



Commentary

First Supplement to USP 43–NF 38

February 5, 2020

In accordance with USP's *Rules and Procedures of the Council of Experts* ("Rules"), and except as provided in Section 7.02 Accelerated Revision Processes, USP publishes proposed revisions to the *United States Pharmacopeia* and the *National Formulary (USP–NF)* for public review and comment in the *Pharmacopeial Forum (PF)*, USP's free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee deems appropriate, the proposal may advance to official status or be republished in *PF* for further notice and comment, in accordance with the *Rules*. In cases when proposals advance to official status without re-publication in *PF*, a summary of comments received and the appropriate Expert Committee's responses are published in the Proposal Status/Commentary page of USPNF.com 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 PF:
[General Notices to USP–NF](#)

General Chapters

[<11> USP Reference Standards](#)
[<31> Volumetric Apparatus](#)
[<432> Determination of Zeta Potential by Electrophoretic Light](#)
[<641> Completeness of Solution](#)
[<659> Packaging and Storage Requirements](#)
[<661> Plastic Packaging Systems and Their Materials of Construction](#)
[<661.1> Plastic Materials of Construction](#)
[<661.2> Plastic Packaging Systems for Pharmaceutical Use](#)
[<731> Loss on Drying](#)
[<733> Loss on Ignition](#)
[<791> pH](#)
[<841> Specific Gravity](#)
[<858> Raman Spectroscopy](#)
[<1229.17> Mycoplasma Sterilization](#)
[<1661> Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact](#)
[<1858> Raman Spectroscopy - Theory and Practice](#)

Monographs

[Anise Oil](#)
[Clomiphene Citrate Tablets](#)
[Clonidine Hydrochloride Injection](#)
[Conjugated Linoleic Acids-Triglycerides](#)
[Coptis Species Rhizome](#)
[Coptis Species Rhizome Dry Extract](#)
[Coptis Species Rhizome Powder](#)
[Cromolyn Sodium](#)
[Diethylcarbamazine Citrate](#)
[Dobutamine Hydrochloride](#)
[Galactose](#)
[Galantamine Oral Solution](#)
[Galantamine Extended-Release Capsules](#)
[Guarana Seed](#)
[Guarana Seed Dry Extract](#)
[Guarana Seed Powder](#)
[Lidocaine, Racepinephrine and Tetracaine Hydrochlorides Compounded Topical Gel](#)
[Mesalamine Delayed-Release Tablets](#)
[Nabumetone Tablets](#)
[Pregabalin](#)
[Propylthiouracil Compounded Oral Suspension](#)
[Pyrroloquinoline Quinone Disodium](#)
[Rabeprazole Sodium](#)
[Selegiline Hydrochloride Tablets](#)
[Terminalia Chebula Fruit](#)
[Terminalia Chebula Fruit Dry Extract](#)
[Terminalia Chebula Fruit Powder](#)
[Valrubicin Intravesical Solution](#)

No comments were received for the following proposals:

Monographs

Anileridine Injection
Anileridine Hydrochloride
Anileridine Hydrochloride Tablets
Antimony Sodium Tartrate
Avobenzone
Benoxinate Hydrochloride Ophthalmic Solution
Betamethasone Cream
Betamethasone Benzoate
Betamethasone Benzoate Gel
Butalbital and Aspirin Tablets
Carteolol Hydrochloride Tablets
Cefamandole Nafate
Cefamandole Nafate For Injection
Cefdinir For Oral Suspension
Cefmenoxime for Injection
Cefmenoxime Hydrochloride
Cefmetazole Injection
Cefmetazole for Injection
Cromolyn Sodium Inhalation Solution
Cromolyn Sodium Nasal Solution
Cromolyn Sodium Ophthalmic Solution
Dichloralphenazone
Inulin in Sodium Chloride Injection
Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules
Lactase
Lauroyl Polyoxylglycerides
Levorphanol Tartrate Injection
Levothyroxine Sodium
Lithium Carbonate
Lithium Hydroxide
Losartan Potassium and Hydrochlorothiazide Tablets
Methylene Blue
Moexipril Hydrochloride and Hydrochlorothiazide Tablets
Potassium Bicarbonate
Prednisolone Acetate Injectable Suspension
Primaquine Phosphate Tablets
Saw Palmetto Capsules
Saw Palmetto Extract
Sucrose Diacetate Hexaisobutyrate
Sulfinpyrazone
Sulfinpyrazone Capsules
Sulfinpyrazone Tablets
Sulfisoxazole Acetyl Oral Suspension
Testosterone Injectable Suspension
Testosterone Propionate Injection
Tetracycline Oral Suspension
Tetracycline Hydrochloride for Injection

Tetracycline Hydrochloride for Topical Solution
Tetracycline Hydrochloride Ophthalmic Suspension
Tetracycline Hydrochloride and Nystatin Capsules
Thiethylperazine Maleate
Thiethylperazine Maleate Suppositories
Thiethylperazine Maleate Tablets
Thiothixene Hydrochloride
Thiothixene Hydrochloride Injection
Thiothixene Hydrochloride for Injection
Thiothixene Hydrochloride Oral Solution
Triamcinolone Tablets
Triamcinolone Diacetate Oral Solution
Triamcinolone Diacetate Injectable Suspension
Trisulfapyrimidines Oral Suspension
Trisulfapyrimidines Tablets
Tubocurarine Chloride
Tubocurarine Chloride Injection
Zinc Sulfate Compounded Injection
Zolpidem Tartrate Tablets

General Notices

General Notices/Section: General Notices/5.80 USP Reference Standards

Expert Committee (EC[s]): Council of Experts

No. of Commenters: 1

Comment Summary #1: The commenter recommended retaining the phrase “tests and assays” in the first sentence of the first paragraph, to make it consistent with the statement in the *Introduction* section of General Chapter <11> *USP Reference Standards*.

Response: Comment incorporated. The sentence is revised as follows: “USP Reference Standards are authentic specimens that have been approved as suitable for use in *USP* or *NF* tests and assays (see *USP Reference Standards* <11>).”

General Chapters

General Chapter/Sections: <11> *USP Reference Standards*/Multiple Sections

Expert Committee: Council of Experts

No. of Commenters: 6

Comment Summary #1: The commenter recommended indicating that a typical chromatogram may also be included in the USP Certificate where necessary for the intended use.

Response: Comment incorporated.

Comment Summary #2: The commenter asked to provide more details about the reference standard qualification process, including examples of mass balance determinations. The commenter also asked to provide more clarity on the minimum qualification/testing requirements that are used to establish the USP Reference Standards for various types of materials.

Response: Comment not incorporated. The types and extent of testing are primarily driven by the official uses of the standard. The method of choice in computing the assigned value of a USP Reference Standard is a mass balance analysis using independently determined components such as moisture, solvent residues, inorganic residues, chromatographic impurities, and ion content. For additional information, please also see the frequently asked questions (<http://www.usp.org/frequently-asked-questions/reference-standards>).

Comment Summary #3: Commenters requested including a designation and providing additional information on the label for the standards established by comparison with the World Health Organization (WHO) international standard (IS). A commenter also suggested that USP consider additional clarity in setting materials apart that qualify as true primary standards.

Response: Comment partially incorporated. In the *USP Reference Standards for USP or NF* section, under Quantitative determinations, the text is revised as follows: "For the USP Reference Standards where an International Standard (IS) established by the WHO exists, the reference standards documentation will indicate when the USP RS has been established by comparison to an International Standard (IS) established by the WHO."

Comment Summary #4: The commenter requested retaining the text stating that the current version of the catalog can be found on the USP website at <http://www.usp.org>.

Response: Comment incorporated.

Comment Summary #5: Commenters requested reinstating the language that the amount of material per individual USP Reference Standard is generally sufficient for several replicates.

Response: Comment not incorporated. The statement regarding "several replicates" was vague and open to interpretation, so the decision was made to remove it. The removal of the statement does not indicate any change in the amount of the packaged material provided.

Comment Summary #6: The commenter asked to clarify the statement regarding possible errors associated with the use of volumetric apparatus of smaller volume.

Response: Comment incorporated. The statement is revised as follows: "Potential errors associated with the use of volumetric apparatus of small volume should be taken into account (see also *General Notices*, 6.50.20.1. *Adjustment to Solutions*)."

Comment Summary #7: The commenter requested that USP work with the other compendia to consider allowance of suitable Reference Standards from other suitable compendia sources as acceptable for purposes that are deemed equivalent.

Response: Comment not incorporated because it is out of scope of the General Chapter. The interchangeability of pharmacopeial reference standards is a regulatory decision.

Comment Summary #8: The commenter suggested that, while understanding that the USP interpretation of room temperature is based on the definition in General Chapter <659>, USP should adopt tighter temperature range definitions for reference materials, more in line with current capabilities and expectations for environmental control, +/- 5°C range for room temperature and +/- 3°C or less for refrigerated or cold storage, especially for newly created materials.

Response: Comment not incorporated. Storage conditions are sufficient to preserve the integrity of the Reference Standard. USP also has to consider the capabilities of customers when defining storage requirements.

Comment Summary #9: The commenter supported the concept of reference standards without a direct link to compendial tests and procedures and indicated that it adds opportunity to provide highly useful materials that can aid the compendial users in the improvement of their measurements. The commenter emphasized the importance of the availability of sufficient and appropriate characterization data as well as additional transparency around the general characterization and qualification approaches that USP uses for these materials. Recognizing that <11> *USP Reference Standards* as a required Chapter may not be the place for this type of information, the commenter suggested to consider a general information chapter to address these topics.

Response: Comment not incorporated. A general information chapter may be considered at a later time. USP acknowledges the commenter's point regarding the importance of characterization data for reference standards for other measurements and determinations.

Comment Summary #10: The commenter suggested including a statement on the reference standard approval process in this chapter.

Response: Comment not incorporated. Currently the reference standards approval process is outlined in Section 7.06 of the *Rules and Procedures of the Council of Experts*.

Comment Summary #11: The commenter recommended clarifying how USP ensures the quality of the standard used for calibration where no WHO standard is currently available.

Response: Comment not incorporated. The chapter already states, “In these instances, the USP standard is established in such a way as to ensure long-term stability and fitness for purpose, which permits the calibration of successive lots of USP RS with increased confidence that drift in the assigned unit can be avoided.” USP routinely monitors the standards as part of the Continued Suitability for Use (CSU) program which is also described in the chapter.

Comment Summary #12: The commenter recommended clarifying that only the reference standards approved as suitable for use in *USP* or *NF* assume official status and legal recognition in the United States and other jurisdictions that recognize the *USP* or *NF*.

Response: Comment incorporated. The text in the second paragraph in the introduction is revised as follows: “USP RS are generally linked to relevant tests and assays in the *United States Pharmacopeia (USP)* or *National Formulary (NF)* documentary standards. They have been approved and established as suitable for use in the context of these applications. When approved as suitable for use in *USP* or *NF* tests and assays, USP RS also assume official status and legal recognition in the United States and other jurisdictions that recognize the *USP* or *NF* (see General Notices, 2.30 *Legal Recognition*).”

Comment Summary #13: The commenter suggested that USP Reference Standards for Other Measurements and Determinations and the USP Reference Standards for *USP* or *NF* be clearly separated in the USP catalog.

Response: Comment not incorporated. All USP Reference Standards are developed using the same robust quality systems. They are differentiated by being called out in documentary standards (USP Reference Standards for *USP* or *NF*) or not called out (USP Reference Standards for Other Measurements and Determinations).

Comment Summary #14: The commenter suggested revising the *Labeling* section to indicate that the affixed RS label also includes a National Drug Code (NDC) number for controlled substances.

Response: Comment not incorporated at this time. Additional updates to the list of attributes typically included on the affixed RS label and/or USP Certificate may be considered at a later time.

Comment Summary #15: The commenter asked about the status of addressing legacy quantitative standards which do not have an assigned value on the label.

Response: This is a request for information, with no change in the chapter text being requested. USP is currently working to ensure that all quantitative USP Reference Standards that do not have an assigned value currently on the affixed label will have it by the official date of this revision (August 1, 2020).

Comment Summary #16: The commenter requested revising the *Packaging* section and move the last sentence to after the second sentence.

Response: Comment not incorporated. The proposed text is included in the currently official chapter. The EC determined that the text is clear as written.

Comment Summary #17: The commenter requested deleting the last two sentences under *Anhydrous Basis, Determine Water Content Titrimetrically at Time of Use* in the *Proper Use* section as procedural, and to continue referencing a general chapter.

Response: Comment not incorporated. The proposed text is included in the currently official chapter and provides important details and recommendations for the titrimetric water determination.

General Chapter: <31> *Volumetric Apparatus*
Expert Committee: General Chapters–Chemical Analysis
No. of Commenters: 3

Comment Summary #1: The commenter requested changing the sentence “Most of the volumetric apparatus available in the United States is calibrated at 20°, although the temperatures generally prevailing in laboratories more nearly approach 25°.” to “Most of the volumetric apparatus available in the United States is calibrated at 20°, and the National Institute of Standards and Technology has adopted 20° as the reference temperature for calibration of laboratory glassware. Such glassware may be used at other temperatures.”

Response: Comment partially incorporated. The text was changed to “Most of the volumetric apparatus available in the United States are calibrated at 20°, and the National Institute of Standards and Technology (NIST) has adopted 20° as the reference temperature for the calibration of laboratory glassware, although the temperatures generally prevailing in laboratories are usually between 20° and 25°.”

Comment Summary #2: The commenter requested adding a footnote to reference the ASTM E1293-02 to the paragraph for capacity tolerances for measuring pipets of up to and including 10 mL capacity because the reference to the source document is useful.

Response: Comment incorporated.

Standards of Accuracy

Comment Summary #3: The commenter suggested changing “the tips” to “the pipet tip” for clarity.

Response: Comment incorporated.

Comment Summary #4: The commenter recommended changing the sentence “Volume readings on burets should be estimated at least to the nearest 0.05 mL for burets of 50-mL or less.” to “Volume readings on burets should be estimated at least to the nearest one-half of a subdivision.” because burets specified within ASTM E287 and E1189 range from 1 mL to 100 mL. In the case of the 1 mL buret, an estimation error of 0.05 mL is 5% of the maximum volume and larger than it needs to be. A requirement based on fractional multiple of a marked subdivision would make for a more uniform percentage error and would be easily trained. Operator repeatability in estimation to a few tenths of a subdivision is attainable. One-half a subdivision is easily attainable.

Response: Comment incorporated.

Comment Summary #5: The commenter recommended changing the subdivisions for 25-mL and 50-mL burets in *Table 3* from 0.1 mL to 0.10 mL

Response: Comment not incorporated because the current subdivisions for glass graduated burets are identical to ASTM E287-02, *Table 1*, Class A.

General Chapter: <432> *Determination of Zeta Potential by Electrophoretic Light Scattering*

Expert Committee: General Chapters–Physical Analysis

No. of Commenters: 2

General

Comment Summary #1: The commenter noted that there were currently five or more terms used somewhat interchangeably (e.g., medium, liquid, dispersion, dispersion liquid, dispersion medium) and recommended using consistent terminology.

Response: Comment incorporated. The EC decided to consistently use the term “dispersion medium” in all those cases.

Introduction

Comment Summary #2: The commenter recommended minor editorial changes in the first paragraph.

Response: Comment incorporated. The EC decided replacing “is placed in a cell that has a pair of electrodes that are used to apply an electrical potential” with “is placed in a cell equipped with a pair of electrodes that are used to apply an electrical potential”, and “attracted toward the opposite sign electrode (this process is known as electrophoresis)” with “attracted toward the opposite sign electrode, a process known as electrophoresis” as recommended.

Comment Summary #3: The commenter suggested including a more precise definition of zeta potential and how it is measured in the second paragraph of the *Introduction*.

Response: Comment incorporated. The EC revised the paragraph to state: “Zeta potential, denoted by the Greek letter ζ (hence the name), is a physicochemical characteristic of colloidal systems (suspensions and emulsions) that describes the electric potential difference between the mobile dispersion medium and the stationary layer of the dispersion medium attached to the dispersed particle.”

Principle

Comment Summary #4: The commenter suggested in the first paragraph the deletion of the algorithm example in parenthesis stating that those examples were not used for as entered in the text.

Response: Comment incorporated. The EC revised the sentence to delete the “(e.g., autocorrelation function)”.

Comment Summary #5: The commenter suggested the first paragraph clarifying that the derivation of Zeta potential is via the Henry function, whereby limit values are either Smoluchowski or Hückel values, and how this is done.

Response: Comment incorporated. The EC revised the sentence to state “Zeta potential is derived from the electrophoretic mobility using the Henry function, which can be approximated by the Smoluchowski equation or Hückel equation according to the relative thickness of the electrical double layer compared to the hydrodynamic radius of the particle”.

Comment Summary #6: The commenter suggested adding a statement explaining why electrophoretic light scattering (ELS) method was selected for this chapter (instead of a different method for deriving the zeta potential).

Response: Comment not incorporated. The EC determined that the current text is suitable and there is no need for further explanation since it is well known that the ELS is the most commonly used technique in pharmaceutical industry for determination of Zeta potential.

Instrument

Comment Summary #7: The commenter suggested in the first paragraph replacing “The instrument should be located in an environment free of dust” with “The instrument should be located in a controlled environment with reduced dust (i.e., ISO class 6, 7, or 8).”

Response: Comment incorporated. The EC revised the text as suggested.

Comment Summary #8: The commenter suggested moving the last three paragraphs of the section to the *Principles* section.

Response: Comment not incorporated. The EC determined that these paragraphs fit better with instrument hardware, not with measurement principles.

Comment Summary #9: Referring to the last sentence of the last paragraph, the commenter stated that it may not be clear to all readers that “sign of the zeta potential” refers to positive versus negative voltage and suggested a different wording.

Response: Comment partially incorporated. The EC revised the sentence adding “(positive or negative voltage)” after the word sign to read, “Thus, the use of a frequency modulator enables the determination of the sign (positive or negative voltage) of the zeta potential.”

Development of the Method

Comment Summary #10: Referring to the text under pH entry, the commenter recommended replacing it with a more detailed text explaining surface chemistry and its pH dependency.

Response: Comment partially incorporated. The EC determined that a detailed discussion of the pH effect was outside the scope of the chapter. The EC revised the text to note that the particle surface chemistry plays a role on pH effect on zeta potential.

Comment Summary #11: The commenter suggested adding a schematic of the double layer including the surface, Stern layer, Debye layer, and where zeta potential is being measured.

Response: Comment not incorporated. The EC determined that the suggestion is out of scope of the chapter. This is a chapter property measurement using an instrument. The user knows what they are measuring.

Comment Summary #12: The commenter suggested that the conductivity units be spelled out in the “conductivity” subsection.

Response: Comment incorporated. The EC revised the text to add “(milli Siemens per cm)” to the sentence to read, “Typically, the conductivity should be within 1-5mS/cm (milli Siemens per cm).”

Comment Summary #13: The commenter stated that it should be a discussion on the impact of using dispersion media containing multivalent ion salts and provided details on the interactions that occur. The commenter recommended adding a section on media considerations and selection/reporting of media composition including viscosity, pH, conductivity, salt/buffers used, and associated ion concentrations.

Response: Comment not incorporated. The EC determined that the current text is suitable. The proposed considerations are discussed in the current text to the extent needed to perform a valid measurement.

Comment Summary #14: The commenter suggested replacing “range” with “concentration range” in the body of the text of the “*Concentration Range of the Colloidal System*” subsection.

Response: Comment incorporated. The EC revised the text to add “concentration” before the word “range” in the entry to read, “The effect of the dispersed material concentration on the zeta potential must be evaluated and the concentration range of a constant zeta potential established.”

Comment Summary #15: The commenter disagreed with the statement of the first sentence in the viscosity subsection and provided a rationale for the disagreement. The commenter further recommended either specifying the other factors and how they affect the viscosity or referencing a chapter or guidance that explains this in more detail.

Response: Comment partially incorporated. The EC revised the text to clarify the entry and added a reference link to General Chapter <1430.4> *Analytical Methodologies Based on Scattering Phenomena—Electrophoretic Light Scattering (Determination of Zeta Potential)*.

Comment Summary #16: The commenter suggested inserting “The change induced by repeated measurement can be verified by measuring particle size before and after measuring zeta potential” before the last sentence of the bullet 1 of the *Sample Stability Considerations* subsection.

Response: Comment not incorporated. The EC determined that the current text is suitable. The suggested topic is discussed in <1430.4>.

Comment Summary #17: The commenter recommended addressing the considerations of the dilution media and provided some rationale.

Response: Comment incorporated. The EC revised the text to add the following paragraph: “It is important to ensure that the diluting dispersion medium has the same electrolyte composition and pH as the dispersion being tested, especially when the goal of the study is the understanding of the formulation properties in that particular medium. However, the resulting

conductivity of the media needs to be within the workable range as shown under Conductivity above.”

Method Validation

Comment Summary #18: The commenter suggested rearranging the content of the first paragraph and provided the following suggested text “In zeta potential analysis by electrophoretic light scattering, specificity, as defined by the International Council for Harmonisation (ICH), range, linearity, DL, and QL are not applicable because it is not possible to discriminate different components of a sample.”

Response: Comment partially incorporated. The EC revised the text to clarify the entry and address the commenter’s point to state: “The range, linearity, DL, and QL as defined in ICH Q2 guidelines and <1225> are also not applicable. Exploring a linear relationship between concentration and response, or a mathematical model for interpolation, is not applicable to this procedure since Zeta potential should be a constant value and should be constant for the optimized concentration range” noting that the DL and QL are independent of component discrimination.

Comment Summary #19: The commenter pointed out to a typo “DQ” instead of “QL” in the first sentence of the second paragraph.

Response: Comment incorporated. The EC corrected the typo.

Data Processing and Interpretation

Comment Summary #20: The commenter, referencing Equations 1–4, stated that only a few variables are defined for these calculations and that many are non-standard variables that impact the zeta potential calculation. The commenter suggested including a definition for each variable.

Response: Comment not incorporated. The EC determined that there was no need to define the variables here since they are already defined in <1430.4> and the chapter has a link to it.

Comment Summary #21: The commenter suggested defining the $\Delta\omega$ as “Doppler frequency shift” in Equations 1 and 2 under the “*Conversion of Doppler Shifts into Electrophoretic Mobility*” subsection.

Response: Comment partially incorporated. The EC revised the first sentence of the subsection to add “ $\Delta\omega$ ” in parenthesis after the Doppler frequency shifts phrase.

Comment Summary #22: The commenter suggested changing λ_0 (laser wavelength in vacuum) to λ in Equations 1 and 2 to be consistent with the notation in <1430.4>.

Response: Comment incorporated. The EC revised the equations as suggested.

Comment Summary #23: The commenter suggested defining the Debye electrical double layer and the associated equation in the “*Conversion of Doppler Shifts into Electrophoretic Mobility*” subsection so a user can determine if their system best fits the assumptions for the Smoluchowski equation (Equation 3) or Hückel equation (Equation 4).

Response: Comment not incorporated. The EC determined that the current text is suitable and that the suggestion is out of scope of the chapter. This is a chapter on property measurement using an instrument; Chapter <1430.4> and references therein have more information on the topic.

Comment Summary #24: The commenter recommended adding some information about reference beam optic alignment and cross beam optic alignment.

Response: Comment not incorporated. The EC determined that the current text is suitable. The different beam optic alignments are defined and respective schematic given in <1430.4>.

Comment Summary #25: The commenter recommended adding additional text regarding the validity for use of the limit values of Henry function in the “*Calculation of Zeta Potential*” subsection.

Response: Comment not incorporated. The EC determined that the current text is suitable. The recommended addition is outside the scope of the chapter. This is a chapter on property measurement using an instrument.

Comment Summary #26: The commenter discussed the use of “reference,” “reference material,” and “standard sample” in the entire section and, noting an inconsistency, recommended developing a more consistent set of terms for a reference versus a standard sample used for verification and qualification.

Response: Comment incorporated. The EC revised the text to replace the above-mentioned terms with the “standard sample” term.

Comment Summary #27: The commenter suggested an editorial revision of the second paragraph.

Response: Comment not incorporated. The EC determined that the current text is suitable.

General Chapter: <641> *Completeness of Solution*
Expert Committee: General Chapters–Physical Analysis
No. of Commenters: 1

Method I

Comment Summary #1: The commenter suggested changing “10-ml glass cylinder” to “10-ml clear glass mixing graduated cylinder” for clarity.

Response: Comment partially incorporated. The text was changed from “10-mL glass cylinder approximately 13 mm x 125 mm in size” to “10-mL color-comparison tube” for consistency with the General Chapters <630> *Visual Comparison* and <631> *Color and Achromicity*.

Comment Summary #2: The commenter suggested changing “fill the cylinder almost to the constriction at the neck” to “fill the cylinder to the 10-ml mark” because this description is more specific, and filling to the 10-ml mark leaves more empty space for mixing.

Response: Comment partially incorporated. The text was changed to “fill the color-comparison tube to the 10-mL mark” for consistency.

Expert Committee-Initiated Change #1: The acceptance criteria was changed from “the solution is not less clear than an equal volume of the same solvent contained in a similar vessel” to “the solution is not less clear than an equal volume of the same solvent contained in a matched color-comparison tube” for consistency.

General Chapter: <659> *Packaging and Storage Requirements*
Expert Committee: General Chapters–Packaging and Distribution
No. of Commenters: 1

General

Comment Summary #1: The commenter recommended updating several *Code of Federal Regulations (CFR)* references in the chapter.

Response: Comment not incorporated. All *CFR* references have been reviewed and updated. These updates appear in *PF* 45(5) [Sep.–Oct. 2019].

General Chapter: <661> *Plastic Packaging Systems and Their Materials of Construction*

Expert Committee: General Chapters–Packaging and Distribution
No. of Commenters: 7

General

Comment Summary #1: The commenter suggested adding the temperature designation of C or F degree so that it is clear as to the temperature units.

Response: Comment not incorporated. USP General Notices states that the degree symbol without a qualifying unit of measure represents degrees Celsius.

Comment Summary #2: The commenter suggested adding a statement to <661> stating that requirements of General Chapter <661.1> *Plastic Materials Of Construction* are met by performing the tests in <661.1> or if the material is used in a packaging component or system that meets the requirements of General Chapter <661.2> *Plastic Packaging Systems for Pharmaceutical Use*.

Response: Comment incorporated.

Scope

Comment Summary #3: The commenter suggested that the title of the referenced <1661> chapter be revised to be consistent with title in *PF 45(2)* [Mar.–Apr. 2019].

Response: Comment incorporated.

Polypropylene Containers

Comment Summary #4: The commenter recommended revising the nonvolatile residue limit from 225 mg to 600 mg or exempting polypropylene containers from this requirement.

Response: Comment not incorporated. Additional information is needed from the commenter to assess this revision request.

General Chapter: <661.1> *Plastic Materials of Construction*
Expert Committee: General Chapters—Packaging and Distribution
No. of Commenters: 8

General

Comment Summary #1: The commenter recommended keeping the extractable elements requirement in General Chapter <661.1> for materials of construction because ICH Q3D clearly states that packaging materials need to be evaluated for potential elemental impurities that could interact with the drug product.

Response: Comment not incorporated. EC has plans to revisit the topic during the 2020–2025 revision cycle.

Comment Summary #2: The commenter recommended referencing General Chapter <232> *Elemental Impurities—Limits*.

Response: Comment not incorporated. It is not appropriate to reference <232> in <661.1>, which is specific for materials of construction and not finished drug products.

Comment Summary #3: The commenter recommended adding information stating that the material supplier should have a certificate of analysis stating compliance to <661.1>.

Response: Comment not incorporated. Compendial standards are meant for drug product manufacturers, and I cannot mandate that a material supplier test or provide specific information.

Scope

Comment Summary #4: The commenter suggested removing the >1000 chapter reference because its placement in <661.1> makes it mandatory.

Response: Comment not incorporated. General Notices specifically state that >1000 chapters that are referenced in <1000 chapters are for informational purposes only.

Comment Summary #5: The commenter suggested that if <661.1> is going to apply to <665>, the text in the chapter needs to reflect this.

Response: Comment incorporated.

Comment Summary #6: The commenter recommended the removal of any references to acceptance criteria for “relevant extractable metals” of plastic materials of construction from chapter <661.1> due to the established low risk to drug product quality and patient safety attributable to elemental impurities from packaging components.

Response: Comment not incorporated. The chapter only mentions “relevant extracted metals” in the introduction, and the statement accurately reflects what the EC intended to convey at this time.

Comment Summary #7: The commenter recommended addressing the conflict between the text regarding unaddressed materials in Scope and what is in *Table 1* related to the application of tests.

Response: Comment incorporated.

Acidity or Alkalinity

Comment Summary #8: The commenter recommended aligning the BRP indicator preparation with *European Pharmacopoeia*.

Response: Comment incorporated.

Total Organic Carbon (TOC)

Comment Summary #9: The commenter suggested giving guidance as to what can be done if a material cannot meet the TOC limit.

Response: Comment not incorporated. The chapter already states that if a material fails the TOC or Absorbance acceptance criteria, it can still be deemed compliant if the chemicals responsible for the result can be established (identity and concentration) and characterized to determine that the probable risk posed by all chemicals is within acceptable parameters.

General Chapter: <661.2> *Plastic Packaging Systems for Pharmaceutical Use*

Expert Committee: General Chapters–Packaging and Distribution

No. of Commenters: 9

General

Comment Summary #1: The commenter suggested listing all dosage forms that apply under “All Other Dosage Forms.”

Response: Comment not incorporated. It is not practical to list all dosage forms.

Comment Summary #2: The commenter recommended referencing General Chapter <232>.

Response: Comment not incorporated. It is not appropriate to reference <232> in <661.2>, which is specific for packaging components and systems, not finished drug products. The EC will revisit the topic in the 2020–2025 revision cycle.

Introduction

Comment Summary #3: The commenter recommended including examples of the types of closures used in packaging systems (e.g., rubber seals, foil closures, laminated closures).

Response: Comment incorporated.

Scope

Comment Summary #4: The commenter recommended adding language stating that material of construction for a low-risk dosage form does not undergo fundamental change during component conversion; therefore, testing is not necessary.

Response: Comment not incorporated. The transformation of plastic material to a plastic component is a fundamental change.

Table 1

Comment Summary #5: The commenter suggested separating the middle column into three columns (i.e., oral liquids, oral solids, and topical dosage forms) and stating that oral solids need not comply.

Response: Comment not incorporated. The EC does not agree with the comment that testing of low-risk packaging components and systems is not necessary.

Comment Summary #6: The commenter suggested clarifying that along with extractables and leachables testing, physicochemical and biological reactivity testing is still necessary.

Response: Comment incorporated.

Biological Reactivity

Comment Summary #7: The commenter suggested that biological reactivity testing is not necessary in <661.2> if testing was performed on the plastic material via <661.1>.

Response: Comment not incorporated. Biological reactivity of a material can be impacted during the component conversion process.

Comment Summary #8: The commenter recommended including information around the appropriate classification for plastic packaging systems via General Chapter <1031> *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants*.

Response: Comment not incorporated. Reference to <1031> has been removed from the chapter to remove any confusion.

Physicochemical Tests (Solution C1)

Comment Summary #9: The commenter suggested that multi-layer blister packaging systems cannot be tested via chapter <661.2>.

Response: Comment not incorporated. With the *PF 45(2)* proposal, the option has been given that a model system could be developed and used, which would negate the need to submerge a multi-layer material.

Comment Summary #10: The commenter suggested giving the option to use an oven if the packaging system needs to be tested at 100° or 70°.

Response: Comment incorporated.

Comment Summary #11: The commenter suggested giving the option to test the system or the component.

Response: Comment not incorporated. The option for component testing is already stated in the *Scope* section.

Comment Summary #12: The commenter recommended defining nominal volume, as it relates to the chapter, for both liquid and solid drug products.

Response: Comment incorporated.

Comment Summary #13: The commenter suggested giving more clarity on what to do when the nominal volume is not known.

Response: Comment not incorporated. The chapter focuses on testing of the final drug product in its packaging system so such information should be known.

Comment Summary #14: The commenter suggested giving more clarity on how to test unique packaging systems and problematic testing materials (e.g., paper lidding for blisters).

Response: Comment not incorporated. In these unique situations, the extraction approach chosen should meet the intentions of the chapter. The impact on the sample data should range from negligible to worst-case scenario. A statement to <1661> will be added regarding this point.

Total Organic Carbon (TOC)

Comment Summary #15: The commenter suggested that TOC testing for components and systems for solid dosage forms is not necessary. It was articulated that the potential for extraction is not relevant, and therefore the listed TOC limits are not relevant or applicable.

Response: Comment not incorporated. It has been discussed previously and decided that TOC and other physicochemical tests are required for solid dosage forms.

Comment Summary #16: The commenter suggested that the chapter should clarify the differences in requirements between packaging systems for long-term storage of liquids and those of short-term storage of liquids, such as reconstitution.

Response: Comment not incorporated. This is beyond the scope of the chapter.

Spectral Transmission

Comment Summary #17: The commenter recommended removing the *Spectral Transmission* section from this chapter and either reinstating this language in General Chapter <671> *Containers—Performance Testing* or creating a new chapter specific to this testing.

Response: Comment not incorporated. The EC will consider a chapter on container performance test, which may include the spectral transmission topic, at a later date.

Comment Summary #18: The commenter suggested adding language to the section stating that if photostability studies are performed during development and the package is shown to provide adequate protection based on these studies, there should be no need to perform spectral transmission testing.

Response: Comment incorporated.

General Chapter: <731> *Loss on Drying*
Expert Committee: General Chapters—Physical Analysis
No. of Commenters: 3

General

Comment Summary #1: The commenters suggested adding wording to clarify the possibility of using an alternate procedure, as a moisture balance analyzer (e.g. an infrared moisture analyzer).

Response: Comment not incorporated because users can use alternate procedures as stated in the USP General Notices, under 6.30. *Alternative and Harmonized Methods and Procedures*. There is no sufficient evidence to incorporate this particular technology in the chapter.

Comment Summary #2: The commenters suggested incorporating text to address situations where the sample and container gain weight at the completion of the testing duration.

Response: Comment not incorporated because this might be an indication that something is wrong in performing the procedure. These results should not be reported but rather be investigated.

Comment Summary #3: The commenter recommended harmonizing more closely with the *European Pharmacopoeia*, e.g., in drying to constant weight, 0.5 mg vs. 0.5 mg/g, and 30 min vs. 60 min additional drying time

Response: Comment not incorporated because the ICH PDG requires further evaluation of impact before incorporating this chapter into its work plan.

Procedure

Comment Summary #4: The commenter recommended changing the wording for the tared glass-stoppered weighing bottle to be more flexible and allow selecting the glassware that will be the best to reduce sample loss and repeat testing.

Response: Comment partially incorporated. The sentence now reads: "Tare an appropriate glass stoppered weighing bottle."

Comment Summary #5: The commenter suggested adding the following text to the paragraph on "dry to constant weight": "Weighing of the residue should be performed on the most precise balance available that is physically capable of taking readings for the weight range (for both the sample and container). A balance should not be used if the capability of the instrument does not allow a difference of at least 0.5 mg per g."

Response: Comment not incorporated because the balance should be capable to measure 0.50 mg per g and the General Chapter <41> *Balances* states the requirements for a suitable balance.

Comment Summary #6: The commenter requested clarifying to perform the weighing after drying with the same requirements for the balance as before drying, from a metrological perspective.

Response: Comment incorporated: “accurately” was added to the weighing after drying.

Comment Summary #7: The commenter requested deleting the sentence with balance requirement of accuracy to 0.01 mg regarding thermogravimetric analysis because metrological instrument requirements based on digital increment are not appropriate.

Response: Comment partially incorporated. The sentence now reads: “Where the individual monograph directs that Loss on Drying be determined by thermogravimetric analysis, a suitable balance is to be used (see Balances <41>).”

Comment Summary #8: The commenter suggested incorporating an adequate specification of the vacuum level for drying under vacuum to avoid arbitrary results depending on actually used vacuum levels.

Response: Comment not incorporated because “vacuum” is defined in the USP *General Notices*, under 8.210. *Vacuum*.

Comment Summary #9: The commenter suggested incorporating requirements for humidity to be maintained in the desiccator to avoid creating weighing uncertainties due to arbitrary moisture uptake between drying and weighing.

Response: Comment not incorporated because there are no specific humidity requirements. Fully effectiveness of the desiccant requires the user to ensure suitability.

General Chapter: <733> *Loss on Ignition*

Expert Committee: General Chapters–Physical Analysis

No. of Commenters: 3

Comment Summary #1: The commenters requested defining “constant weight” within this chapter even though it is already defined within *General Notices*, under 6.40.10. to prevent its incorrect interpretation. There is a precedence for this request in <731> and the *General Notices*, under 6.40.20.

Response: Comment incorporated.

Comment Summary #2: The commenter requested clarifying to perform the weighing after ignition with the same requirements for the balance as before ignition, from a metrological perspective.

Response: Comment incorporated. “Accurately” was added to the weighing after ignition.

General Chapter: <791> *pH*

Expert Committee: General Chapters–Physical Analysis

No. of Commenters: 13

General

Comment Summary #1: The commenters suggested updating the text of the chapter with a clear definition of multiple-point calibration, if it is resulting in multiple slopes and offsets.

Response: Comment incorporated with the addition of two footnotes, one for a multiple-point calibration process (three or more calibration buffers plus at least one verification buffer) and one for a multiple-segment calibration process (three or more calibration buffers with at least two slopes and offsets plus at least one verification buffer for each segment).

Calibration

Comment Summary #2: The commenter recommended moving the complete calibration section to an informational chapter to allow flexibility for instrumentation in usage.

Response: Comment not incorporated because the chapter states: “Because of variations in the nature and operation of the available pH measurement systems, it is not practical to provide

universal directions for the calibration of the measurement system. However, the general principles to be followed are set forth in the following paragraphs.”

Comment Summary #3: The commenters suggested keeping the multipoint calibration process with the evaluation of a single slope and offset for the entire calibrated range combined with the relevant use of the points of verification in between the calibration points to ensure a reliable and accurate pH measurement.

Response: Comment incorporated. A clarifying sentence was added before the calibration steps: “The procedure below allows for several calibration methodologies (two-point calibration, multiple-point calibration, and multiple-segment calibration).”

Comment Summary #4: The commenters recommended clarifying between non-segmented multipoint linear curve (resulting in one slope and one offset) vs. multipoint “segmented” calibration (resulting in three or more measured points with a slope and offset each range).

Response: Comment incorporated in two footnotes:

“NOTE—If a multiple-point calibration process (three or more calibration buffers) plus at least one verification buffer are used, then repeat steps 9–14, assuring that the pH sensor slope and offset criteria (see step 10) and the calibration accuracy (see step 14) of this range are met. The value of the verification buffers shall be between the highest and lowest calibration buffers of the range.

NOTE—If a multiple-segment calibration process (three or more calibration buffers with at least two slopes and offsets) plus at least one verification buffer for each segment are used, then repeat steps 9–14 for each segment, assuring that the pH sensor slope and offset criteria (see step 10) and the calibration accuracy (see step 14) of each segment are met. The value of each verification buffer shall be between the highest and lowest calibration buffers for each segment.”

General Chapter: <841> *Specific Gravity*
Expert Committee: General Chapters—Physical Analysis
No. of Commenters: 3

General

Comment Summary #1: The commenter recommended changing temperature units from “°” to “°C” to for clarity.

Response: Comment not incorporated because the USP *General Notices* under 8.180. *Temperatures* states that temperatures are expressed in centigrade (Celsius) degrees.

Comment Summary #2: The commenter recommended replacing d_t^t with SG throughout the chapter for clarity.

Response: Comment not incorporated because the symbols are correct and in alignment with the *European Pharmacopoeia*.

Comment Summary #3: The commenter suggested replacing t° with “t degree” and $t^{\circ'}$ with “t' degree” to avoid the potential confusion on t and t° (or t' and $t^{\circ'}$) referring to different temperatures.

Response: Comment partially incorporated. t° and $t^{\circ'}$ were changed to t and t' respectively throughout the document.

Comment Summary #4: The commenter requested changing the units of viscosity from “mPa” to “mPa·s”.

Response: Comment incorporated.

Introduction

Comment Summary #5: The commenter suggested defining specific gravity replacing the first sentence with the following text: “Specific gravity (SG) is the ratio of the density of a substance to the density of water at a specific temperature.”

Response: Comment not incorporated. The EC determined that the current text in the first paragraph is clear and more complete.

Comment Summary #6: The commenter suggested replacing the second definition with the following text: “The specific gravity (SG) can also be given as the ratio of the mass of a volume of a substance to the mass of the same volume of water, both at a specific temperature t.”

Response: Comment not incorporated. The EC determined that the current text in the third paragraph is clear and more complete.

Comment Summary #7: The commenter suggested retaining the sentence, “Unless otherwise directed in the individual monograph, use Method 1.” This is not the type of test where if method 1 fails you move on to method 2.

Response: Comment not incorporated. Either method 1 or method 2 could be used to run the test.

Method I

Comment Summary #8: The commenter requested changing “scrupulously clean” to “clean” because the word “scrupulously” is unnecessary.

Response: Comment incorporated.

Method II

Comment Summary #9: The commenter requested changing the first sentence to “This procedure includes the use of an oscillating transducer density meter.”

Response: Comment partially incorporated. The sentence was changed to “The procedure requires the use of the oscillating transducer density meter.”

Comment Summary #10: The commenter suggested changing the wording for density correction to “Samples with viscosities <1 mPa-s can be accurately measured without a density correction. Samples with viscosities >1 mPa-s must be measured with a density correction. If a density correction is not possible for a sample with >1 mPa-s viscosity, use Method I.” because the viscosity of water at 20°C is 1 mPa-s, the discrete standard changes from 10 mPa-s to 1 mPa-s. If you have any standard for setting 10 mPa-s, include the rationale for setting 10 mPa-s in the chapter.

Response: Comment not incorporated because the threshold is not a function of the viscosity of the reference (water), but of the magnitude of the correction as a function of viscosity.

Method II/Calibration

Comment Summary #11: The commenter recommended replacing “The results displayed for the control measurement using degassed water do not deviate from the reference value” with “The results from the control measurement using degassed water should not deviate from the reference value” for clarity.

Response: Comment incorporated.

Comment Summary #12: The commenter suggested replacing ρ_{25} with ρ^{25} because per definition of density at temperature t, ρ should have a superscript of 25 instead of a subscript.

Response: Comment not incorporated because the terminology is standard and in alignment with the *European Pharmacopoeia*.

Expert Committee-Initiated Change #1: The notation for viscosity was changed from ρ^t_s to $\rho_{s,t}$ and ρ^t_w to $\rho_{w,t}$ for consistency in this chapter.

Method II/Procedure

Comment Summary #13: The commenter recommended replacing “>10 mPa” with “>1 mPa-s” because the viscosity of water at 20°C is 1 mPa-s.

Response: Comment not incorporated because the threshold is not a function of the viscosity of the reference (water), but of the magnitude of the correction as a function of viscosity.

Comment Summary #14: The commenter recommended replacing “If necessary, equilibrate the liquid to be examined at 25° before introduction into the tube” with “If necessary, equilibrate the sample at 25° before introduction into the tube.”

Response: Comment partially incorporated. The sentence was changed to “If necessary, equilibrate the liquid at 25° before introduction into the tube”

General Chapter/Sections: <858> *Raman Spectroscopy*/Multiple Sections

Expert Committee: General Chapters—Chemical Analysis

No. of Commenters: 6

General

Comment Summary #1: The commenter recommended that the USP harmonize with the *European Pharmacopoeia* 2.2.48 and *Japanese Pharmacopoeia (JP)* 2.26 chapters on Raman spectroscopy, including the acceptance criteria for Raman instrumentation.

Response: Comment not incorporated. The EC asserts that this General Chapter contains best scientific practices.

Qualification of Raman Spectrometers

Comment Summary #2: The commenter recommended reformatting the acceptance criteria for qualitative applications from “ $\pm 3 \text{ cm}^{-1}$ ” to “ $\pm 3.0 \text{ cm}^{-1}$.” to be consistent with those established in *Table 1*.

Response: Comment incorporated.

Comment Summary #3: The commenter suggested that the proposed tolerances in *Table 1* are achievable by handheld RMI instruments and the higher tolerances reduce the potential for false positives. The commenter preferred to have tolerances segregated by usage intent (quantitative and qualitative), rather than the instrument type a (benchtop and handheld), but it would be helpful if there was harmonization across global pharmacopeias.

Response: Comment not incorporated. The general chapter does not distinguish between handheld and benchtop instruments but establishes acceptance criteria based on the intended purpose. Text edited to clarify the application of the acceptance criteria.

Comment Summary #4: The commenter suggested that the acceptance criteria in *Table 1* appear to be applicable to calibration models for quantitative analysis, and not qualitative analysis.

Response: Comment not incorporated. The section describes operational qualification criteria, and not validation of calibration models for qualitative and/or quantitative methods.

Comment Summary #5: The commenter indicated that the acceptance criterion for the acetaminophen peaks in General Chapter <858> should be consistent with those in the *EP* and *JP* at the tighter tolerance for all peaks unless a justification for differing from those well-established values is presented. There does not appear to be logic in having a tolerance of $\pm 2.5 \text{ cm}^{-1}$ for the 797.2 cm^{-1} peak when the tolerance of all others are consistent with values in the *European Pharmacopoeia* and *JP* benchtop instrument criteria.

Response: Comment incorporated. The acceptance criterion for 797.2 cm^{-1} peak changed to $\pm 1.5 \text{ cm}^{-1}$.

Comment Summary #6: The commenter suggested changing “Cyclohexane R” to “Cyclohexane Reference Material” in the footnote of *Table 1*.

Response: Comment incorporated.

Comment Summary #7: The commenter indicated that clarification was needed as to whether the wavelength accuracy tolerance applies to quantitative, qualitative, or both applications. For qualitative applications, many modeling procedures normalize the data, so in most cases it would not apply.

Response: Comment not incorporated. As stated in the paragraph following “Operational Qualification”, “The requirements for OQ are application and user dependent. Therefore, the

user needs to specify fitness for purpose requirements for that application and use selection from below as appropriate."

Comment Summary #8: The commenter requested the scientific justification for the photometric precision acceptance criterion of a tolerance of 10% and details on how it be should tested.

Response: Comment partially incorporated. A justification is provided in the sentence prior, and the test is described as "...from reference measurements made from the reference material is applied." The acceptance criterion was edited to indicate 10% is a maximum allowable tolerance.

Comment Summary #9: The commenter indicated that the term "wavelength uncertainty" had been changed to "wavelength accuracy" at several instances, but "wavelength uncertainty" is still used in two occasions.

Response: Comment incorporated. All instances of "wavelength uncertainty" changed to "wavelength accuracy".

Comment Summary #10: The commenter suggested the use of external performance verification standards are not intended for handheld dispersive systems since the wavenumber accuracy is guaranteed by the He-Ne laser that references the interferometer.

Response: Comment not incorporated. External performance verification standards are used to ensure performance verification for all Raman instrumentation in order to mitigate risk of generating inaccurate results.

Procedure

Comment Summary #11: The commenter suggested that additional sampling factors should be considered through the chapter. For example, the commenter indicated that sampling can impact the Raman spectrum for solids and slurries, and care must be taken to measure several sample spots or use a large spot area for measurement of solids which exhibit non-homogeneity. For slurries, the commenter advised stirring the sample gently to maintain the slurry in suspension throughout the measurement.

Response: Comment not incorporated. Sampling factors are described in corresponding General Chapter <1858> *Raman Spectroscopy—Theory and Practice*.

Comment Summary #12: The commenter recommended that the following text be revised for clarity: "Any intensity difference is to sample non-homogeneity and sampling area difference among different measurement geometry."

Response: Comment incorporated. Text edited in order to clarify intention.

Validation and Verification

Comment Summary #13: The commenter suggested using parallel phrasing for drug substance and drug product acceptance criteria for validation. For example, the validation criteria under "Accuracy" and "Precision – Intermediate Repeatability" use "drug substances" and "drug product assays." The commenter suggested changing "drug substances" to "drug substance assays."

Response: Comment not incorporated. Validation criteria were formatted in order to be consistent with all spectroscopy general chapters below 1000.

Comment Summary #14: The commenter indicated that in the following text, "depending on the category of the test, the process for analytical procedure validation for Raman spectroscopy requires the testing of accuracy, precision, specificity, detection limit, quantitation limit, linearity, range, and robustness," the phrase "requires the testing" should be replaced by "may require" as not all the tests, especially detection and quantification limits, are necessary when the drug load is high.

Response: Comment incorporated.

Comment Summary #15: The commenter suggested the spiking procedure in order to validate *Accuracy* may not be feasible, scientifically justified for quantitative analysis of solid samples.

Response: Comment incorporated. Text edited to remove reference to spiked samples and replaced with "prepared samples or appropriate reference materials."

Comment Summary #16: The commenter indicated that not all samples tested in the *Repeatability* subsection are liquid. The commenter suggested removing the word "solutions" from the following text: "Alternatively, this assessment can be based on measurements of three replicates of three separate samples solutions at different concentrations."

Response: Comment incorporated.

Comment Summary #17: The commenter suggested the text in subsection *Intermediate Precision* allows researchers some flexibility when selecting various factors for experiments, the minimum of two variable factors could be increased to 3, 4, 5, etc. The total number of experiments would depend on how many factors are selected. Therefore, for clarity, the commenter suggested better defining the total number of experiments given the number of variable factors that could be selected.

Response: Comment incorporated. Text edited to indicate that "at least" six experiments are required to validate intermediate precision of the procedure.

Comment Summary #18: The commenter indicated that Identification, in subsection *Specificity*, may be established by visual comparison when using bench top FT-Raman system or Raman microscope systems, in addition to chemometric methods used.

Response: Comment incorporated. Text edited to include flexibility in the means of establishing identity.

Comment Summary #19: The commenter suggested that studying the effect of the particle size on the predictions is not an indication of specificity. It is an indication of robustness, and recommended removing the last bullet point in subsection *Specificity*.

Response: Comment partially incorporated. Bullet point rephrased to indicate specificity determined as part of robustness studies.

Comment Summary #20: The commenter indicated that multivariate methods, such as Raman, can have quantitative limits, and suggested it should be calculated when working with low dose samples.

Response: Comment partially incorporated. Text edited to indicate fitness for purpose demonstrated over "operational range".

Comment Summary #21: The commenter requested the definition of 'the Raman spectral response' in subsection *Linearity and Calibration Models* and requested clarity as to whether it refers to the Raman signal at a specific Raman shift, the relationship between X and Y scores in a chemometric model or predicted values obtained with a chemometric model.

Response: Comment not incorporated. The term "Raman spectral response" is intended to be broad in nature.

Comment Summary #22: The commenter requested clarification on the requirements for linearity.

Response: Comment partially incorporated. Text edited for clarification.

Comment Summary #23: The commenter indicated the text in subsection *Range* is only applicable to univariate methods.

Response: Comment partially incorporated. Text redrafted to align with General Chapter <856> *Near-Infrared Spectroscopy*.

Comment Summary #24: The commenter suggested that range of the method should be confirmed with an independent test set. If the linearity, precision and accuracy requirements are met, the commenter commented that the validation criteria that follow are superfluous, since the range needed for a method is application dependent and already defined with test samples.

Response: Comment not incorporated. The wording of the section provides flexibility in validating the range of a procedure.

Comment Summary #25: The commenter suggested that a robustness test could preferably be set up as an experimental design that systematically varies the parameters of interest in few experiments.

Response: Comment not incorporated. Proposal for revision not clear from the comment.

Comment Summary #26: The commenter indicated the subsection head *VERIFICATION* is written in all capital letters while the other subheadings under this section are not.

Response: Comment incorporated. The formatting of the subsection heading *Verification* was edited to lower case letters.

Comment Summary #27: The commenter suggested the General Chapter state that for quantitative calibration models, the linearity can be calculated on the predicted vs. reference plot used from the validation set, and that the use of the Raman spectral response is not always valid for multivariate models.

Response: Comment not incorporated. Revision proposal not appropriate for a below 1000 General Chapter.

General Chapter: General Chapter <1229.17> *Mycoplasma Sterilization*

Expert Committee: General Chapters–Microbiology

No. of Commenters: 3

Comment Summary #1: The commenter suggested changing the title of the chapter to *Mycoplasma Removal*.

Response: Comment not incorporated. This suggestion is inconsistent with the titles of other filtration related USP chapters.

Comment Summary #2: The commenter indicated that sterilization conditions are not always achievable for mycoplasmas. The methods stated to minimize the presence of mycoplasmas, autoclaving and irradiation, do not necessarily reduce the prefiltration bioburden, as parts of the dead organisms remain in the process stream.

Response: Comment not incorporated. The conditions of sterilization are not mentioned in this sub-chapter and are the responsibility of the end user. There is no risk of contamination from dead microorganisms.

Comment Summary #3: The commenter stated that there is no discussion in the chapter on how mycoplasmas are introduced into biopharmaceutical manufacturing processes or explanation why mycoplasma contamination is less likely for small molecule pharmaceutical processes.

Response: Comment not incorporated. The EC determined that none of this is directly relevant to the sterilization process.

Comment Summary #4: The commenter indicated that mycoplasma contamination of biological product cell cultures is rare (this may have been more common in the past and recommended replacing the second sentence, “Mycoplasmas are contaminants commonly found...”) with the following: “Mycoplasmas infect a variety of eukaryotic cells and may contaminate mammalian cell culture processes.”

Response: Comment incorporated. Changes made to the text.

Comment Summary #5: The commenter suggested adding a statement to emphasize that microbiological growth media should be sterilized by heat or subjected to gamma radiation prior to its use to inactivate mycoplasmas.

Response: Comment not incorporated. The sentence in place already indicates that.

Comment Summary #6: The commenter indicated that mycoplasma filtration is not typically claimed in sterile finished drug product processes.

Response: Comment not incorporated. The sentence says simply that mycoplasmas must be considered where sterilizing filtration is employed.

Comment Summary #7: The commenter suggested clarifying the context for traditional mycoplasma culture detection in order to differentiate from QPCR (quantitative polymerase chain reaction) methods that may detect residual mycoplasma DNA.

Response: Comment not incorporated. Adding “viable” mycoplasma seems to be an unnecessary refinement and while technically correct, it is likely to confuse readers.

Comment Summary #8: The commenter suggested replacing the term bioburden in the context of mycoplasma filtration with mycoplasma bioburden.

Response: Comment incorporated. Change made.

General Chapter: <1661> *Evaluation of Plastic Packaging Systems and Their Materials of Construction with Respect to Their User Safety Impact*

Expert Committee(s): General Chapters–Packaging and Distribution

No. of Commenters: 2

General

Comment Summary #1: The commenter suggested removing the >1000 chapter reference in <661.1> because its placement makes it mandatory.

Response: Comment not incorporated. General Notices specifically state that >1000 chapters that are referenced in <1000 chapters are for informational purposes only.

Comment Summary #2: The commenter recommended the removal of any references to acceptance criteria for “relevant extractable metals” of plastic materials of construction from chapter <661.1> due to the established low risk to drug product quality and patient safety attributable to elemental impurities from packaging components.

Response: Comment not incorporated. The chapter only mentions “relevant extracted metals” in the introduction, and the statement accurately reflects the intent of what the EC wanted to convey.

General Chapter/Sections: <1858> *Raman Spectroscopy – Theory and Practice*/Multiple Sections

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 2

General

Comment Summary #1: The commenter indicated that the general chapter does not contain information on method (model) calibration, and many applications in the chapter require chemometric multivariate methods. The commenter recommended adding a brief section on method development that would address this concern.

Response: Comment incorporated. Reference to General Chapter <1039> *Chemometrics* incorporated in the *Applications* section.

Comment Summary #2: The commenter indicated that the terms “Rayleigh scatter,” “Rayleigh scattered light,” and “scattered light” are inconsistently interchanged or combined throughout the chapter and recommended using one term throughout for consistency.

Response: Comment incorporated. All instances changed to “Rayleigh scatter”.

Theory

Comment Summary #3: The commenter recommended deleting the first sentence in the *Theory* section because it doesn’t provide any useful information and suggested that the following sentence is a better introduction to the general chapter.

Response: Comment incorporated. Sentence removed.

Comment Summary #4: The commenter suggested replacing the text “where there is center of symmetry” in the *Theory* section with “where the molecule has a center of symmetry.”

Response: Comment not incorporated. Rephrasing the text would impact the meaning and adversely affect the sentence structure.

Comment Summary #5: The commenter recommended replacing the term “spectrochemistry” throughout the chapter with “spectroscopy.”

Response: Comment incorporated. Replaced all instances of "spectrochemistry" with "spectroscopy."

Comment Summary #6: The commenter indicated that the term “virtual state” is not clearly defined and, elsewhere in the General Chapter, other terms are used for the excited state of the sample. For clarity, the commenter suggested either defining “virtual state” or replacing it with “final state” or “excited state.”

Response: Comment incorporated. Replaced instance of "virtual state" with "excited state."

Applications

Comment Summary #7: The commenter suggested that the *Applications* section is redundant and can be rewritten to be more concise and follow a more logical order. The commenter recommended either condensing this section into a list of applications (with the details in the list) or writing introductory material followed by a list.

Response: Comment not incorporated. The EC determined that the existing text is suitable.

Qualitative and Quantitative Raman Measurements

Comment Summary #8: The commenter requested that the terms in the equation be further explained.

Response: Comment incorporated. Two sources of the equation are provided for further reference.

Sampling Factors

Comment Summary #9: The commenter suggested deleting the following text from the *Sampling Factors* section, “This situation can be contrasted with absorption spectrochemistry, where the intensity at the detector is at a maximum in the absence of a sample.”

Response: Comment not incorporated. The text conveys an important difference between more traditional spectroscopy techniques.

Comment Summary #10: The commenter indicated that the following text is unclear and requested a revision for clarity: “Alternatively, the analyst can use a band due to a moiety such as an aromatic ring, the Raman intensity of which does not change with the way the sample is prepared. For solution spectra, an isolated solvent band can be used because the solvent will remain relatively unchanged from sample to sample. In a formulation, an excipient peak can possibly be used if it is present in a substantial excess, when compared to the analyte, in a homogeneous matrix.”

Response: Comment not incorporated. The EC determined that the existing text is sufficiently clear.

Apparatus

Comment Summary #11: The commenter indicated that the following text requires clarification as to whether it refers to a third type of spectrometer, “In addition, process Raman sensor technologies are also available.”

Response: Comment incorporated. Text clarified to refer to a third type of Raman analyzers, “In addition, process Raman analyzers used as Process Analytical Technology are also available.”

Comment Summary #12: The commenter indicated that the following text is redundant and is described in more detail earlier in the General Chapter: “All modern Raman measurements involve irradiating a sample with a laser, collecting the scattered radiation, rejecting the Rayleigh

scattered light, differentiating the Raman photos by wavelength, and detecting the resulting Raman spectrum.”

Response: Comment incorporated. Text removed.

Comment Summary #13: The commenter suggested moving the following text to the beginning of the subsection *Excitation Source (Laser)*: “Table 1 identifies several common lasers used for pharmaceutical applications or Raman spectroscopy.”

Response: Comment incorporated.

Comment Summary #14: The commenter suggested deleting the text “and therefore are not visible to the eye” in the sentence, “are outside of the visible region, i.e. in either the UV or NIR regions and are therefore not visible to the eye” in subsection *Excitation Source (Laser)* because it is redundant.

Response: Comment incorporated.

Comment Summary #15: The commenter indicated that the nominal laser λ (nm) for Ar-Ion should be 488 nm, not 488–632.8 nm.

Response: Comment partially incorporated. Nominal laser wavelength updated to 488.0–514.5 nm.

Comment Summary #16: The commenter suggested that the sentence in subsection *Filtering Device*, “Notch filters are almost universally used for this purpose and provide excellent rejection and stability combined with small size” appears to be incomplete.

Response: Comment not incorporated. The text is phrased correctly as written.

Specialized Techniques

Comment Summary #17: The commenter suggested including surface-enhanced resonance Raman scattering (SERRS) as another specialized technique.

Response: Comment not incorporated. The list in section *Specialized Techniques* was not intended to be exhaustive, and other techniques may be available but are not referenced or discussed within this general chapter.

Comment Summary #18: The commenter recommended rewriting the subsection *Confocal Microscopy/Imaging* for clarity and to define its purpose.

Response: Comment not incorporated. Revision proposal not provided by commenter.

Comment Summary #19: The commenter indicated the abbreviations “SORS” and “DUVRRS” should be introduced upon their first instance of use.

Response: Comment not incorporated. The abbreviations for all specialized techniques described are defined in the paragraph following the section heading *Specialized Techniques*.

Comment Summary #20: The commenter recommended rephrasing the following text in subsection *Spatially Offset Raman Spectroscopy*: “The two spectra can be subtracted using a scalar to produce two spectra representing the subsurface and surface spectra” to “...representing the surface and subsurface spectra.”

Response: Comment incorporated.

Comment Summary #21: The commenter indicated that the list of major advantages of DUVRRS procedures is four points, not three, and can be listed as bullet points.

Response: Comment incorporated.

Calibration

Comment Summary #22: The commenter suggested including the following text that applies to both Method A and Method B of intensity calibration to the paragraph prior to both Method sections: “Most manufacturers will provide appropriate calibration sources and software for this approach. If the manufacturer does not provide a procedure or method, the user can accomplish the task using a source obtained from NIST and appropriate software. If a manufacturer’s method is used, attention must be paid to the calibration procedure and source validity. The

user should obtain appropriate documentation from the manufacturer to ensure a qualified approach.”

Response: Comment incorporated. Text moved to prior section under *Intensity* subsection.

Sample-Based Factors That Affect Measurement Performance

Comment Summary #23: The commenter recommended deleting the subheading *Sample-Based Factors* and the first paragraph that follows because it is redundant.

Response: Comment partially incorporated. Portions of the text have been moved to the *Components* subsection.

Comment Summary #24: The commenter suggested that photo-bleaching is also a big problem for quantitative applications and should be mentioned under the list of sample-base factors that deleteriously affect quantitative Raman spectroscopy.

Response: Comment incorporated. Photo-bleaching included as problematic for quantitative Raman applications, and the text in this section was redrafted to read, “Fluorescence in solids can sometimes be mitigated by photo-bleaching, where the sample is exposed to the laser radiation for a period of time before measurement, and operates by degrading the highly absorbing species. Although being typically a factor to avoid, photo-bleaching may be used in exceptional circumstances to mitigate the effect of fluorescence, if no other pre-processing of the sample is possible. Photo-bleaching is less effective in liquids, where the sample is mobile, or if the amount of fluorescent material is more than a trace.”

Comment Summary #25: The commenter requested that the following terms be explained, ($\nu_L - \nu_\beta$) or replaced with the appropriate terms.

Response: Comment partially incorporated. The terms have been removed from the text, and the following additional text has been included: “As the intensity of Raman scattering is proportional to the fourth power of the absolute wavenumber of scattered light, a significant improvement in Raman scattering efficiency can be expected when higher exciting wavenumbers are used.”

Monographs

Monograph/Section: Amlodipine and Benazepril Hydrochloride Capsules/Organic Impurities
Expert Committee: Chemical Medicines Monographs 2
No. of Commenters: 1

Comment Summary #1: The commenter indicated that the impurity profile is missing common degradation products controlled in the FDA-approved products. The commenter recommended including additional degradation products to be consistent with the FDA-approved products.

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

Monograph/Section: Anise Oil/Identification A
Expert Committee: Excipients Monographs 1
No. of Commenters: 0

Expert Committee-Initiated Change #1: A note was added to the chromatographic similarity acceptance criteria that recommended comparing the chromatogram of the Standard to the reference chromatogram provided with the lot of USP Anise Oil RS being used. The chromatograms should be similar. This comparison addresses any changes in USP Anise Oil RS composition due to physical state change during storage and shipment.

Expert Committee-Initiated Change #2: A note was added to the Foeniculin acceptance criteria providing information about a compound, myristicin, that may interfere with foeniculin

and artificially increase its content. The note recommends using GC-MS with Electron Ionization and Chemical Ionization to confirm whether or not foeniculin is present in the *Sample*.

Monograph/Section: Clomiphene Citrate Tablets/Organic Impurities

Expert Committee: Chemical Medicines Monographs 5

No. of Commenters: 1

Comment Summary #1: The commenter noted that the acceptance criteria are different from that in the FDA-approved application.

Response: Comment not incorporated. The acceptance criteria are consistent with the FDA-approved application.

Monograph/Sections: *Coptis* Species Rhizome/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 3

Comment Summary #1: In *Identification A*, the directions in the *Analysis* are not clear and should be revised for clarity.

Response: Comment incorporated. The directions were modified according to the commenter's suggestion.

Comment Summary #2: The HPTLC method in current *European Pharmacopoeia* monograph offers good reproducibility and sharper zones with similar finger printer; recommend adopting the HPTLC mobile phase used in the *European Pharmacopoeia* monograph.

Response: Comment incorporated. The HPTLC mobile phase in *European Pharmacopoeia* monograph was adopted. The description for both *System suitability requirements* and *Acceptance criteria* were modified accordingly.

Comment Summary #3: EC requested adding a caution label with the content, "Dosage forms prepared with this article should bear the following statement: *Coptis* Species Rhizome contains berberine which may interact with medications. Consult your healthcare provider before using."

Response: A caution label was added under labeling.

Monograph/Sections: *Coptis* Species Rhizome Powder/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 3

Comment Summary #1: In *Identification A*, the directions in the *Analysis* are not clear and should be revised for clarity.

Response: Comment incorporated. The directions were modified according to the commenter's suggestion.

Comment Summary #2: The HPTLC method in current *European Pharmacopoeia* monograph offers good reproducibility and sharper zones with similar finger printer; recommend adopting the HPTLC mobile phase used in *European Pharmacopoeia* monograph.

Response: Comment incorporated. The HPTLC mobile phase in *European Pharmacopoeia* monograph was adopted. The description for both *System suitability requirements* and *Acceptance criteria* were modified accordingly.

Expert Committee-Initiated Change #1: EC added a caution label with the content of "Dosage forms prepared with this article should bear the following statement: *Coptis* Species Rhizome contains berberine which may interact with medications. Consult your healthcare provider before using."

Monograph/Sections: *Coptis* Species Rhizome Dry Extract/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 4

Comment Summary #1: In *Identification A*, the directions in the *Analysis* are not clear and should be revised for clarity.

Response: Comment incorporated. The directions were modified according to the commenter's suggestion.

Comment Summary #2: The HPTLC method in the current *EP* monograph offers good reproducibility and sharper zones with similar finger printer; recommend adopting the HPTLC mobile phase used in the *EP* monograph.

Response: Comment incorporated. The HPTLC mobile phase in the *EP* monograph was adopted. The description for both *System suitability requirements* and *Acceptance criteria* were modified accordingly.

Comment Summary #3: In *Table 1*, only data for one species was available. The content ratios for the other two species should be provided.

Response: Comment incorporated. Content ratios for all three species were provided based on the data included in the plant monographs because the ratios between plant and extract were not significant different according to test results.

Expert Committee-Initiated Change #1: The EC added a caution label with the content, "Dosage forms prepared with this article should bear the following statement: *Coptis* Species Rhizome contains berberine which may interact with medications. Consult your healthcare provider before using."

Monograph/Section: Cromolyn Sodium/Organic Impurities

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 3

Comment Summary #1: The commenters requested widening the acceptance criterion from NMT 0.15% to NMT 0.25% for the unidentified specified impurity, which has a relative retention time of 1.57 as well as identifying this impurity to be consistent with what has been approved. The commenter provided LC-MS data to support the identification of this impurity.

Response: Comment incorporated.

Comment Summary #2: The commenter requested revising the acceptance criteria for 2-acetylresorcinol, cromolyn related compound A, cromolyn related compound B, and total impurities for consistency with what has been approved.

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

Expert Committee-Initiated Change #1: The trivial name for the impurity with a relative retention time of 1.57 was added to *Table 2*.

Monograph/Section: Clonidine Hydrochloride Injection/Multiple Sections

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the *Acceptance criteria* for any unspecified impurity and total impurities under *Organic Impurities* to be consistent with the FDA-approved products.

Response: Comment partially incorporated. The *Acceptance criterion* of total impurities is revised from NMT 0.6% to NMT 0.75%. The EC will consider a future revision as needed for the limit of any unspecified impurity upon receipt of supporting data.

Comment Summary #2: The commenter recommended revising the *Acceptance criterion* for *pH* to be consistent with the FDA-approved products.

Response: Comment not incorporated. The proposed *Acceptance criterion* is consistent with the sponsor's FDA-approved application. The EC will consider a future revision upon receipt of supporting data.

Comment Summary #3: The commenter recommended removal of the *Color and Light Transmission* test as it is not applicable to all of the FDA-approved products.

Response: Comment incorporated.

Comment Summary #4: The commenter recommended deleting the use of NLT 10 vials of Injection to prepare the *Sample stock solution* under *Assay*, to be consistent with the validation.

Response: Comment incorporated. The *Sample stock solution* from the proposal is deleted and the *Sample solution* is revised from, “Sample solution: Nominally 0.01 mg/mL of clonidine hydrochloride from the *Sample stock solution*, diluted with *Diluent*” to “Sample solution: Nominally 0.01 mg/mL of clonidine hydrochloride from the Injection, diluted with *Diluent*.”

Comment Summary #5: The commenter suggested clarifying that 70% perchloric acid is used to prepare *Solution A* in the *Assay* to be consistent with the validation data.

Response: Comment incorporated.

Comment Summary #6: The commenter requested revising the *Chromatographic system* of the *Organic Impurities* test from, “Chromatographic system: Proceed as directed in the *Assay*, except for the Flow rate” to “Chromatographic system: Proceed as directed in the *Assay*, except for the Flow rate and the Run time.”

Response: Comment incorporated.

Expert Committee-Initiated Change #1: The EC revised the footnote in *Table 2* from, “process impurity for peak identification only; not to be reported or included in the total degradation products” to “process impurity for peak identification only; not to be reported or included in the total impurities.”

Monograph/Sections: Conjugated Linoleic Acids—Triglycerides/Multiple sections

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 1

Comment Summary #1: In the limits of polymerized Triglycerides, the current draft monograph proposal states a limit of NMT 3% of polymerized Triglycerides. The commenter proposes reducing this number to NMT 2%. The rationale for the lower limit of NMT 2% is that proper process control can deliver much lower numbers ($\leq 3\%$) and result in high-quality CLA triglycerides.

Response: Comment not incorporated. Further revisions may be considered based on receipt of supporting information.

Comment Summary #2: The current draft monograph proposal lists monodocosahexaenoin, didocosahexaenoin, and tridocosahexaenoin for *System Suitability test* in the “Content of Conjugated Linoleic Acids – Tri-, Di-, Monoglycerides, and Polymerized Triglycerides” procedure. The commenter proposes to use mono-, di- and triglycerides of linoleic acid (C18:2 cis, cis). The rationale for this is that the glycerides of DHA are cost prohibitive, while glycerides of linoleic acid are commercially available at more affordable prices. In addition, linoleic acid is chemically similar to the investigated fatty acids of CLA rather than DHA.

Response: Comment not incorporated. Further revisions may be considered based on receipt of supporting information.

Comment Summary #3: In the alternate method for Fatty Acid Composition, the draft proposal refers to the USP method 401 for the determination of fatty acid composition. This GC method describes saponification first, and then formation of methyl esters. The commenter proposes using the method with base-catalyzed ethanolysis for transesterification resulting in ethyl esters of fatty acids directly, with no separate saponification step. The commenter employs ethylation process resulting in ethyl esters, similar to methylation to form methyl esters in transesterification. The rationale for this procedure is that “base-catalyzed methylation is recognized to be best for esterified lipids as acid catalysis can cause isomerization of CLA.

Response: Comment not incorporated. Further revisions may be considered based on receipt of supporting information.

Monograph/Section: Diethylcarbamazine Citrate/Organic Impurities

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended renaming, “Any individual impurity” as “Any individual unspecified impurity” in the test for *Organic impurities, Procedure 2*.”

Response: Comment incorporated.

Comment Summary #2: The commenter requested confirming if the Total impurities limit in the test for *Organic impurities, Procedure 2* is from both Organic impurities procedures combined.

Response: Comment not incorporated. The EC determined that the Total impurities limit only corresponds to the impurities in *Organic impurities, Procedure 2*.

Expert Committee-Initiated Change #1: The concentration of Impurity solution A and Impurity solution B were corrected from 10 mg/mL to 0.1 mg/mL to be consistent with the method in the test for *Organic impurities, Procedure 1*.

Expert Committee-Initiated Change #2: The EC determined to include the description of the stationary phase for clarity in the test for *Organic impurities, Procedure 1*.

Monograph/Sections: Dobutamine Hydrochloride/Identification C

Expert Committee: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter suggested replacing the dry chloride test with General Chapter <191> *Identification Tests—General, Chloride, Test A*

Response: Comment not incorporated. The proposed revision for General Chapter <191> *Identification Tests—General*, the *Chloride* subsection includes the deletion of the test C for dry chlorides. In order to avoid the cross referencing of a nonexistent test procedure, the experimental details for the dry chlorides test are included in the monograph. A future revision is planned to be proposed to replace the dry chlorides test with General Chapter, <191> *Identification Tests—General, Chloride, Test A*.

Monograph/Section: Galactose/Related Substances

Expert Committee: Excipients Monographs 1

No. of Commenters: 0

Expert Committee-Initiated Change #1: The preparation of the *Sensitivity solution* was changed from a proportional dilution of the *System suitability solution* to a preparation from individual compounds. This approach will prevent introduction of additional amount of lactose typically present in Galactose and will provide a correct response of the lactose peak in the *Sensitivity solution*.

Monograph/Section: Galantamine Extended-Release Capsules/Multiple Sections

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold as the appropriate value will vary based on product-specific factors that should be addressed as an application assessment issue.

Response: Comment not incorporated. The EC has updated the style of the existing disregard statement to use the term, “reporting threshold.” Removal of the existing disregard statement or reporting threshold is outside of the scope of the proposed revision. A general position regarding the inclusion or absence of reporting thresholds in monographs is still under discussion. The EC will consider future revisions to the monograph upon the receipt of the necessary supporting data.

Expert Committee-Initiated Change #1: The formatting of the chemical information for USP Galantamine Hydrobromide Related Compounds Mixture RS in the USP Reference Standards section was revised to be consistent with current USP style.

Monograph/Section: Galantamine Oral Solution/Multiple Sections

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter requested adding an additional Identification test.

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

Comment Summary #2: The commenter requested revising the acceptance criteria for *N*-Desmethyl galantamine for consistency with what has been approved.

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

Comment Summary #3: The commenter requested removing the reporting threshold as the appropriate value will vary based on product-specific factors that should be addressed as an application assessment issue.

Response: Comment not incorporated. The EC has updated the style of the existing disregard statement to use the term reporting threshold. Removal of the existing disregard statement or reporting threshold is outside of the scope of the proposed revision. A general position regarding the inclusion or absence of reporting thresholds in monographs is still under discussion. The EC will consider future revisions to the monograph upon the receipt of the necessary supporting data.

Expert Committee-Initiated Change #1: The run time requirement of NLT 3.5 times the retention time of galantamine in the Assay was removed as this procedure uses a gradient; this requirement did not add value to the public standard.

Expert Committee-Initiated Change #2: In the test for organic impurities, the *Sensitivity solution* concentration (0.5 µg/mL of USP Galantamine Hydrobromide RS) was retained as the procedure is not suitably sensitive to support the *Signal-to-noise ratio* requirement of NLT 10 using the proposed concentration (0.26 µg/mL of USP Galantamine Hydrobromide RS).

Expert Committee-Initiated Change #3: The formatting of the chemical information for USP Galantamine Hydrobromide Related Compounds Mixture RS in the USP Reference Standards section was revised to be consistent with current USP style.

Monograph/Section: Guarana Seed /Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 1

Identification

Expert Committee-Initiated Change #1: In the *Identification test A*, a note was included under *Derivatization reagent* to indicate the type of derivatization technique and volume of reagent needed, as follows: “NOTE—Use the spray derivatization technique with 5 mL of reagent.”

Expert Committee-Initiated Change #2: In the *Identification test B*, under *Acceptance criteria*, the peak originally assigned to (-)-epigallocatechin was renamed as “unknown B-type dimeric procyanidin” after confirmation of peak identity by mass spectrometry. Corresponding changes were made in several sections of the monograph to update the name of this compound.

Composition

Expert Committee-Initiated Change #3: Under *Analysis*, the relative retention time (RRT) of theobromine was corrected from 0.8 to 0.3.

Expert Committee-Initiated Change #4: Under *Standard Solution B*, solvent composition was changed from methanol: water (80:20) to water: methanol (80:20).

Expert Committee-Initiated Change #5: Under *System suitability*, the tailing factor of caffeine was changed from NMT 1.5 to NMT 2

Monograph/Section: Guarana Seed Dry Extract /Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

Definition

Expert Committee-Initiated Change #1: The following changes were made to the *Definition*: (1) inclusion of a limit of NMT 12% caffeine on the dried basis; (2) change on the labeled amount of caffeine from NLT 90% and NMT 110% to NLT 80.0% and NMT 120.0%; and (3) inclusion of the content ratio of caffeine to total flavonoids of NMT 3.

Identification

Expert Committee-Initiated Change #2: In the *Identification test A*, a note was included under *Derivatization reagent* to indicate the type of derivatization technique and volume of reagent needed, as follows: “NOTE—Use the spray derivatization technique with 5 mL of reagent.”

EC Initiated Change #3: In the *Identification test B*, under *Acceptance criteria*, the peak originally assigned to (-)-epigallocatechin was renamed as “unknown B-type dimeric procyanidin” after confirmation of peak identity by mass spectrometry. Corresponding changes were made in several sections of the monograph to update the name of this compound.

Expert Committee-Initiated Change #4: In the *Identification test B*, the *Analysis* was changed as follows: “Proceed as directed in the test for Content of Caffeine and Flavonoids.”

Expert Committee-Initiated Change #5: In the *Identification test B*, under *Acceptance criteria*, the ratio content of caffeine to total flavonoids was corrected from NMT 3% to NMT 3.

Composition

Expert Committee-Initiated Change #6: *Standard Solution B* was included as follows: “0.20 mg/mL of USP (-)-Epicatechin RS, 0.3 mg/mL of USP (+)-Catechin RS, and 0.10 mg/mL of USP Procyanidin B2 RS in Solvent. Sonicate to dissolve.”

Expert Committee-Initiated Change #7: Under *System suitability*, requirements for compounds in *Standard Solution B* were included as follows: Tailing factor (NMT 1.5 for catechin, epicatechin, and procyanidin B2, *Standard solution B*) and relative standard deviation (NMT 5.0% for catechin, epicatechin, and procyanidin B2 in repeated injections, *Standard solution B*).

Expert Committee-Initiated Change #8: Under *System suitability*, the tailing factor for caffeine was changed from NMT 1.5 to NMT 2.

Expert Committee-Initiated Change #9: Under *Analysis*, the RRT of theobromine was corrected from 0.8 to 0.3.

Expert Committee-Initiated Change #10: Under *Analysis*, calculations for the individual percentages of procyanidin B1, catechin, procyanidin B2 and epicatechin, as well as that for total flavonoids, were included.

Expert Committee-Initiated Change #11: The *Acceptance criteria* were modified as follows: “NMT 12% caffeine calculated on the dried basis; NLT 80.0% and NMT 120.0% of the labeled amount of caffeine calculated on the dried basis. The content ratio of caffeine to total flavonoids is NMT 3 on the dried basis.”

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

Identification

Expert Committee-Initiated Change #1: In the *Identification test A*, a note was included under *Derivatization reagent* to indicate the type of derivatization technique and volume of reagent needed, as follows: “NOTE—Use the spray derivatization technique with 5 mL of reagent.”

Expert Committee-Initiated Change #2: In the *Identification test B*, under *Acceptance criteria*, the peak originally assigned to (-)-epigallocatechin was renamed as “unknown B-type dimeric procyanidin” after confirmation of peak identity by mass spectrometry. Corresponding changes were made in several sections of the monograph to update the name of this compound.

Composition

Expert Committee-Initiated Change #3: Under *Analysis*, the RRT of theobromine was corrected from 0.8 to 0.3.

Expert Committee-Initiated Change #4: Under *Standard Solution B*, solvent composition was changed from methanol: water (80:20) to water: methanol (80:20).

Expert Committee-Initiated Change #5: Under *System suitability*, the tailing factor of caffeine was changed from NMT 1.5 to NMT 2.

Monograph/Section: Lidocaine, Racementhine and Tetracaine Hydrochlorides
Compounded Topical Gel

Expert Committee: Compounding

No. of Commenters: 1

Comment Summary #1: The commenter recommended that the EC consider whether there is need for additional labeling to add safety warnings for the use of the formulation by the topical route. The commenter noted that there may be safety concerns with multiple active ingredients in the formulation when applied topically due to their potential for system (dose-related) absorption. The commenter noted that lidocaine hydrochloride, racementhine hydrochloride, and tetracaine hydrochloride can each exhibit pharmacological effects on various tissue and organ systems, including the cardiovascular system. It is unclear whether these pharmacologic effects become more acute when these active ingredients are administered together and applied into or near broken skin in preparation for suturing. Patients and providers may not know the amount of Topical Gel that can be applied safely. The commenter recommended that the EC balance the need for the monograph with the potential risk.

Response: Comment not incorporated. The formulation is used as a topical anesthetic for sutures and has been used safely in the clinical setting. In this setting, the gel is not applied by patients but by trained practitioners. The monograph was developed based on a stability-indicating assay to ensure that the formulation is stable. The committee balanced the safety concerns with the need to have a quality standard for the formulation and determined that there is a medical need for the monograph.

Comment Summary #2: The commenter recommended switching the order of listing the ingredients in the compounding instruction to match the order the ingredients listed in the monograph title and the formula table.

Response: Comment incorporated.

Comment Summary #3: The commenter recommended adding General Chapters <61> *Microbiological Examination of Nonsterile Products: Microbial Enumerations Tests* and <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* to the list of specific tests required in the monograph. The commenter noted that these tests are required for drug product monographs for conventionally manufactured FDA-approved products that are applied to a wound area.

Response: Comment not incorporated. Compounded preparations are prepared in much smaller batch sizes than conventionally manufactured products and have much shorter beyond-use dates as compared to expiration dates. The Topical Gel is compounded in a preserved base. In addition, clinical use of the compounded topical gel is typically followed by application of a disinfectant.

Comment Summary #4: The commenter recommended adding the phrase, “Label it to indicate that it is for external use only” to the *Labeling* section of the monograph.

Response: Comment incorporated.

Comment Summary #5: The commenter recommended adding the phrase “The Topical Gel is not to be used if its color is pinkish or darker than slightly yellow or if it contains a precipitate” to the existing *Labeling* requirement. The commenter noted that similar phrasing currently appears in the monograph for Racepinephrine Inhalation Solution and in nearly all the monographs for epinephrine-containing drug products.

Response: Comment incorporated.

Expert Committee-Initiated Change #1: The phrase “Package in a calibrated single-use container” was added to the *Packaging and Storage* section of the monograph.

Monograph/Section: Mesalamine Delayed-Release Tablets/Organic Impurities

Expert Committees: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter indicated that the *Acceptance criteria* is outdated and recommended including specified degradation products with appropriate *Acceptance criteria* and deleting the *Acceptance criteria* for individual impurity to be consistent with FDA-approved applications.

Response: Comment not incorporated. This comment is outside of the revision scope and the EC will consider a future revision upon receipt of supporting data.

Comment Summary #2: The commenter noted the *Acceptance criteria* for any other individual impurity is not consistent with the ICH Q3B identification threshold and recommended tightening the acceptance criterion.

Response: Comment not incorporated. This comment is outside of the scope of the revision. The EC will consider a future revision upon receipt of supporting data.

Monograph/Sections: Nabumetone Tablets/Multiple sections

Expert Committees: Chemical Medicines Monographs 2

No. of Commenters: 3

Comment Summary #1: The commenter indicated that all specified impurities in *Organic Impurities Table 3* are process-related impurities and not degradation products and the acceptance criterion for total degradation products is NMT 1.0%. The process-related impurities are not controlled in their FDA-approved application.

Response: Comment incorporated. The EC determined that all specified impurities in *Organic Impurities Table 3* are process-related impurities and do not need to be controlled in the drug product monograph. The *Analysis* section and *Table 3* are updated to delete the nabumetone alcohol and nabumetone cyclohexanone analog and include the *Acceptance criterion* of NMT 0.10% for any unspecified degradation product and NMT 1.0% for total degradation products to be consistent with FDA approved applications. A footnote is added to *Table 3* to indicate that nabumetone-related compound A is for peak identification only and is not included in total degradation products.

Comment Summary #2: The commenter indicated that the *Acceptance criteria* for the specified impurities—Nabumetone alcohol, Nabumetone related compound A, and Nabumetone cyclohexanone analog—and total impurities under the *Organic Impurities Table 3* are different from those in the FDA-approved applications.

Response: Comment incorporated. See response to comment #1.

Comment Summary #3: The commenter suggested changing the concentration of nabumetone related compound A from 0.015 mg/mL to 0.0015 mg/mL in *System suitability solution* in *Organic Impurities* test to be consistent with the approved procedure for their product.

Response: Comment incorporated.

Comment Summary #4: The commenter suggested specifying the concentration of *Standard solution* in the *Dissolution* test.

Response: Comment not incorporated. The EC determined that the current dissolution test procedure is suitable for the intended use and will consider a future revision, if necessary, upon receipt of supporting data.

Monograph/Section: Pregabalin/General Chapter <221> *Chloride and Sulfate, Chloride*

Expert Committees: Chemical Medicines Monographs 2

No. of Commenters: 1

Comment Summary #1: The commenter indicated that *Sample solution* preparation as described in General Chapter <221> should be clarified, and 1 mL of nitric acid is needed to dissolve the sample.

Response: Comment not incorporated. The EC determined that the description of *Sample solution* preparation is adequate for the intended use.

Monograph: Propylthiouracil Compounded Oral Suspension

Expert Committee: Compounding

No. of Commenters: 1

Comment Summary #1: The commenter expressed concerns with USP creating a compounding monograph for a preparation that may present particular safety risks given the limited labeling that generally accompanies compounded drug products. FDA-approved propylthiouracil tablets are labeled with a boxed warning related to severe liver injury and acute liver failure. Because of the serious side effects that can occur with the use of this drug, the commenter recommended that an approved package insert should be available to inform both practitioner and patient of the serious side effects and provide recommendations for appropriate follow up. Such package inserts are not required and will not be available for this compounded drug.

Response: Comment not incorporated. There is currently no commercially available liquid formulation of propylthiouracil, and the EC determined that a quality standard for a stable formulation is needed. Practitioners should be aware of the safety considerations when compounding formulations. Further, USP monographs for drug substances, drug products, and compounded preparations typically do not contain safety information but include standards for identity, potency, purity, and strength of compendial articles.

Monograph/Sections: Pyrroloquinoline Quinone Disodium (PQQ)/Multiple Sections

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 3

Comment Summary #1: Literature references show that PQQ crystallized from different solvents show very different X-ray powder diffraction patterns. Proprietary and specific crystallization procedures may prevent other users from successfully employing the same crystallization procedure for identification tests.

Response: Comment incorporated. The X-Ray Powder Diffraction (XRPD) identification method will be removed from the monograph. The commenter submitted an NMR procedure, which will be evaluated for an identification method to be added in future revision.

Comment Summary #2: A commenter reported that an impurity observed in a synthetically manufactured PQQ sample possesses structural alert for genotoxicity and, therefore, its safety should be evaluated.

Response: Comment incorporated. The USP Dietary Supplements Admission Evaluations Joint Standards-Setting Subcommittee (DS AE JS3) admitted the PQQ produced with fermentation process and deferred the admission of the synthetic PQQ pending safety studies of the impurity.

[Additional information added February 5, 2020]

The safety concerns related to structural alerts for mutagenicity have recently been addressed by a manufacturer through a series of *in vitro* mutagenicity and genotoxicity studies conducted on the impurity. The DSAE JS3 evaluated the study data and recently admitted synthetic PQQ for monograph development. However, due to uncertainty of the timing of these studies at the time of ballot, the Expert Committee recommended proceeding with the approval of the monograph for fermentative PQQ and revising the monograph in the future to include synthetic PQQ after it is admitted by the DSAE JS3. A revision proposal to remove the restriction of synthetic PQQ is targeted to be published in PF in near future.

Comment Summary #3: A commenter reported that laboratory data show a sodium content that falls beyond 12.0%–12.6% as originally proposed in the *PF*.

Response: Comment incorporated. The USP internal laboratory tests also confirmed this, and the range for the content of sodium has been widened to 10.5%–12.9%, consistent with the original specifications of the monograph sponsor.

Comment Summary #4: A commenter stated that the theoretical water content of the trihydrate form of PQQ is equal to 12.6%. Therefore, the limit should be widened from NMT 12.0% to NMT 12.6%.

Response: Comment incorporated.

Monograph/Section: Rabeprazole Sodium/Organic Impurities

Expert Committee: Chemical Medicines Monographs 3

No. of Commenters: 1

Comment Summary #1: The commenter requested replacing, “Any other individual impurity” with “Any specified impurity” in *Table 2*.

Response: Comment incorporated.

Comment Summary #2: The commenter commented that the “reporting threshold” should not be included in the monograph.

Response: Comment not incorporated. The EC has updated the style of the existing disregard statement to use the term “reporting threshold.” Removal of the existing disregard statement or reporting threshold is outside of the scope of the proposed revision. The EC will consider future revisions to the monograph upon the receipt of the necessary supporting data.

Monograph/Sections: Selegiline Hydrochloride Tablets/Multiple Sections

Expert Committee: Chemical Medicines Monographs 4

No. of Commenters: 0

Expert Committee-Initiated Change #1: In the tests for *Assay, Organic Impurities Procedure 1* and *Organic Impurities Procedure 2*, the text, “add 80% of *Mobile phase* of the flask volume” was changed to “add 80% of the flask volume of *Mobile phase*” in order to improve the clarity of the text.

Monograph/Sections: *Terminalia chebula* Fruit/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 0

Expert Committee-Initiated Change #1: EC commented that the *Definition* should be changed from, “*Terminalia chebula* Fruit consists of the dried fruit” to “*Terminalia chebula* Fruit consists of the pericarp of the dried ripe fruit” in *Definition*.

Response: Change incorporated

Expert Committee-Initiated Change #2: EC requested that the family name of the Family *Combretaceae* be italicized in the *Definition*.

Response: Change incorporated

Expert Committee-Initiated Change #3: The EC requested that the column temperature be changed from 25° to 35° in the Chromatographic system in the *Composition*.

Response: Change incorporated

Expert Committee-Initiated Change #4: EC suggested changing the phrase, “NLT 2.0 between the chebulagic acid peak and the peak after” to “NLT 2.0 between the chebulagic acid peak and the following peak” in the *System suitability* in the *Composition*.

Response: Change incorporated

Monograph/Sections: *Terminalia chebula* Fruit Powder/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 0

Expert Committee-Initiated Change #1: EC changed the Definition from “*Terminalia chebula* Fruit consists of the dried fruit” to “*Terminalia chebula* Fruit consists of the pericarp of the dried ripe fruit” in Definition.

Expert Committee-Initiated Change #2: EC added italics to the family name of the Family *Combretaceae* in the *Definition*.

Expert Committee-Initiated Change #3: EC changed the column temperature from 25° to 35° in the Chromatographic system in the *Composition*.

Expert Committee-Initiated Change #4: EC changed the phrase, “NLT 2.0 between the chebulagic acid peak and the peak after” to “NLT 2.0 between the chebulagic acid peak and the following peak” in the *System suitability* in the *Composition*.

Monograph/Sections: *Terminalia chebula* Fruit Dry Extract/Multiple Sections

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

No. of Commenters: 0

Expert Committee-Initiated Change #1: EC changed the Definition from “*Terminalia chebula* Fruit consists of the dried fruit” to “*Terminalia chebula* Fruit consists of the pericarp of the dried ripe fruit.”

Expert Committee-Initiated Change #2: EC added italics to the family name of the Family *Combretaceae* in the *Definition*.

Expert Committee-Initiated Change #3: EC changed the column temperature from 25° to 35° in the Chromatographic system in the *Composition*.

Expert Committee-Initiated Change #4: EC changed the phrase, “NLT 2.0 between the chebulagic acid peak and the peak after” to “NLT 2.0 between the chebulagic acid peak and the following peak” in the *System suitability* in the *Composition*.

Monograph/Section: Valrubicin Intravesical Solution/Organic Impurities

Expert Committee: Chemical Medicines Monographs 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended providing chemical names and structures for four specified unidentified impurities included by RRT in *Table 1*.

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 including additional degradation products that are controlled in approved applications with appropriate chemical names and structures.

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