trademarked column ZearalaTest™ as a footnote rather than in the text.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that a short column was used for sample preparation in the test of *Limit of Zearalenone*, but the text did not describe how to control the flow rates.
Response: Comment partially incorporated. When a short column is used for pre-purifying the sample, the specific flow rates can be controlled manually. The units “drops/s” was added in brackets after “mL/min” for the flow rate to make users easier to follow how to control the flow rate.

Monograph/Sections: Coix Seed Powder/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 3
Comment Summary #1: The commenter indicated that ID B refers to *Standard solution A* and *Standard solution B* as defined in the test for *Content of Triglycerides*. The *Standard solutions* in the test for *Content of Triglycerides* are defined as 1-6.
Response: Comment incorporated. The monographs were modified to make the terms consistent.
Comment Summary #2: The commenter recommended referring to the trademarked column ZearalaTest™ as a footnote rather than in the text.
Response: Comment incorporated.
Comment Summary #3: The commenter indicated that a short column was used for sample preparation in the test of *Limit of Zearalenone*, but the text did not describe how to control the flow rates.
Response: Comment partially incorporated. When a short column is used for pre-purifying the sample, the specific flow rates can be controlled manually. The unit “drops/s” was added in brackets after “mL/min” for the flow rate to make users easier to follow how to control the flow rate.

Monograph/Sections: Dorzolamide Hydrochloride and Timolol Maleate Ophthalmic Solution/Multiple Sections
Expert Committee: Chemical Medicines 3
No. of Commenters: 1
Comment Summary #1: The commenter requested updating the chemical name for USP Dorzolamide Related Compound B RS to reflect that it is a racemic mixture in <11> *USP Reference Standards*.
Response: Comment incorporated.

Expert Committee-initiated Change #1: To be consistent with current USP style, the statement “Disregard any impurity peaks less than 0.10%” was replaced with “The reporting threshold is 0.10%” in the test for *Organic Impurities*.

Monograph/Section: Flax Seed Oil/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1

Comment Summary #1: The commenter indicated that there is a special variety of flax that produces oil with at least 70% alpha-linolenic acid (ALA), which causes the oil to have a slightly different fatty acid profile as well as higher iodine values. The commenter recommended either expanding the limit for ALA in the fatty acid composition and the iodine value, or developing a new monograph for Flax Seed Oil with high ALA content.

Response: Comment not incorporated. The Expert Committee recommended soliciting a sponsorship from industry to develop a new monograph for Flax Seed Oil with high ALA content.

Monograph/Section: Glyceryl Tricaprylate/Bacterial Endotoxins Test
Expert Committee: Excipients Monographs 1
No. of Commenters: 1

Comment Summary #1: The commenter suggested clarifying that the *Bacterial Endotoxins Test* is only a requirement when the product is used in parenteral applications.

Response: Comment incorporated. The following sentence was deleted: “The level of bacterial endotoxins is such that the requirement in the relevant dosage form monograph(s) in which Glyceryl Tricaprylate is used can be met.”

Monograph/Sections: Glycine/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 7

Impurities—Related compounds test

Comment Summary #1: The commenter suggested modifying the gradient elution table, including a cleaning step to eliminate the artifacts observed in the blank (*Diluent*).

Response: Comment not incorporated. The artifacts, if observed in the blank, are mainly due to the impurities of the reagents used to prepare the *Diluent*. Because these artifacts are early eluted peaks, a cleaning step would not help prevent their appearance in subsequent injections. The only way to minimize the appearance of the artifacts is to use high-purity reagents.

Comment Summary #2: The commenter indicated that the glycine peak response from the *Standard solution* was low, and it was difficult to meet the repeatability requirement.

Response: Comment not incorporated. Validation data from the USP labs and other collaborative labs showed that the glycine peak response had a signal-to-noise (S/N) ratio of NLT 10, and the relative standard deviation for the repeated injections met the requirement of NMT 5.0%.

Comment Summary #3: The commenter indicated that the name of the impurity for glycine, Imido-diacetic acid, was incorrectly spelled. The correct name for this impurity is Iminodiacetic acid.

Response: Comment incorporated.

Comment Summary #4: The commenter indicated that they found a very small peak (artifact) from the blank that interfered with the glycine anhydride peak in the *Standard solution*. The area of the artifact peak was approximately 0.07% of the area of the glycine anhydride peak.

Response: Comment was partially incorporated. Because the artifact is very small, it has no significant impact on the determination of glycine anhydride impurity. To address the issue, the Expert Committee recommended that the following requirement be added to the System suitability requirements: "The area of any peak from the *Blank* that overlaps or co-elutes with the amino acid peak from the *Standard solution* is NMT 2.0% of the area of that amino acid peak."

Comment Summary #5: The commenters suggested changing the analytical ultraviolet (UV) wavelength from 200 nm to 210 nm because 200 nm is out of the calibration range for some instruments. In addition, they commented that 200 nm is close to the acetonitrile UV cut off.

Response: Comments not incorporated. At 210 nm, Glycine's impurities (such as hexamethylenetetramine) have shown a poor response, and the detection has been below the limit of quantitation.

Comment Summary #6: The commenter indicated that it is difficult to identify monochloroacetic acid and iminodiacetic acid based on the relative retention times.

Response: Comment not incorporated. The identification of monochloroacetic acid in the *Sample solution* should be based on the retention time of monochloroacetic acid observed from the *Standard solution*. While the identification of iminodiacetic acid is based on the relative retention times listed in *Table 2*, if the analyst is in doubt, they can inject the substance separately to confirm the identity of the impurity.

Comment Summary #7: The commenter suggested changing the limit requirement for monochloroacetic acid from NMT 0.05% to "the limit should be controlled as per ICH M7." The requirement is stated in footnote #1 of *Table 2*.

Response: Comment incorporated.

Comment Summary #8: The commenter suggested changing the limit requirement for the unspecified impurities from NMT 0.1% to "the limit should be based on the Maximum Daily Dose (MDD) of the drug products." The requirement is stated in footnote #2 of *Table 2*.

Response: Comment incorporated.

Packaging and Storage

Comment Summary #9: The commenter suggested adding a temperature requirement to the Glycine storage requirements.

Response: Comment incorporated.

Monograph/Section: Levocarnitine/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

Comment Summary #1: The commenter recommended adding a temperature requirement under “Packaging and Storage.”

Response: Comment incorporated.

Comment Summary #2: The commenter recommended adding a test for Organic impurities (OI).

Response: Comment not incorporated. Due to the absence of a validated OI procedure at this time, adding the test for an OI procedure will be pursued in future revisions.

Monograph/Section: Lidocaine/Packaging and Storage
Expert Committee: Chemical Medicines 6
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the storage conditions from “store at room temperature” with “store at controlled room temperature.”

Response: Comment not incorporated. The Expert Committee determined that the proposal as written is consistent with the validation data and is suitable for the intended purpose.

Monograph/Section: Methotrexate Injection/Organic Impurities
Expert Committee: Chemical Medicines 3

Expert Committee-initiated Change #1: The statement “Disregard any unspecified degradation product peaks less than 0.1%” was replaced with “The reporting threshold is 0.1%” in the test for *Organic Impurities*, to be consistent with current USP style.

Monograph/Sections: Miconazole Nitrate/Multiple sections
Expert Committee: Chemical Medicines 6
No. of Commenters: 2

Comment Summary #1: The commenter suggested adding structures for the organic impurities in the monograph.

Response: Comment not incorporated. The proposal is consistent with the current USP style, and organic impurity structures will be provided upon manufacturer’s request.

Comment Summary #2: The commenter recommended adding “controlled room temperature” under *Packaging and Storage*.

Response: Comment incorporated. Additional storage requirement is added based on the supporting data.

Monograph/Section: Minocycline Hydrochloride/Multiple Sections
Expert Committee: Chemical Medicines 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended adding an Identification test for chloride.

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

Comment Summary #2: The commenter recommended including chemical structures for impurities.

Response: Comment not incorporated. Inclusion of structures for impurities will be considered in the future.

Comment Summary #3: The commenter recommended including a storage temperature.

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

Monograph/Sections: Nicotine Transdermal System/Multiple Sections

Expert Committee: Chemical Medicines 4

No. of Commenters: 2

Comment Summary #1: The commenter indicated that the assay acceptance criterion is inconsistent with what has been approved by the FDA.

Response: Comment incorporated. The assay acceptance criterion is consistent with what has been approved by the FDA for the monograph sponsor when normalized to reflect the label claim.

Comment Summary #2: The commenter indicated that formulation differences would prevent the successful determination of the Assay due to incomplete extraction of nicotine from the sample matrix.

Response: Comment incorporated. An alternative sample preparation procedure that allows for the complete extraction of nicotine was added. The same *Sample solution* can also be used for the *Organic impurities* test.

Comment Summary #3: The commenter indicated that the System suitability solution in Drug Release test 2 uses an incorrect conversion factor.

Response: Comment incorporated. The appropriate correction factor has been included.

Comment Summary #4: The commenter indicated that the proposed limits for *Organic impurities* are tighter than the FDA approved limits for their product.

Response: Comment incorporated by widening the limits to be consistent with what has been approved by the FDA.

Comment Summary #5: The commenter requested that an identification test based on General Chapter <1119> *Near-Infrared Spectroscopy* be added as an alternative test.

Response: Comment not incorporated. The current identification tests are suitable for their intended use. The commenter can use an alternative test as described in *General Notices Section 6.30*, "Alternative and Harmonized Methods and Procedures."

Expert Committee initiated Change #1: The Assay acceptance criterion was widened to be consistent with the FDA approved limits.

Monograph/Section(s): Omega-3-Acid Ethyl Esters capsules/Assay

Expert Committee: Non- Botanical Dietary Supplements

No. of Commenters: 1

Comment Summary: The commenter indicated that there were differences between the Assay procedures described in the current Omega-3 Acid Ethyl Esters and the Omega-3 Acid Ethyl Esters Capsules monographs.

Response: Comment not incorporated. The comment was not related to the revision subject and can therefore be addressed through the regular revision in the future if necessary.

Monograph/Sections: Pantoprazole Sodium/Multiple Sections

Expert Committee: Chemical Medicines 3

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the *Packaging and Storage* section to state “store at controlled room temperature” instead of “room temperature.”

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

Expert Committee-Initiated Change: The note stating “Protect solutions containing pantoprazole sodium from light, and use amber autosampler vials and low actinic glassware” was replaced with “Protect solutions containing pantoprazole sodium from light” to provide flexibility in the *Assay* and the test for *Organic Impurities*.

Monograph/Sections: Pentazocine/Multiple Sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the limits for Norpentazocine and Pentazocine hydration products to be consistent with ICH limits.

Response: Comment incorporated. As confirmed by FDA, the Expert Committee determined to revise the specified impurity limits from 0.10% to 0.15% for Norpentazocine and Pentazocine hydration products to be consistent with ICH limits.

Comment Summary #2: The commenter recommended adding “controlled room temperature” to the storage conditions.

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

Monograph/Sections: Prasugrel Hydrochloride/Multiple sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 4

Comment Summary #1: The commenter recommended adding “controlled room temperature” as the storage condition.

Response: Comment not incorporated. The Expert Committee will consider a future revision based on the receipt of supporting documentation.

Comment Summary #2: The commenter requested widening the limit for water determination, as the drug substance is known to be hygroscopic.

Response: Comment not incorporated. The Expert Committee determined that the acceptance criterion for water determination is consistent with the FDA-approved specification.

Comment Summary #3: The commenters indicated that the retention time for prasugrel using *Organic impurities, Procedure 1* is different than the proposed retention time for prasugrel.

Response: Comment not incorporated. The Expert Committee determined that the proposed retention time is consistent with the validation data and is provided for informational purposes only.

Comment Summary #4: The commenter indicated that desacetyl prasugrel diastereomer 1 and desacetyl prasugrel diastereomer 2 are very closely eluting under *Organic Impurities, Procedure 2* and requested that USP adopt their procedure for the impurity analysis.

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

Comment Summary #5: The commenter indicated that *Organic impurities, Procedure 1* uses a sample cooler indicating that there could be solution stability concern; however, the conditions are different for *Organic Impurities, Procedure 2*.

Response: Comment not incorporated. The Expert Committee determined that the chromatographic conditions are consistent with the validation data and the FDA-approved application.

Comment Summary #6: The commenter indicated that they are unable to comment on the impurities that are not available at USP and that there is not enough time to synthesize before the comment period.

Response: Comment not incorporated. The Expert Committee will consider a future revision as needed.

Comment Summary #7: The commenter indicated that O-acetyl Thiolactone Hydrochloride is an impurity that is not listed in the proposed *Organic Impurities Procedure 1* and is eluted near the dwell volume.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of additional supporting data.

Comment Summary #8: The commenter indicated that under *Organic Impurities Procedure 1*, the signal/noise ratio using the *sensitivity solution* dropped below 10 after about 30 hrs.

Response: Comment not incorporated. The Expert Committee determined that the proposed signal/noise ratio in the *sensitivity solution* is consistent with the validation data and is suitable as written for the intended purpose.

Comment Summary #9: The commenter indicated that a negative baseline was observed at the retention time of desacetyl prasugrel in the blank under *Organic Impurities Procedure 1*.

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

Comment Summary #10: The commenter indicated that the prasugrel 2,3-C isomer not listed in *USP* is co-eluting with the prasugrel peak under *Organic Impurities Procedure 2*.

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

Comment Summary #11: The commenter indicated that 3-fluro prasugrel is not well separated from prasugrel under *Organic Impurities Procedure 2*.

Response: Comment not incorporated. The 3-fluro prasugrel is monitored using *Organic Impurity Procedure 1*, and the Expert Committee will consider future revisions as needed.

Comment Summary #12: The commenter indicated that the baseline is not satisfactory at the Retention Time around 18 min and 25 min in *Organic Impurities Procedure 2*.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Comment Summary #13: The commenter indicated that the sample solution is unstable at 25° and no autosampler temperature was mentioned in *Organic Impurities Procedure 2*.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Comment Summary #14: The commenter indicated that prasugrel thiolactone, a specified impurity, is coeluting with 4-fluoro prasugrel and closely eluting with 3-fluoro prasugrel under *Organic Impurities Procedure 1*.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data and full product approval by FDA.

Comment Summary #15: The commenter indicated that the resolution of NLT 1.5 between desacetyl prasugrel diastereomer 1 and desacetyl prasugrel diastereomer 2 decreased with time under *Organic Impurities Procedure 1*.

Response: Comment not incorporated. The Expert Committee determined that the requirements in the proposal are consistent with the validation data.

Comment Summary #16: The commenter indicated that an in-house impurity (methyl keto impurity) is closely eluting with des fluoro prasugrel and co-eluting with the prasugrel peak under *Organic Impurities Procedure 2*.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Comment Summary #17: The commenter indicated that fluoro prasugrel and an in-house impurity (thiophene) are co-eluting with the prasugrel peak under *Organic Impurities Procedure 2*.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Comment Summary #18: The commenter indicated that the proposed HPLC column for *Organic Impurities Procedure 2* is not stable in the mobile phase as indicated by the column pressure after repeated injections, and requested that USP adopt their in-house procedure.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting data.

Monograph/Sections: Pravastatin Sodium/Multiple sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the acceptance criterion for “Organic impurities,” “pH,” and “Water Determination,” tests are different from those in the FDA-approved applications.

Response: Comments not incorporated. The Expert Committee determined that the acceptance criteria are a part of the currently official *USP* monograph and will consider future revisions as needed.

Monograph/Section: Pralidoxime Chloride/Multiple Sections

Expert Committee: Chemical Medicines 3

No. of Commenters: 2

Comment Summary #1: The commenter recommended adding decimal places to the limits of all the impurities in the test for *Organic Impurities*.

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

Comment Summary #2: The commenter recommended updating System suitability requirements for Tailing factor and Relative standard deviation to specify the peak.

Response: Comment incorporated. The Tailing factor and Relative standard deviation requirements were updated to include “pralidoxime chloride peak.”

Monograph/Section: Pralidoxime Chloride for Injection/Packaging and Storage

Expert Committee: Chemical Medicines 3

No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the Packaging and Storage section to include “store at controlled room temperature.”

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

Comment Summary #2: The commenter recommended updating System suitability requirements for Tailing factor and Relative standard deviation to specify the peak.

Response: Comment incorporated. The Tailing factor and Relative standard deviation requirements were updated to include “pralidoxime chloride peak.”

Monograph/Section: Raltegravir Tablets/Identification

Expert Committee: Chemical Medicines 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended including the option to perform either the ultraviolet diode array detector (UV-DAD) or an infrared (IR) test for *Identification* to provide a flexible approach and harmonize with the European Directorate for the Quality of Medicines (EDQM).

Response: Comment not incorporated. USP typically does not provide flexibility for *Identification* tests.

Monograph/Section: Raltegravir Chewable Tablets/Assay

Expert Committee: Chemical Medicines 1

No. of Commenters: 1

Comment Summary #1: Commenter requested revising the wording in the Assay to clarify the Sample stock solution preparation.

Response: Comment incorporated.

Monograph/Sections: Rizatriptan Benzoate Orally Disintegrating Tablets/
Multiple Sections

Expert Committee: Chemical Medicines 4

No. of Commenters: 3

Comment Summary #1: The commenter requested that the cuvette path length be specified in *Dissolution test 1*.

Response: Comment not incorporated. As per General Chapter <857> *Ultraviolet-Visible Spectroscopy*, "Unless otherwise directed in the monograph, analysts make determinations at room temperature using a path length of 1 cm."

Comment Summary #2: The commenter indicated that in *Dissolution test 2*, a shift was observed in the analyte retention time when using the L7 column listed in the proposal and some other brands of L7 columns that were evaluated.

Response: Comment not incorporated. The sponsor used the column listed in the proposal during the validation; other brands of L7 columns are available to use for the test. The Expert Committee will consider future revisions to the monograph upon receipt of necessary supporting data.

Comment Summary #3: In the *Organic impurities* procedure, the commenter requested that the relative response factors listed as 1.0 in *Table 1* be investigated further because their experimentally determined values for the same degradation products were outside of the 0.8-1.2 range and thus should not be rounded to 1.0.

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

Monograph/Sections: Rosuvastatin Calcium/Multiple Sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 5

Comment Summary #1: The commenter requested clarifying the purpose of the System suitability solution prepared by using four different solutions in *Assay* and *Organic Impurities* and verifying whether there is a need for a 10°C auto sampler temperature.

Response: Comment not incorporated. The Expert Committee determined that the proposal as written is consistent with the validation data with no requirement for a 10°C auto sampler temperature, and indicated that the *System suitability solution* is used for resolution and also for peak identification.

Comment Summary #2: The commenter requested providing the chemical name for the Rosuvastatin dehydro analog under *Organic Impurities*.

Response: Comment incorporated. The chemical name for the Rosuvastatin dehydro analog, (S,2ZE,6E)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethyl-sulfonamido)pyrimidin-5-yl]-5-hydroxyhepta-2,6-dienoic acid, is included as a footnote in *Table 2*.

Comment Summary #3: The commenter requested revising the chemical name for Rosuvastatin B2 to Rosuvastatin ketone under *Organic Impurities* to be consistent with the drug product proposal.

Response: Comment incorporated.

Comment Summary #4: The commenter requested deleting the reference to footnote d for Rosuvastatin lactone under *Organic Impurities*, as it is a specified impurity and has an acceptance criterion similar to a specified impurity.

Response: Comment incorporated.

Comment Summary #5: The commenter recommended including a quantitative test for calcium.

Response: Comment not incorporated. The Expert Committee determined that the *Identification* test for calcium, together with other identification tests and quantitative tests, is adequate for monitoring the drug substance quality.

Comment Summary #6: The commenter recommended including a storage temperature.

Response: Comment not incorporated. The Expert Committee revised the proposed storage temperature from “store at controlled cold temperature” to “store at controlled room temperature” to be consistent with the product package insert.

Comment Summary #7: The commenter recommended adding an X-ray Identification test and a microbial test.

Response: Comment not incorporated. The Expert Committee determined that the proposal as written is suitable for the intended purpose and will consider future revisions as needed.

Comment Summary #8: The commenter recommended adding a test for a process-specific impurity, Rosuvastatin 6,7-dihydro, along with acceptance criteria under *Organic Impurities*, as it is currently not listed in the proposal.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #9: The commenter recommended adding butylatedhydroxyanisole as a stabilizer under the *Definition* section.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #10: The commenter recommended including a storage temperature of up to 25°C.

Response: Comment incorporated. The Expert Committee revised the proposed storage temperature from “store at controlled cold temperature” to “store at controlled room temperature” to be consistent with the product package insert.

Monograph/Sections: Rosuvastatin Tablets/Multiple Sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 6

Comment Summary #1: The commenter requested including their in-house procedures in this monograph.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #2: The commenter requested revising the transcription error in column length from 25 cm to 5 cm under *Dissolution Test 1*.

Response: Comment incorporated.

Comment Summary #3: The commenter requested deleting *Dissolution Test 2*

Response: Comment not incorporated. The Expert Committee determined that the proposal as written is consistent with the FDA-approved applications.

Comment Summary #4: The commenter requested adding a new Dissolution test based on their FDA-approved application.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #5: The commenter indicated that the Assay procedure is not specific, as the rosuvastatin diastereomer is not well separated from the rosuvastatin peak.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #6: The commenter indicated that the USP Rosuvastatin Calcium RS is not completely soluble in the *Diluent* mentioned in *Dissolution Test 1*.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #7: The commenter indicated that the Rosuvastatin diastereomer is coeluting with the main peak in the sample solution, although it is separated in the *System suitability solution*.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #8: The commenter recommended revising the concentration of rosuvastatin in the *System suitability solution* under *Organic Impurities* from 50 ppm to 1000 ppm.

Response: Comment not incorporated. The Expert Committee determined that the proposal as written is consistent with the validation data and will consider future revisions as needed.

Comment Summary #9: The commenter indicated that under *Organic Impurities*, the peak shape of Rosuvastatin Related compound A is not satisfactory, as an unknown peak is coeluting with it.

Response: Comment not incorporated. The Expert Committee will consider future revisions upon receipt of supporting information.

Comment Summary #10: The commenter requested widening the disregard limit under *Organic Impurities* from <0.5% to <1.0% based on the ICH guidelines.

Response: Comment not incorporated. The Expert Committee deleted the disregard limit from the monograph to allow the individual manufacturers meet the disregard requirements in accordance with their FDA-approved applications.

Monograph/Section: Sodium Fluoride Oral Solution/Assay

Expert Committee: Chemical Medicines 6

No. of Commenters: 2

Comment Summary #1: The commenter recommended adding an alternative column that meets the performance criteria in addition to the one defined in the monograph proposal based on the supporting equivalency data.

Response: Comment incorporated. The Expert Committee added the alternative column specifications to the column database as a suitable alternative column for the proposed Assay procedure.

Comment Summary #2: The commenter recommended retaining the currently official ion-selective electrode (ISE) based procedure for Assay.

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is specific and is suitable as written.

Monograph/Section: Sodium Fluoride and Acidulated Phosphate Topical Solution/Assay

Expert Committee: Chemical Medicines 6

No. of Commenters: 1

Comment Summary #1: The commenter recommended retaining the currently official ion-selective electrode (ISE) based Assay procedure

Response: Comment not incorporated. The Expert Committee determined that the proposed procedure is specific and is suitable as written.

Monograph/Sections: Somatropin/Multiple Sections

Expert Committee: Biologics 2 - Proteins

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the text in the briefing that describes the preparation of the Sample Solution in the test for *Total Protein Content*.

Response: Comment not incorporated. The briefing will not remain in the chapter when it moves to the official publication.

Comment Summary #2: The commenter requested clarifying the intended purpose of the <857> *Ultraviolet –Visible Spectroscopy* method used in the calculation of total protein.

Response: Comment incorporated. The statement, “The method is used in the calculation of total protein in the assay of bulk solution,” was added to the Specific Tests: Total Protein Content section after the text, “(See Ultraviolet –Visible Spectroscopy <857>).”

Monograph/Section: Sumatriptan Nasal Spray/Limit of Sumatriptan Related Compound A

Expert Committee: Chemical Medicines 4

Expert Committee-initiated Change #1: The definition of C_s in the test Limit of Sumatriptan Related Compound A was corrected from “concentration of USP Sumatriptan Succinate RS (mg/mL)” to “concentration of USP Sumatriptan Related Compound A RS (mg/mL).”

EC-initiated change #2: The concentration of the standard solution was changed from 7 $\mu\text{g/mL}$ to 0.007 mg/mL of USP Sumatriptan Succinate Related Compound A to match the units used in the calculation formula.

Monograph/Section: Taurine/Multiple Sections

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 3

Comment Summary #1: The commenter reported that they found the method to be adequate for determining taurine, but they had some difficulty in consistently meeting the proposed requirement of NLT 0.995 for the correlation coefficient of the regression

line. Since the %RSD is 2.0% for the proposed Assay, the proposed correlation coefficient may be too restrictive. The method also appears to be quite sensitive to minor variations in conditions. Based on these observations, they recommended modifying the proposal to reflect a correlation coefficient of NLT 0.99.

Response: Comment not incorporated. The USP collaborative tests consistently showed that they met the method's acceptance criteria and achieved a correlation coefficient of 0.9999. It is advised that the linearity curve be plotted on a log-log scale, and therefore it is expected to be sufficiently linear.

Comment Summary #2: The commenter noted that the HPLC method uses an unconventional evaporative light scattering detector (ELSD), which may not be available in many laboratories. Therefore, they recommended the use of alternative approaches, such as detection with traditional UV detectors using post-column derivatization with o-Phthalaldehyde.

Response: Comment not incorporated. ELSD has been employed due to the lack of chromophore groups in the taurine molecule and the common drawbacks of derivatization methods.

Monograph/Section: Tranexamic Acid Injection/Organic Impurities

Expert Committee: Chemical Medicines 2

No. of Commenters: 2

Comment Summary #1: The commenter requested revising the acceptance criterion for "Total impurities" to be consistent with what has been approved by the FDA.

Response: Comment not incorporated. The Expert Committee revised the unspecified impurity limit from NMT 0.10% to NMT 0.1% to be consistent with the FDA-approved applications.

Comment Summary #2: The commenter recommended including the acceptance criteria for specified impurities in the monograph.

Response: Comments not incorporated. The Expert Committee will consider future revisions as needed.

Monograph/Section: Tranlycypromine Tablets/Organic impurities

Expert Committee: Chemical Medicines 4

Expert Committee-initiated Change #1: The name of the reference standard in the *Standard solution* was corrected from "USP Tranlycypromine RS" to "USP Tranlycypromine Sulfate RS."

Monograph/Section: Triamterene/Organic Impurities

Expert Committee: Chemical Medicines 2

No. of Commenters: 2

Comment Summary #1: The commenter indicated that the *Standard stock solution 1* was hazy when prepared at the proposed concentration using the instructions in the *Organic Impurities* procedure.

Response: Comments incorporated. The Expert Committee revised the concentration of the *Standard stock solution* from 1 mg/mL to 0.25 mg/mL to aid in solubility.

Comment Summary #2: The commenter recommended revising the concentration of the Sample solution due to solubility issues under the *Organic Impurities* procedure.

Response: Comment not incorporated. The Expert Committee included a note to indicate that “Sonication may be needed to aid the dissolution.”

Monograph/Section: Valerian Root Dry Extract Capsules;
Valerian Root Powder Capsules

Expert Committee: Botanical Dietary Supplements and Herbal Medicines
Expert Committee

No. of Commenters: 1

Comment Summary: The commenter indicated that the Family for Valerian has been revised to Caprifoliaceae and suggested rephrasing the family name as “(Fam. Caprifoliaceae, formerly Valerianaceae) in the *Definition* of both monographs for clarity.

Response: Comment incorporated.