



Commentary

USP 42–NF 37

November 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.

For further information, contact:
USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA

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

General Chapters

[General Notices to USP-NF](#)

[<7> Labeling](#)

[<197> Spectrophotometric Identification Tests](#)

[<561> Articles of Botanical Origin](#)

[<630> Visual Comparison](#)

[<855> Nephelometry, Turbidimetry, and Visual Comparison](#)

[<1090> Assessment of Drug Product Performance--Bioavailability, Bioequivalence, and
Dissolution](#)

[<1217> Tablet Breaking Force](#)

Monographs

[Acarbose Tablets](#)

[Azithromycin](#)

[Azithromycin for Oral Suspension](#)

[Bendroflumethiazide](#)

[Beta Carotene Capsules](#)

[Betahistine Hydrochloride](#)

[Calcium Acetate Capsules](#)

[Cefprozil](#)

[Chlorothiazide Compounded Oral Suspension](#)

[Citicoline Sodium](#)

[Clomipramine Hydrochloride Capsules](#)

[Cytarabine](#)

[Dexamethasone Ophthalmic Suspension](#)

[Dichlorphenamide](#)

[Dihydrocodeine Bitartrate](#)

[Disulfiram Tablets](#)

[Doxylamine Succinate](#)

[Doxylamine Succinate Tablets](#)

[Estriol](#)

[Ethosuximide Capsules](#)

[Ethosuximide Oral Solution](#)

[Felodipine Extended-Release Tablets](#)

[Fenofibrate Capsules](#)

[Fentanyl Citrate and Bupivacaine Hydrochloride Compounded Injection](#)

[Fentanyl Citrate Compounded Injection](#)

[Fentanyl Citrate and Ropivacaine Hydrochloride Compounded Injection](#)

[Fluconazole](#)

[Fluorescein Injection](#)

[Guanabenz Acetate Tablets](#)

[Heparin Lock Flush Solution](#)

[Heparin Sodium Injection](#)

[Hydrochlorothiazide Capsules](#)

[Isosorbide Dinitrate Tablets](#)

[Levalbuterol Hydrochloride](#)

[Levalbuterol Inhalation Solution](#)

[Loperamide Hydrochloride](#)
[Mefenamic Acid Capsules](#)
[Methoxsalen Capsules](#)
[Methoxsalen Topical Solution](#)
[Metoprolol Tartrate Injection](#)
[Mitoxantrone Hydrochloride](#)
[Mitoxantrone Injection](#)
[Mycophenolate Mofetil for Injection](#)
[Mycophenolate Mofetil for Oral Suspension](#)
[Nicotine Polacrilex](#)
[Nifedipine Capsules](#)
[Oxazepam](#)
[Trandolapril](#)
[Triamcinolone Acetonide Nasal Spray](#)
[Vitamins with Minerals Oral Powder](#)

No comments were received for the following proposals:

General Chapters

<1160> Pharmaceutical Calculations in Pharmacy Practice
<1176> Prescription Balances and Volumetric Apparatus Used In Compounding

Monographs

Altretamine
Altretamine Capsules
Ashwagandha Root
Bisacodyl
Butylated Hydroxyanisole
Calcitriol
Cefepime Hydrochloride
Chromium Cr 51 Edetate Injection
Chromic Phosphate P 32 Suspension
Doxycycline Hyclate Delayed-Release Tablets
Eleuthero Root and Rhizome Dry Extract Capsules
Eleuthero Root and Rhizome Dry Extract Tablets
Emetine Hydrochloride
Emetine Hydrochloride Injection
Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension
Ethosuximide
Fenofibrate Tablets
Fingolimod Hydrochloride
Guaifenesin Compounded Injection, Veterinary
Indium In 111 Ibritumomab Tiuxetan Injection
Indium In 111 Satumomab Pendetide Injection
Iobenguane I 131 Injection
Iodohippurate Sodium I 123 Injection
Iodohippurate Sodium I 131 Injection
Krill Oil Capsules
Krill Oil Delayed-Release Capsules
Lycopene

Lycopene Preparation
Methoxsalen
Paroxetine Hydrochloride
Phenmetrazine Hydrochloride
Phenmetrazine Hydrochloride Tablets
Powdered Ashwagandha Root
Powdered Ashwagandha Root Extract
Promethazine and Phenylephrine Hydrochloride Oral Solution
Propylene Glycol Diacetate
Rhodiola rosea Capsules
Rhodiola rosea Tablets
Risperidone Orally Disintegrating Tablets
Rose Bengal Sodium I 131 Injection
Sodium Phosphate P 32 Solution
Suprofen
Suprofen Ophthalmic Solution
Technetium ^{99m}Tc Fanolesomab Injection
Technetium Tc 99m Albumin Colloid Injection
Technetium Tc 99m Albumin Injection
Technetium Tc 99m Apcitide Injection
Technetium Tc 99m Arcitumomab Injection
Technetium Tc 99m Depreotide Injection
Technetium Tc 99m Etidronate Injection
Technetium Tc 99m Gluceptate Injection
Technetium Tc 99m Lidofenin Injection
Technetium Tc 99m Nofetumomab Merpentan Injection
Temozolomide for Injection
Terazosin Tablets
Tienchi Ginseng Root and Rhizome
Tienchi Ginseng Root and Rhizome Dry Extract
Tienchi Ginseng Root and Rhizome Dry Extract Capsules
Tienchi Ginseng Root and Rhizome Dry Extract Tablets
Tienchi Ginseng Root and Rhizome Powder
Tienchi Ginseng Root and Rhizome Powder Capsules
Tienchi Ginseng Root and Rhizome Powder Tablets
Tomato Extract Containing Lycopene
Valproic Acid Oral Solution
Verapamil Hydrochloride Injection
Vincristine Sulfate
Witch Hazel
Xenon Xe 127
Xenon Xe 133 Injection
Zinc Oxide Compounded Ointment
Zinc Oxide Compounded Paste

General Chapters

General Chapter/Section(s): General Notices/Section 2.20 Official Articles
Expert Committee: Council of Experts
No. of Commenters: 10

2.20. Official Articles

Comment Summary #1: USP received significant comments from the U.S. Food and Drug Administration (FDA) and other stakeholders, requesting that USP not proceed with the proposed revision. USP received permission from stakeholders to make comments on this proposal publicly available, which they are at the following [link](#).

Response: Comment incorporated. The Council of Experts decided, in light of comments received, to defer the portion of the proposal that addresses nomenclature of biologics. USP acknowledges FDA's concerns expressed in its comments regarding the proposed approach and also notes the diversity of views expressed by other stakeholders in their comments on the *General Notices* proposal. In the spirit of working collaboratively with FDA and other stakeholders, USP will not move forward the portion of the *General Notices* proposal that addresses biological product nomenclature until USP has further engagement to better understand the implications of the *General Notices* proposal.

For further information, see the following links: USP press release announcing intent not to pursue GN biologics nomenclature revision and accompanying Compendial Notice; USP response to FDA comments on proposal.

General Chapter/Section(s): <7> Labeling
Expert Committee: Nomenclature and Labeling
No. of Commenters: 6

Comment Summary #1: The commenter requested removal of the sentence, "This chapter applies to the labeling of both human and animal drug products and compounded preparations" in the *Introduction*.

Response: Comment incorporated.

Comment Summary #2: The commenter requested providing an exception for products submitted as Investigational New Drugs (IND) in the introduction.

Response: Comment not incorporated. Products subject to IND are not official articles as defined in *General Notices*, Section 2.20. *Official Articles*. USP does not develop monographs for IND products.

Comment Summary #3: The commenter requested clarification for the labeling for storage conditions.

Response: Comment incorporated. The text will refer to three labeling options that must ensure appropriate mean kinetic temperature.

Comment Summary #4: The commenter requested clarification on the format of the date in reference to the expiration date and the beyond use date.

Response: Comment incorporated.

Comment Summary #5: The commenter requested clarification on the definition of the expiration date and the beyond use date.

Response: Comment incorporated.

General Chapter/Sections: <197> Spectrophotometric Identification Tests
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 5

General

Comment Summary #1: Commenter questioned the chapter requirement to use USP Reference Standards (RSs) for identification. Commenter stated that x-ray powder diffraction (XRPD) patterns as well as IR spectra, for example, can be found in the literature with characteristic peak positions. Can literature data therefore be used to create an internal reference standard?

Response: Comment not incorporated. The Expert Committee (EC) determined that the existing text was suitable and stated that this is a requirement backed by a rigorous USP RS development program, which guarantees their suitability for intended use in the *USP-NF* test and procedures. The commenter should consult *USP General Notices*, Section 5.80. *USP Reference Standards* concerning the requirement for using USP RSs.

Introduction and Scope

Comment Summary #2: Commenter suggested revising the second sentence of the second paragraph by adding the term “emit” to read: “... to substances that absorb, transmit, *emit*, reflect or scatter” in order to account for fluorescence.

Response: Comment not incorporated. The EC determined that the existing text is suitable and there is no need for adding “emit” since no ID test in *USP-NF* involves fluorescence.

Comment Summary #3: Commenter questioned the use of XRPD as method for chemical identification reasoning that a good part of the material may be amorphous and thus may be invisible to XRPD pattern. This amorphous part may be chemically different from the crystalline part, and the XRPD pattern is not related directly to chemical composition.

Response: Comment not incorporated. The EC determined that the existing text is suitable and refers the commenter to *USP General Notices*, Section 3. *Conformance to Standards*. The XRPD will be used as an ID test only if it is referenced in the monograph. Referencing in the monograph means that the test has been validated as suitable for its intended use.

Comment Summary #4: The commenter requested acknowledgment by USP that appropriate reference substances for Near-infrared Spectroscopy (NIR) analysis include materials obtained from the manufacturer of a material that meets USP monograph requirements and proposed adding the following text: “when a chemometric model is utilized for identification of a substance, representative reference substances which have demonstrated compliance to the USP monograph may be used to establish a robust model” before the last two sentences of the section.

Response: Comment not incorporated. The EC determined that the existing text was suitable. Only the USP RSs must be used in the ID tests of *USP-NF* articles.

Identification Methodology

Comment Summary #5: The commenter requested removing the word absorption from the “IR absorption spectrum” and “UV absorption spectrum” phrase entries in the section reasoning that it should also account for the reflectance and/or Kubelka-Munk depending on how the data was collected.

Response: Comment incorporated.

Infrared Spectroscopy

Comment Summary #6: The commenter suggested for clarity replacing the term “intimately” with “thoroughly” in Table 1.

Response: Comment not incorporated. The EC determined that the existing text was suitable, and the suggestion is a style issue. The term “intimately” is widely used in the infrared spectroscopy literature.

Comment Summary #7: The commenter suggested revising the last sentence of the first paragraph and proposed a revision.

Response: Comment partially incorporated. The EC revised the paragraph to read: “If there are differences in *between* the spectra and the sample spectrum was compared with a previously obtained...”

Comment Summary #8: The commenter proposed revising the text of acceptance criteria by adding “(or as specified within a given monograph)” to state: “The comparison must establish that the IR spectrum of the preparation of the sample exhibits maxima at the same wavenumbers (or as specified within a given monograph) as that of the appropriately prepared corresponding USP Reference Standard.”

Response: Comment not incorporated. The EC determined that the existing text was suitable. *General Notices, Section 3.10 Applicability of Standards* addresses the case when the monograph requirements are different.

Comment Summary #9: The commenter requested revising the text that addresses comparison to a previously obtained and electronically stored spectrum of the USP RS to state that “an individual may repeat the comparison with a freshly prepared USP Reference Standard” instead of “the comparison must be repeated concomitantly with a freshly prepared USP Reference Standard”, reasoning that there might be other reasons for non-matches such as an incorrect material used by a technician.

Response: Comment not incorporated. The EC determined that the existing text was suitable. The other possible reasons given are outside the scope of USP test and are addressed by firm’s internal SOP.

Comment Summary #10: The commenter requested revising the text that addresses comparison to a previously obtained and electronically stored spectrum of the USP RS to include a root cause analysis for the spectra differences prior to resorting to repeating the comparison concomitantly with a freshly prepared USP RS. The commenter reasoned that there might be other reasons for non-matches, such as differences in solid state form.

Response: Comment not incorporated. The EC determined that the existing text was suitable. The text addresses the solid state differences that are observed when using solid state techniques, and the monograph does not specify a particular crystal form. The recommendation is outside the scope of USP and is handled via laboratory investigation report.

Near-Infrared and Raman Spectroscopy

Comment Summary #11: The commenter suggested revising the second to last sentence of the first paragraph to state: “...through the use of multivariate analysis *with or without data preprocessing*”.

Response: Comment not incorporated. The EC determined that the existing text was suitable, and there is no need for additional guidance on how to perform the multivariate analysis.

Comment Summary #12: The commenter suggested revising the first sentence of the second paragraph for clarification and proposed a revised text.

Response: Comment incorporated. The EC revised the text to read: “In both techniques, samples can be directly interrogated with minimal or no sample preparation” as proposed.

Comment Summary #13: The commenters questioned not recommending the comparison of Raman spectra by simple overlay stating that each peak of Raman spectrum relates to vibration of specific bond; therefore it should be characteristic of chemical structure. Another commenter stated that Raman spectroscopy does not necessarily require multivariate techniques to identify a material.

Response: Partially incorporated. The EC revised the text to read: “comparison or simple overlay of the spectra alone may not be sufficient and additional evaluation may be needed.” The opinion of the experts in the applications of Raman spectroscopy in the pharmaceutical industry is that Raman spectroscopy does not provide sufficient specificity if a simple overlay technique similar to Mid-IR is used.

Comment Summary #14: The commenter suggested revising the second sentence of the second paragraph to: “...and data collection can often be made through *transparent* glass or plastic containers”.

Response: Comment not incorporated. The EC determined that the existing text was suitable. There is no need for the containers to be transparent when performing these tests.

Ultraviolet-Visible Spectroscopy

Comment Summary #15: See Comment Summary #5 and response under “Infrared Spectroscopy”.

X-Ray Powder Diffraction

Comment Summary #16: The commenter suggested revising the first sentence of the second paragraph for clarification and proposed a revised text.

Response: Comment incorporated. The EC revised the text to read: “Record the diffraction pattern in a 2θ -range from as near to 0° as possible to at least 32° ” as proposed.

Comment Summary #17: The commenter requested clarification for the third paragraph, which includes the acceptance criteria, to define the word “conform” and stated that this acceptance criterion is interpreted as pattern match instead.

Response: Comment not incorporated. The EC determined that the existing text was suitable. The text clearly states that the line positions are compared and not the intensities.

Equivalent/Alternative Tests

Comment Summary #18: The commenter suggested that “it may be beneficial to reference USP General Chapter <853> Fluorescence Spectroscopy in this section.”

Response: Comment not incorporated. The EC determined that the existing text was suitable and referencing <853> was not needed since no monograph in *USP-NF* uses fluorescence spectroscopy as ID.

Comment Summary #19: The commenter asked if USP could provide details on what steps should be taken to demonstrate that an alternative procedure is equivalent to or better than the specified procedure.

Response: Comment not incorporated. The EC determined that the existing text was suitable. The request is outside the scope of the chapter.

Expert Committee-initiated Change #1: The following entries were incorporated: 1) for the title: “Use of the chapter title Spectrophotometric Identification Tests is permitted until May 1, 2020”; 2) for the Infrared Spectroscopy Section Title: “Use of the section title Infrared Absorption is permitted until May 1, 2020”; and 3) for the Ultraviolet-Visible Section Title: “Use of the section title Ultraviolet Absorption is permitted until May 1, 2020”.

General Chapter/Section(s):	<561> Articles of Botanical Origin/Multiple Sections
Expert Committee:	Botanical Dietary Supplements and Herbal Medicines
No. of Commenters:	1

Comment Summary #1: The commenter suggested replacing the term “drug” with “material” in the following sections of the chapter:

- *Methods of Analysis/crude fiber.* Replace “drug” with “material” in the sentence: “Exhaust a weighed quantity of the *Test Sample*, representing about 2 g of the drug, with ether.”

- *Methods of Analysis/Volatile Oil Determination.* Replace “drug” with “material” in the first paragraph: “...Place a suitable quantity of the drug, accurately weighed, in the flask, and fill it one-half with water. Attach the condenser and the proper separator. Boil the contents of the flask, using a suitable amount of heat to maintain gentle boiling for 2 h, or until the volatile oil has been completely separated from the drug and no longer collects in the graduated tube of the separator.”

Response: Comment incorporated.

Comment Summary #2: The commenter suggested simplifying the solvent mixture ratios in the following sections of the chapter:

- *Test for Aflatoxins/Method II/Test solution/ Cleanup procedure with IAC.* Change “a mixture of methanol and water (60:40)” to “a mixture of methanol and water (6:4)”.
- *Test for Aflatoxins/Method III/System suitability solution.* Change “the mixture of methanol and 0.5% sodium bicarbonate (700:300)” to “the mixture of methanol and 0.5% sodium bicarbonate (7:3)”.
- *Test for Aflatoxins/Method III/Chromatographic system/Mobile phase.* Change “Water, methanol, and acetonitrile (600:250:150)” to “Water, methanol, and acetonitrile (60:25:15)” and “a mixture of water, methanol, and acetonitrile (600:250:150)” to “a mixture of water, methanol, and acetonitrile (60:25:15)”.

Response: Comment incorporated.

General Chapter/Sections(s): <630> Visual Comparison
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 4

General

Comment Summary #1: Commenter, noting that the entire first paragraph served as the introduction to the chapter, recommended revising and expanding the section to include definitions and test recommendations and provided several suggestions.

Response: Comment not incorporated. The EC determined that the existing text was suitable and stated that the scope of the new General Chapter <630> *Visual Comparison* is very limited to the visual comparison as per the references in a few monographs to a section of old General Chapter <855> *Nephelometry, Turbidimetry, and Visual Comparison*.

Comment Summary #2: Commenter noted that <630> seems to exclude potential occasions where secondary instrumental assessment may be necessary and suggested adding these. Another commenter also suggested the option of using a suitable instrument instead of the visual comparison.

Response: Comments not incorporated. The EC determined that the existing text is suitable noting that the use of an instrumental method to replace the visual method is not specified in this chapter since instrumental methods are covered in their respective chapters. If a user would consider using an instrumental method instead of the visual comparison referenced in the monograph, they will have to validate it as an “Alternative Method” as per *General Notices*, Section 6.30. *Alternative and Harmonized Methods and Procedures*.

Title

Comment Summary #3: Commenter questioned the naming of <630> suggesting that it should be more detailed to convey intended usage.

Response: Comments not incorporated. The EC determined that the existing title is suitable and clearly conveys what test is being performed.

Comparison Vessels

Comment Summary #4: Commenter suggested revising the “Comparison vessels” text by adding the “depth of sample solution” to read: “Color-comparison tubes matched as closely as possible in internal diameter, depth of sample solution, and all other respects should be used”.

Response: Comment incorporated.

Viewing Conditions for Turbidity Comparison

Comment Summary #5: The commenter recommended adding acceptance criteria and possibly a reference to <855> to determine respective concentration of permissible turbidity.

Response: Comment not incorporated. The EC determined that the existing text was suitable and stated that the acceptance criteria could not be general. They will be considered on a case by case basis and are included in the individual monographs that reference the chapter.

Comment Summary #6: The commenter recommended adding “vertically examination” as an alternative and proposed revising the text to state: “Tubes should be viewed horizontally or vertically against a black background...” instead of “Tubes should be viewed horizontally against a dark background...”.

Response: Comment not incorporated. The EC determined that the existing text was suitable and stated that it has been used in the industry for a long time.

Comment Summary #7: The commenter suggested that in order to aid the end user, an example of an appropriate light source set-up using an image would be helpful.

Response: Comment not incorporated. The EC determined that the existing text was suitable and stated that generalized examples do not add value and may be misleading at times.

Viewing Conditions for Color Comparison

Comment Summary #8: The commenter recommended revising the text by adding to the phrase “from the top” to read: “Tubes should be viewed downward from the top against a white background”.

Response: Comment not incorporated. The EC determined that the existing text was suitable and the additional qualifier would not add clarity or value.

General Chapter/Sections:	<855> Nephelometry, Turbidimetry, and Visual Comparison
Expert Committee:	General Chapters—Chemical Analysis
No. of Commenters:	7

Applications

Comment Summary #1: The commenter suggested providing an example of low turbidity for clarity.

Response: Comment not incorporated. The EC determined that the existing text was suitable and already addresses the low turbidity.

Instrumentation

Comment Summary #2: The commenter noted that the text discusses technology using 90° scattering and the availability of instruments that accommodate the 180° scattering. They suggested revising the text to include some discussion on these instruments.

Response: Comment not incorporated. The EC determined that the existing text was suitable and already discusses all types of instruments.

Formazin Turbidity Standards

Comment Summary #3: The commenter requested changing the temperature requirements for preparation of Formazin Standards to $25 \pm 3^\circ\text{C}$ from $25 \pm 1^\circ\text{C}$ as currently proposed to ensure alignment to other pharmacopeias.

Response: Comment not incorporated. The EC determined that the existing text was suitable. The information in the chapter represents the current scientific knowledge on the topic. USP reached out to other pharmacopeias and they may align with this updated information in the future.

Comment Summary #4: The commenter questioned the statement “All procedures of the Formazin standards must be performed at $20 \pm 2^\circ$ ”, stating that it contradicts the following statement: “Allow the preparation to stand for 48 h at $25 \pm 1^\circ$ before using”.

Response: Comment not incorporated. The EC determined that the existing text was suitable. There is no discrepancy since the first statement refers to the temperature for handling (volumetric dilution) of the solutions and the second statement refers to the equilibration time. However, the EC added a clarification in parenthesis that refers the reader to General Chapter <31> *Volumetric Apparatus*.

Qualification of Turbidimeters and Nephelometers

Comment Summary #5: The commenter questioned including a qualification section in the chapter stating that qualifications should be in a companion chapter over 1000.

Response: Comment partially incorporated. The EC revised the existing text to remove the general information on these topics and referenced General Chapter <1058> *Analytical Instrument Qualification*. Only the information specific to the qualification of these instruments not covered in <1058> was left in <855>.

Comment Summary #6: The commenter stated that the entry “...and the fundamental parameters of stray light must be established” had information that conflicts with the text of section 4 *Instrumentation* and proposed revising the entry to say “The fundamental parameters of stray light must be established for all instruments but ratio turbidimetric systems”.

Response: Comment partially incorporated. The EC revised the entry to state “and meets the requirements for stray light”.

Comment Summary #7: The commenter suggested revising the accuracy section reasoning that some parts were not feasible and proposed a revised text.

Response: Comment partially incorporated. The EC revised the text to read: “The instrument reading accuracy must be $\pm 10\%$ of the reading + 0.01 NTU for the measurement range from 0–19.9 NTU; and $\pm 7.5\%$ of the reading for the measurement range from 20–1100 NTU”.

Procedures

Comment Summary #8: The commenter questioned the entry “However, the sample cells must be matched (the difference in readings for a standard prepared at nominal sample concentration from two different sample cells must be within ± 0.005 NTU or below the measurement precision requirement, whichever is lower)” stating that it is beyond the capability of most (any) available instrumentation and proposed deleting the sentence and instead add a repeatability criterion to Section 6.2 *Operational Qualification*.

Response: Comment not incorporated. The EC determined that the existing text was suitable. The same requirement is included in the instrumentation manuals from major instrument vendors.

Validation and Verification

Comment Summary #9: The commenter suggested including language to clarify that the degree of turbidity or clarity needs to be validated and verified using appropriate standard(s), spiked sample(s), and placebo(s).

Response: Comment not incorporated. The EC determined that the existing text was suitable. The use of standards is included in the text. The spiking and use of placebo are not relevant to these tests.

Comment Summary #10: The commenter questioned including a Validation/Calibration section in the chapter stating that they should be in a companion chapter over 1000.

Response: Comment partially incorporated. The EC revised the existing text to remove the general information on these topics and referenced <1058> and General Chapter <1225> *Validation of Compendial Procedures* instead. Only specific information needed to successfully perform these procedures not covered elsewhere was included.

General Chapter/Section(s): <1090> Assessment of Drug Product Performance—
Bioavailability, Bioequivalence, and Dissolution/
Background

Expert Committee: General Chapters—Dosage Forms

No. of Commenters: 1

Comment Summary #1: The commenter indicated that a reference to General Chapter <1094> *Capsules—Dissolution Testing and Related Quality Attributes* is missing from a list of USP general chapters describing performance tests.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested that for simplification, the wording “same molar dose” could be replaced by “same dose” as the basis of bioequivalence of the test and reference drug products.

Response: Comment incorporated.

Comment Summary #3: The commenter requested that in addition to the Biopharmaceutics Classification System (BCS) or an In Vitro Correlation to include a specific reference for the use of In Vitro to In Vivo Extrapolation (in vitro work plus Physiologically-Based Pharmacokinetics modeling) as a justification to replace a Bioavailability study.

Response: Comment not incorporated. The inclusion of a specific paper as a reference in this commentary could provide an unintended endorsement for a particular approach.

Comment Summary #4: The commenter recommended that the wording, “the ability to analyze the drug and/or metabolites where appropriate” be used under the discussion of bioequivalence (BE) studies design to recognize that BE studies may sometimes be based on both the drug substance as well as metabolites.

Response: Comment incorporated.

Comment Summary #5: The commenter recommended that the limits for the 90% confidence intervals for the geometric mean ratios have the appropriate two-decimal-place presentation under the discussion of the two one-sided tests procedure.

Response: Comment incorporated.

Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution/Dissolution and In Vitro Product Performance

Comment Summary #6: The commenter suggested that the new draft FDA guidance, *Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs* (2015), be mentioned.

Response: Comment incorporated.

Comment Summary #7: The commenter requested mentioning model independent comparison approaches (e.g., multivariate confidence region), as well as physiologically based models.

Response: Comment not incorporated. This information will be considered for a future revision of the chapter.

Comment Summary #8: The commenter suggested that under the discussion of biowaiver based on dosage form proportionality, an additional criterion such as “meets an appropriate in vitro dissolution profile comparison criterion ($f_2 \geq 50$) or other justified alternative method” could be added.

Response: Comment not incorporated. The section has adequate qualifying language to support the use of other justified alternative methods.

Comment Summary #9: Under the discussion of biowaiver based on the BCS, the commenter requested mention of the draft FDA guidance *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* when finalized.

Response: Comment incorporated. The guidance was made final in December 2017.

Comment Summary #10: The commenter requested mention of the incorporation of BCS Class 3 drug substances as allowed for biowaiver under the discussion of biowaiver based on the BCS.

Response: Comment incorporated.

Comment Summary #11: Under the discussion of biowaiver based on the BCS, the commenter requested mentioning that for biowaiver, dissolution tests for both the test and reference products should be carried out using the same or different dissolution instruments.

Response: Comment not incorporated. This change will be considered for a future revision.

Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution/ Dissolution as a Quality Control Test and a BE Test

Comment Summary #12: The commenter requested that the title be updated to read “Dissolution as a Quality Control Test and an In-vitro Equivalence Test.” Additionally, the references to BE within the paragraph should be removed.

Response: Comment incorporated.

Assessment of Solid Oral Drug Product Performance and Interchangeability, Bioavailability, Bioequivalence, and Dissolution/Appendix

Expert Committee-initiated Change #1: The reference to World Health Organization (WHO) *Annex 7* guidelines on transfer of technology in pharmaceutical manufacturing was updated.

Expert Committee-initiated Change #2: The draft FDA documents *Guidance for Industry, Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations* (2014) and *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (2013) were included in this section as relevant information.

Expert Committee-initiated Change #3: For completeness, mentioned that other bioequivalence guidances may exist outside of those specifically listed in the chapter.

Expert Committee-initiated Change #4: The references were updated to acknowledge draft FDA guidances, *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations*, and *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*.

Expert Committee-initiated Change #5: Reference to FDA *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* was updated.

Expert Committee-initiated Change #6: Mentions of the WHO, FDA, and European Medicines Agency (EMA) approaches for biowaiver were found to be redundant based on the content of Table 1 in the *Appendix* and were removed.

Expert Committee-initiated Change #7: The entries were updated to incorporate the latest versions of the relevant WHO, FDA, and EMA documents.

General Chapter/Section: <1217> Tablet Breaking Force/Introduction
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 2

Comment Summary #1: The commenter requested that a distinction be made between tablets and lozenges. The chapter lists lozenges among the dosage forms for which the tablet breaking force test may be applied, and yet they are not tablets.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended the first sentence of the first paragraph in the chapter be reworded for clarity.

Response: Comment incorporated.

Comment Summary #3: The commenter indicated that two reasons are given for concern for tablets that may chip or abrade following loss of drug substance. The commenter requested that these reasons be reordered so that the impact on subsequent manufacturing operations is given higher significance than perceived elegance by the customer.

Response: Comment incorporated.

Comment Summary #4: Under *Dependence of Breaking Force on Tablet Geometry and Mass*, the commenter suggested clarifying that the tablet orientation and failure of the sample in testing is consistent with what was observed during product development.

Response: Comment incorporated.

Breaking Force/Tensile Strength

Comment Summary #5: The commenter recommended adding a derived equation for the tensile stress of convex-faced tablets.

Response: Comment incorporated. Additionally, a statement was added to indicate that other examples may be found in the literature.

Tablet Breaking Force/References

Comment Summary #6: The commenter recommended adding a reference (Pitt, K., Heasley, M. Determination of the tensile strength of elongated tablets. Powder Technology. 2013; 238:169–175) to the chapter.

Response: Comment incorporated.

Monographs

Monograph/Section(s): Acarbose Tablets/Multiple Sections
Expert Committee: Biologics 3 - Complex
No. of Commenters: 5

Comment Summary #1: The commenter requested modifying the main text of the Identification B method by changing the word “solution” to “preparation” in the line: “The spectrum obtained from the *sample solution*...” for clarification purposes and to reflect an appropriate sampling technique/preparation.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended the following modifications to the Assay method in line with their in-house method: use 4 mg/mL of both Standard and Sample preparations; remove the system suitability solution and requirements. The commenter also asked whether the USP Acarbose System Suitability Mixture RS is equivalent to the European Pharmacopoeia (EP) Acarbose for peak identification Chemical Reference Substance (CRS).

Response: Comment not incorporated. The EC determined that the proposed monograph was suitable based on the information from the four sponsors. See also *USP General Notices* Section 6.30. *Alternative and Harmonized Methods and Procedures* for further information.

Additionally, there is no information available as to whether USP Acarbose System Suitability Mixture RS is equivalent to the EP Acarbose for peak identification CRS.

Impurities

Comment Summary #3: The commenter requested revising the acceptance criteria of Impurity A to the one approved by the regulatory agency.

Response: Comment not incorporated. This monograph was sponsored by four U.S.-approved manufacturers, and confirmation of the specifications was requested by USP following this public comment. Three sponsors confirmed the agency approved acceptance criterion for Impurity A to be the same as was published in the monograph. One sponsor confirmed the acceptance criterion for Impurity A to be narrower than the one published in the monograph. Based on these approved specifications, the EC found the proposed range in the monograph suitable.

Comment Summary #4: The commenter requested the rationale for including Impurities B, C, and D in Table 1 of the proposed monograph since these are listed as process impurities in the Acarbose monograph.

Response: Comment not incorporated. As per the updated information from the sponsors who submitted this monograph, either impurity B, C, or D or all three are also possible degradants of the product and can therefore be included in the monograph.

Comment Summary #5: The commenter indicated that the Impurity C specification should be consistent in the Acarbose and Acarbose Tablets monographs.

Response: Comment not incorporated. The EC noted that the information in the Acarbose Tablets monograph is recently confirmed compared to the Acarbose monograph. Manufacturers of Acarbose will be contacted to obtain updates on Impurity C specifications in case the drug substance monograph needs revision.

Comment Summary #6: The commenter proposed to change the 0.2% Standard Preparation to a 0.05% Standard Preparation in line with their in-house method's disregard limit. In addition, the commenter proposed to change 2.0% Standard preparation with a Relative Standard Deviation (RSD) requirement of Not More Than (NMT) 2% in the monograph with their approved 5% Standard preparation with an RSD requirement of NMT 5.0%.

Response: Comment not incorporated. The EC determined that the proposed monograph was suitable based on the information from the four sponsors and noted that the 0.2% Standard preparation in the Impurities method includes the sensitivity requirement.

Monograph/Section(s): Azithromycin/Organic Impurities

Expert Committee: Chemical Medicines 1

No. of Commenters: 1

Comment Summary: The commenter recommended reverting the limits for erythromycin A iminoether and erythromycin A oxime impurities to NMT 0.5% in the test for *Organic Impurities* based on FDA-approved acceptance criteria.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended revising the limits for azaerythromycin A and any individual unidentified impurity in the test for *Organic Impurities*.

Response: Comment not incorporated. The current limits are based on FDA-approved acceptance criteria. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section(s): Azithromycin for Oral Suspension/Organic Impurities
Expert Committee: Chemical Medicines 1
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the limits for 3'-(N,N-didemethyl)-3'-N-formylazithromycin and N-Demethylazithromycin in the test under *Organic Impurities*.

Response: Comment not incorporated. The current limits are based on FDA-approved acceptance criteria. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section(s): Bendroflumethiazide/Packaging and Storage
Expert Committee: Chemical Medicines 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended including a storage temperature.

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

Monograph/Section(s): Beta Carotene Capsules/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 2

Comment Summary #1: The commenter proposed to change the relative response factor of all-*trans*-Alpha carotene in Table 1 from 1.0 to 1.05 to harmonize with the Association of Analytical Communities (AOAC)-recommended value of 1.05.

Response: Comment incorporated.

Comment Summary #2: The commenter noted that during monograph revision submitted to PF 37(1), where the UV-Vis spectrometric procedure in the Assay was replaced by HPLC procedure, the acceptance criteria in the *Definition* for low limit of total beta carotene were accidentally changed from Not Less Than (NLT) 90.0% to NLT 90% and thus recommended to return the previously established NLT 90.0% limit.

Response: Comment incorporated.

Monograph/Section(s): Betahistine Hydrochloride/Packaging and Storage
Expert Committee: Chemical Medicines 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended including a storage temperature.

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

Monograph/Section(s): Calcium Acetate Capsules/Dissolution
Expert Committee: Chemical Medicines 6
No. of Commenters: 2

Comment Summary #1: The commenter recommended adding a dissolution test to be consistent with an FDA-approved drug product.

Response: Comment not incorporated. The EC determined to add the Dissolution Test 2 via a future revision.

Comment Summary #2: The commenter recommended adding a dissolution test to accommodate FDA-approved drug products in the new Calcium Acetate Capsules USP monograph proposal.

Response: Comment not incorporated. The EC determined to add the Dissolution Test 2 via a future revision.

Monograph/Section(s): Cefprozil/Packaging and Storage
Expert Committee: Chemical Medicines 1
No. of Commenters: 1

Comment Summary #1: The commenter recommended including a temperature requirement in the *Packaging and Storage* section.

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

Monograph/Section(s): Chlorothiazide Compounded Oral Suspension
Expert Committee: Compounding
No. of Commenters: 1

Comment Summary #1: The commenter noted that the compounded preparation monograph is essentially a copy of an FDA-approved product and such preparation should not be compounded unless the patient has a specific medical need.

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

Comment Summary #2: The commenter noted that the molecular formula for chlorothiazide should be corrected to Cl rather than CL.

Response: Comment incorporated.

Monograph/Section(s): Citicoline Sodium/Impurities
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1

Comment Summary #1: The commenter suggested adding the test for sulfate to the *Impurities* section.

Response: Comment incorporated.

Monograph/Section(s): Clomipramine Hydrochloride Capsules/Organic Impurities
Expert Committee: Chemical Medicines 4
No. of Commenters: 3

Comment Summary #1: The commenter requested widening the acceptance criteria for individual unknown impurities from NMT 0.1% to NMT 0.5% for consistency with FDA-approved limits.

Response: Comment incorporated.

Comment Summary #2: The commenter requested widening the acceptance criteria for imipramine from NMT 0.2% to NMT 1.0%, unknown impurities from NMT 0.1% to NMT 0.2%, and total impurities from NMT 1.0% to NMT 2.0% for consistency with FDA-approved limits.

Response: Comment incorporated. See Comment Summary #1.

Comment Summary #3: The commenter requested revising the acceptance criteria for impurities. The commenter indicated that the method was performed poorly in the commenter's laboratory.

Response: Comment not incorporated. The commenter did not provide acceptance criteria. The method issues were not observed during validation.

Expert Committee-initiated Change #1: In the test for *Organic Impurities*, replaced the statement "Disregard any impurity peak less than 0.03%" with "The reporting threshold is 0.03%" to make it consistent with the current USP style.

Monograph/Section(s): Cytarabine/Multiple Sections
Expert Committee: Chemical Medicines 3
No. of Commenters: 1

Comment Summary #1: The commenter requested including the chemical names for Impurity 1 and Impurity 2 in *Table 2* in the test for *Organic Impurities*.

Response: Comment incorporated. Impurity 1 and Impurity 2 are revised to Cyclocytidine and Cytosine, respectively, and the chemical names are added as footnotes.

Comment Summary #2: The commenter recommends including a temperature requirement under *Packaging and Storage*.

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

Monograph/Section(s): Dexamethasone Ophthalmic Suspension/Organic Impurities

Expert Committee: Chemical Medicines 5

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criteria for any individual unspecified degradation product to be consistent with FDA- approved limits.

Response: Comment incorporated. The acceptance criterion for any individual unspecified degradation product was widened from NMT 0.20% to NMT 0.2%.

Comment Summary #2: The commenter recommended revising total degradation products to be consistent with FDA approved limits.

Response: Comment not incorporated. The proposed limit of NMT 0.5% for total degradation products is consistent with FDA-approved limits.

Monograph/Section(s): Dichlorphenamide/Organic Impurities

Expert Committee: Chemical Medicines 3

No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the limit for 3,4-Dichlorobenzenesulfonamide in the test for *Organic Impurities* from NMT 0.10% to NMT 0.15%, which is consistent with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3A guidelines.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended revising the term “Any individual impurity” in the test for *Organic Impurities* to “Any unspecified impurity”.

Response: Comment incorporated.

Comment Summary #3: The commenter requested correcting the calculation in the test for *Organic Impurities* to include the relative response factors listed in *Table 2*.

Response: Comment incorporated.

Comment Summary #4: The commenter requested revising the RSD requirement from NMT 5.0% to NMT 10.0%.

Response: Comment incorporated.

Monograph/Section(s): Dihydrocodeine Bitartrate/Organic Impurities

Expert Committee: Chemical Medicines 2

No. of Commenters: 1

Comment Summary #1: The commenter noted that the acceptance criterion for Total impurities is different from the limit in the FDA-approved applications.

Response: Comment not incorporated. The acceptance criterion for Total impurities is consistent with the FDA-approved sponsor’s application. The EC will consider future revisions upon receipt of supporting data.

Monograph/Section(s): Disulfiram Tablets/Organic Impurities
Expert Committee: Chemical Medicines 4
No. of Commenters: 1

Comment Summary #1: The commenter requested revision of the acceptance criteria for individual impurities to be widened from NMT 0.20% to NMT 0.2% and total impurities to be widened from NMT 0.5% to NMT 1.0% for consistency with FDA-approved specifications.

Response: Comment incorporated.

Expert Committee-initiated Change #1: The category “Performance Tests” was corrected to “Impurities”.

Expert Committee-initiated Change #2: The *Analysis* section was updated to “in the portion of Tablets taken” instead of “in the portion of Disulfiram taken”.

Monograph/Section(s): Doxylamine Succinate/Organic Impurities
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1

Comment Summary: The commenter requested widening the acceptance criteria for the Doxylamine pyridine-4-yl isomer, Doxylamine alcohol, 2-Benzoyl pyridine from NMT 0.10% to NMT 0.15% and Total impurities from NMT 0.7% to NMT 1.0%.

Response: Comment incorporated.

Monograph/Section(s): Doxylamine Succinate Tablets/Organic Impurities
Expert Committee: Chemical Medicines Monographs 6
No. of Commenters: 1

Comment Summary: The commenter requested widening the acceptance criteria for the Total impurities from NMT 1.0% to NMT 2.0%

Response: Comment incorporated.

Monograph/Sections: Estriol/Organic Impurities
Expert Committee: Chemical Medicines 5
Expert Committee-initiated Change #1: The preparation of the *System suitability solution* was changed from a one-step dilution to a two-step dilution to ensure the solubility of all compounds.

Monograph/Section(s): Ethosuximide Capsules/Organic Impurities
Expert Committee: Chemical Medicines 4
No. of Commenters: 1

Comment Summary #1: The commenter requested the inclusion of an *Organic Impurities* test with acceptance criteria for specified impurities, unspecified impurities, and total impurities.

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

Monograph/Section(s): Ethosuximide Oral Solution/Organic Impurities
Expert Committee: Chemical Medicines 4
No. of Commenters: 1

Comment Summary #1: The commenter requested the inclusion of an *Organic Impurities* test with acceptance criteria for specified impurities, unspecified impurities, and total impurities.

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

Monograph/Section(s): Felodipine Extended-Release Tablets/Organic Impurities
Expert Committee: Chemical Medicines 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended tightening the proposed acceptance criteria of NMT 3.0% for total impurities in *Table 4*.

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

Monograph/Section(s): Fenofibrate Capsules/Uniformity of Dosage Units <905>
Expert Committee: Chemical Medicines 2
No. of Commenters: 1

Comment Summary #1: The commenter suggested providing flexibility to use either the weight variation or the specified HPLC content uniformity procedure because of the dosage form strength.

Response: Comment incorporated. The "Meet the requirements" statement was moved to read as "Uniformity of dosage units <905>: Meet the requirements", indicating that it is applicable to any procedure used to determine content uniformity.

Monograph/Section(s): Fentanyl Citrate Compounded Injection
Expert Committee: Compounding
No. of Commenters: 1

Comment Summary #1: The commenter indicated that the compounded preparation monograph has the same or similar formulation as an FDA-approved product.

Response: Comment not incorporated. The EC does not encourage compounding where there is a suitable commercially available product. However, there may be situations where there is a specific medical need where the preparation will need to be compounded.

Monograph/Section(s): Fentanyl Citrate and Bupivacaine Hydrochloride
Compounded Injection
Expert Committee: Compounding

No. of Commenters: 1

Comment Summary #1: The commenter suggested adding a labeling requirement for compounded preparation intended to be administered via a pump device to decrease the likelihood of administration without the use of a pump.

Response: Comment not incorporated. The route of administration is out of the scope of compounded monographs and General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations*.

Monograph/Section(s): Fentanyl Citrate and Ropivacaine Hydrochloride
Compounded Injection
Expert Committee: Compounding

No. of Commenters: 1

Comment Summary #1: The commenter suggested adding a labeling requirement for compounded preparation intended to be administered via a pump device to decrease the likelihood of administration without the use of a pump.

Response: Comment not incorporated. The route of administration is out of the scope of compounded monographs and General Chapter <797> *Pharmaceutical Compounding – Sterile Preparations*.

Monograph/Section(s): Fluconazole/Assay
Expert Committee: Chemical Medicines 1
No. of Commenters: 3
Comment Summary #1: The commenter noted that the column particle size listed in the Assay is incorrect.
Response: Comment incorporated. The column particle size is revised from 3.5 µm to 3 µm.

Monograph/Section(s): Fluorescein Injection/Organic Impurities
Expert Committee: Chemical Medicines 3
Expert Committee-initiated Change #1: The limit for unspecified impurities in the test for *Organic Impurities* is changed from NMT 0.10% to NMT 0.2%, which is consistent with ICH Q3B guidelines.

Monograph/Section(s): Guanabenz Acetate Tablets/Organic Impurities
Expert Committee: Chemical Medicines 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the acceptance criteria for impurities and include a limit for unspecified impurities and total impurities to be consistent with the FDA-approved drug products.
Response: Comment not incorporated. The EC will consider a future revision upon receipt of the supporting information.

Monograph/Section(s): Heparin Lock Flush Solution/Additional Requirements/Labeling
Expert Committee: Biologics Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter suggested deleting “For further information, see the entirety of *Injections and Implanted Drug Products <1>*”, due to the fact that General Chapter <1> *Injections and Implanted Drug Products (Parenterals)—Product Quality Tests* no longer contains discussion on quantity and total volume of injectable products.
Response: Comment not incorporated. The EC will consider this in a future revision.

Monograph/Section(s): Heparin Sodium Injection/Additional Requirements/Labeling
Expert Committee: Biologics Monographs 3
No. of Commenters: 1
Comment Summary #1: The commenter suggested deleting “For further information, see the entirety of *Injections and Implanted Drug Products <1>*”, due to the fact that <1> no longer contains discussion on quantity and total volume of injectable products.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Monograph/Section(s): Hydrochlorothiazide Capsules/Organic Impurities
Expert Committee: Chemical Medicines 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended not including the reporting threshold in a public standard as it is based on certain product-specific factors.
Response: Comment incorporated.

Monograph/Section(s): Isosorbide Dinitrate Tablets/Organic impurities
Expert Committee: Chemical Medicines 2
No. of Commenters: 1
Comment Summary #1: The commenter recommended revising the acceptance criteria for isosorbide mononitrate related compound A, isosorbide mononitrate, and any unspecified degradation product.
Response: Comment not incorporated. The proposed limits are based on acceptance criteria in the FDA-approved sponsor's application. The EC will consider a future revision to the monograph upon receipt of supporting data.

Monograph/Section(s): Levalbuterol Hydrochloride/Organic Impurities
Expert Committee: Chemical Medicines 4
No. of Commenters: 1
Comment Summary #1: The commenters requested retaining the reference standards for Levalbuterol Related Compounds D, E, F, and H in the monograph section since they are specified impurities.
Response: Comment partially incorporated by retaining the RS for Levalbuterol Related Compound D, a degradation product. The reference standards for Levalbuterol Related Compounds E, F, and H are not needed to establish the system suitability and are called out by relative retention time in the monograph.

Monograph/Section(s): Levalbuterol Inhalation Solution/Multiple sections
Expert Committee: Chemical Medicines 4
No. of Commenters: 2
Comment Summary #1: The commenter recommended the removal of the reporting threshold from the test for organic impurities as it will vary based on product-specific factors.
Response: Comment not incorporated. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.
Comment Summary #2: The commenter requested retaining the % RSD requirement in the *Limit of S-Albuterol* test.
Response: Comment not incorporated. No standard solution is used in the test. A precision requirement is not necessary when area normalization is used.
Comment Summary #3: The commenter requested replacing the terms "ampuls" and "vials" with unit-dose container in the *Packaging and Storage* section.
Response: Comment incorporated.
Comment Summary #4: The commenter requested that the composition of the mobile phase in the *Limit of S-Albuterol* test be changed to "Acetonitrile and methanol (50:50). To each liter of the solution add 3 mL of acetic acid and 1 mL of trimethylamine."
Response: Comment incorporated.
Expert Committee-initiated Change #1: Retained the reference standard for Levalbuterol related compound D, a degradation product in the monograph to be consistent with the Levalbuterol Hydrochloride monograph decision. The reference standards for Levalbuterol Related Compounds E, F, and H are not needed to establish the system suitability and are called out by relative retention time in the monograph.

Monograph/Section(s): Loperamide Hydrochloride/Multiple sections
Expert Committee: Chemical Medicines 3
No. of Commenters: 2
Comment Summary #1: The commenter requested not to tighten the assay limit from 98.0% - 102.0% to 99.0% - 101.0% in the *Assay* and in the *Definition* to accommodate their approved acceptance criteria.

Response: Comment incorporated. The assay limits of 98.0% - 102.0% were retained.

Monograph/Section(s): Mefenamic Acid Capsules/Multiple Sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 2

Comment Summary #1: The commenter recommended the addition of Infrared Absorption test to *Identification*.

Response: Comment not incorporated. The EC has determined that the two ID tests as shown in the *PF* proposal can adequately establish identity of the drug product and will consider future revision if necessary.

Comment Summary #2: The commenter indicated that there are slight differences in the HPLC procedure for the dissolution test between the USP method and their method and recommended that USP adopts their method in the monograph.

Response: Comment not incorporated. The EC has determined that the existing HPLC procedure for dissolution test is suitable for the intended use.

Comment Summary #3: The commenter indicated that the specified impurity 2,3-dimethylaniline in *Organic Impurities* is a process impurity and should not be controlled in the drug product monograph.

Response: Comment incorporated. The impurity 2,3-dimethylaniline and the associated USP Reference Standard (USP 2,3-Dimethylaniline RS) are deleted from the *Organic Impurities* test.

Comment Summary #4: The commenter indicated that only degradation products should be controlled in *Organic Impurities* for the drug product monograph and the acceptance criteria are 0.16% and 1.0% for any individual degradation product and total degradation products, respectively.

Response: Comment incorporated.

Monograph/Section(s): Methoxsalen Capsules/Multiple Sections

Expert Committee: Chemical Medicines 3

No. of Commenters: 2

Comment Summary #1: The commenter requested reverting from the proposed RSD requirement of NMT 1.0% to the original NMT 2.0% in the *Assay*, as this limit is more suitable for the procedure than the tighter limit that was proposed.

Response: Comment incorporated.

Comment Summary #2: The commenter requested correcting the term *Standard solution* in the *System suitability solution* description in the test for *Organic Impurities* to *Standard stock solution*, to obtain the right concentration.

Response: Comment incorporated.

Monograph/Section(s): Methoxsalen Topical Solution/Assay

Expert Committee: Chemical Medicines Monographs 3

Expert Committee-initiated Change #1: Based on comments received for the RSD requirement in the *Assay* for the monograph for Methoxsalen Capsules, the proposal to tighten the RSD requirement to NMT 1.0% in the *Assay* was canceled. The limit reverts to the original NMT 2.0%, which is more suitable for the procedure.

Monograph/Section(s): Metoprolol Tartrate Injection/Multiple Sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 2

Comment Summary #1: The commenter recommended retaining the existing infrared test for *Identification*.

Response: Comment not incorporated. The proposal eliminates the use of chloroform, the hazardous solvent used in sample preparation. The EC determined the two proposed ID tests can adequately establish the identity of the drug product and will consider future revision if necessary.

Comment Summary #2: The commenter recommended revising the acceptance criteria for metoprolol related compound A, metoprolol related compound B, metoprolol related compound C, any unspecified degradation product, and total degradation products in the *Organic Impurities* test.

Response: Comment not incorporated. The proposed limits are based on FDA- approved acceptance criteria in the sponsor's application. The EC will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Mitoxantrone Hydrochloride/Packaging and Storage
Expert Committee: Chemical Medicines 3
No. of Commenters: 1

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

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

Monograph/Section(s): Mitoxantrone Injection/Labeling
Expert Committee: Chemical Medicines 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended updating the labeling statement to remove the option for using water as diluent because water would make the solution hypotonic.

Response: Comment incorporated. The labeling section is updated from "Label Injection to indicate that it is to be diluted to appropriate strength with water and other suitable fluid before administration" to "Label Injection to indicate that it is to be diluted to appropriate volume with suitable fluid before administration."

Monograph/Section(s): Mycophenolate Mofetil for Injection/Assay
Expert Committee: Chemical Medicines 3
No. of Commenters: 1

Comment Summary #1: The commenter requested reverting from the proposed RSD requirement of NMT 1.0% to the original NMT 2.0% in the *Assay* as this limit is more suitable for the procedure than the tighter limit that was proposed.

Response: Comment incorporated.

Monograph/Section(s): Mycophenolate Mofetil for Oral Suspension/Assay
Expert Committee: Chemical Medicines 3

Expert Committee-initiated Change #1: Based on comments received for the RSD requirement in the *Assay* section of the monograph for Mycophenolate Mofetil for Injection, the proposal to tighten the RSD requirement to NMT 1.0% in the *Assay* was canceled. The limit reverts to the original NMT 2.0%, which is more suitable for the procedure.

Monograph/Section(s): Nicotine Polacrilex/Specific Tests
Expert Committee: Chemical Medicines 4
No. of Commenters: 1

Comment Summary #1: The commenter requested that it be explicitly noted that the loss on drying test should be used for glycerin free Nicotine Polacrilex and the water determination test should be used for Nicotine Polacrilex containing glycerin.

Response: Comment incorporated.

Monograph/Section(s): Nifedipine Capsules/Multiple Sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the sample stock solution preparation in the *Assay*.

Response: Comment incorporated.

Comment Summary #2: The commenter recommended adding the acceptance criteria for any individual impurity and total impurities in the *Organic Impurities* test.

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

Monograph/Section(s): Oxazepam/Packaging and Storage

Expert Committee: Chemical Medicines 4

No. of Commenters: 1

Comment Summary #1: The commenter recommended including a temperature requirement under the *Packaging and Storage* section.

Response: Comment not incorporated. The temperature requirement will be added when USP receives supporting data from approved manufacturers.

Monograph/Section(s): Trandolapril/Multiple Sections

Expert Committee: Chemical Medicines 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the storage temperature requirement.

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

Comment Summary #2: The commenter recommended correcting the structure of USP Trandolapril Related Compound D RS in General Chapter <11> *USP Reference Standards*.

Response: Comment incorporated.

Monograph/Section(s): Triamcinolone Acetonide Nasal Spray/Multiple sections

Expert Committee: Chemical Medicines 4

No. of Commenters: 1

Comment Summary #1: The commenter requested revising the limit for Triamcinolone Acetonide Related Compound C to be consistent with the approved specification in the *Organic Impurities* test.

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

Comment Summary #2: The commenter recommended the removal of the reporting threshold as it will vary based on product-specific factors.

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

Comment Summary #3: The commenter requested the revision of acceptance criteria for *Delivered Dose Uniformity* to be consistent with approved specifications.

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

Monograph/Section(s): Vitamins with Minerals Oral Powder/Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 4

Comment Summary #1: The commenter suggested increasing the acceptance criteria upper limit for vitamin A from NMT 150% to NMT 165% due to the stability issue under the proposed use conditions in the developing regions of the world.

Response: Comment incorporated. The recommended increase of the upper limit is in agreement with the current limits established in the monographs for Oil- and Water-Soluble Vitamins with Minerals finished products.

Comment Summary #2: The commenter proposed adopting the procedures for *Vitamin A, Method 1*; *Vitamin A, Method 2*; or *Vitamin A Method 3* and *Vitamin E, Method 3* from the Oil- and Water-Soluble Vitamins and Minerals Capsules monograph as *Method 2 for Strength, Content of Vitamin A and Vitamin E*.

Response: Comment not incorporated. The EC concluded that is the data provided is insufficient to consider the addition of *Method 2 for Content of Vitamin A and Vitamin E*. The EC will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Comment Summary #3: The commenter proposed to add their in-house developed procedures for *Content of Vitamin A and Vitamin E*, and *Content of Cholecalciferol (Vitamin D)* as *Method 2* for respective vitamins.

Response: Comment not incorporated. The EC concluded that the information provided is insufficient to consider the addition of the recommended procedures. The EC will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Comment Summary #4: The commenter proposed to use *Niacin or Niacinamide, Pyridoxine Hydrochloride, Riboflavin, and Thiamine, Method 1* and *Folic Acid, Method 2* from Oil- and Water-Soluble Vitamins with Minerals Capsules monograph as *Method 2 for Content of Vitamins B1, B2, B3, B6, and Folic Acid*.

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

Comment Summary #5: The commenter proposed to add their in-house developed method for vitamins B1, B2 (as riboflavin), B3, B6, and B9 (folic acid) as *Method 2 for Content of Vitamins B1, B2, B3, B6, and Folic Acid*.

Response: Comment not incorporated. The EC concluded that the information provided is insufficient to consider the inclusion of the recommended procedures. The EC will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Comment Summary #6: The commenter proposed to add a procedure for determination of riboflavin-5-phosphate since many micronutrient powder products contain riboflavin-5-phosphate as the source of riboflavin.

Response: Comment not incorporated. The EC has concluded that the information provided is insufficient to consider the inclusion of the recommended procedure. The EC will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Comment Summary #7: The commenter proposed to use *Cyanocobalamin, Method 2* (bioassay) from the Oil- and Water-Soluble Vitamins with Minerals Capsules monograph as *Method 2 for Content of Vitamin B12*.

Response: Comment not incorporated. The EC concluded that the data provided is insufficient to consider the inclusion of the recommended procedure. The EC will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Comment Summary #8: The commenter recommended making the following modifications to the section *Content of Vitamin B12*: a) introduce a System suitability solution containing cyanocobalamin and riboflavin, b) add the requirements for resolution between cyanocobalamin and riboflavin peaks as NLT 1.5, and c) increase an equilibration time after each run from 1 min

to 10 min to cover equilibration with about 15 column volumes with ion pair reagent and improve a resolution.

Response: Comment incorporated.

Comment Summary #9: The commenter proposed adding *Cyanocobalamin, Method 1* from the Oil- and Water-Soluble Vitamins with Minerals Tablets monograph as Method 2 for *Content of Vitamin B12*.

Response: Comment incorporated. The previously proposed method for *Content of Vitamin B12* is named as *Method 1*.

Comment Summary #10: The commenter proposed adding their in-house developed method for vitamin C as Method 2 for *Content of Vitamin C*.

Response: Comment not incorporated. The EC concluded that the data provided is insufficient to consider the inclusion of the recommended procedure. The EC will consider further revisions to the monograph upon the receipt of the necessary supporting data.

Comment Summary #11: The commenter recommended adding the atomic absorption procedures as Method 2 for *Content of Copper, Iron, Selenium, and Zinc* in addition to the recommended inductively coupled plasma (ICP) method.

Response: Comment incorporated. The previously proposed ICP method for *Content of Copper, Iron, Selenium, and Zinc* is named as *Method 1*.

Comment Summary #12: The commenter proposed adding an HPLC procedure with L1 column and UV detection as Method 2 for *Content of Iodine*.

Response: Comment not incorporated. The EC concluded that the data provided is insufficient to consider the inclusion of the recommended procedure. The EC will consider further revisions to the monograph upon the receipt of the necessary supporting data.