



Commentary

USP–NF 2022 Issue 3

June 1, 2022

In accordance with USP's *Rules and Procedures of the Council of Experts* ("Rules"), and except as provided in Section 9.02 *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 (EC) deems appropriate, the proposal may advance to official status or be re-published in PF for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status, a summary of comments received and the appropriate Expert Committee's responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of USP.NF.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 or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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

[General Notices to USP-NF](#)
[0.1 N Sodium Hydroxide VS Reagent](#)
[Methanol Reagent](#)

General Chapters

[<206> Aluminum](#)
[<211> Arsenic](#)
[<241> Iron](#)
[<251> Lead](#)
[<261> Mercury](#)
[<291> Selenium](#)
[<771> Ophthalmic Products - Quality Tests](#)
[<781> Optical Rotation](#)
[<857> Ultraviolet-Visible Spectroscopy](#)
[<1857> Ultraviolet-Visible Spectroscopy - Theory and Practice](#)

Monographs

[Amantadine Hydrochloride Tablets](#)
[Amiloride Hydrochloride Tablets](#)
[Argatroban Injection](#)
[Candesartan Cilexetil](#)
[Candesartan Cilexetil Tablets](#)
[Chlordiazepoxide and Amitriptyline Hydrochloride Tablets](#)
[Chlordiazepoxide Hydrochloride Capsules](#)
[Choline Bitartrate](#)
[Colistin Sulfate](#)
[Cranberry Fruit Juice](#)
[Cranberry Fruit Juice Concentrate](#)
[Doxycycline](#)
[Enzacamene](#)
[Etravirine](#)
[Etravirine Tablets](#)
[Fluticasone Propionate](#)
[Fosamprenavir Calcium](#)
[Latanoprost](#)
[Menthol](#)
[Molindone Hydrochloride](#)
[Naloxone Hydrochloride](#)
[Pramipexole Dihydrochloride](#)
[Primidone Tablets](#)

[Propionic Acid](#)
[Propranolol Hydrochloride Injection](#)
[Rivaroxaban](#)
[Saquinavir Mesylate](#)
[Siler Root](#)
[Siler Root Dry Extract](#)
[Siler Root Powder](#)
[Streptococcus thermophilus](#)
[Sodium Propionate](#)
[Tamsulosin Hydrochloride Capsules](#)
[Tiotropium Bromide](#)
[Zinc Acetate](#)

No comments were received for the following proposals:

Monographs

Codeine
Cranberry Fruit Dry Juice
Diphenhydramine Hydrochloride Oral Powder
Emedastine Ophthalmic Solution
Emedastine Difumarate
Erythromycin Ethylsuccinate Injection
Erythromycin Ethylsuccinate Oral Suspension
Ethionamide
Fish Oil Omega-3 Acid Ethyl Esters Concentrate
Fish Oil Containing Omega-3 Acids
Fish Oil Containing Omega-3 Acids Capsules
Fish Oil Containing Omega-3 Acids Delayed-Release Capsules
Fumaric Acid
Insulin Glargine
Insulin Glargine Injection
Krill Oil
Krill Oil Capsules
Krill Oil Delayed-Release Capsules
Lactiplantibacillus Plantarum
Ligilactobacillus Salivarius
Liotrix Tablets
Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream
Neomycin Sulfate and Flurandrenolide Cream
Neomycin Sulfate and Flurandrenolide Lotion
Neomycin Sulfate and Hydrocortisone Acetate Cream
Neomycin Sulfate and Hydrocortisone Acetate Lotion
Neomycin And Polymyxin B Sulfates Cream
Neomycin And Polymyxin B Sulfates and Gramicidin Cream

Neomycin And Polymyxin B Sulfates, Gramicidin, And Hydrocortisone Acetate Cream
Nystatin
Omega-3-Acids Ethyl Esters
Omega-3 Free Fatty Acids
Omega-3 Acids Triglycerides
Trichlormethiazide
Zinc Sulfate

General Notices

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

The following is Commentary in response to a proposed revision to General Notices. This revision will be official on December 1, 2022.

Revision language:

Revise [Section 2.20 Official Articles](#) to add the following language at the end of the second paragraph: “For a biologic product licensed under the Public Health Service Act, the *official title* shall be the title specified in the relevant monograph plus any prefix and/or suffix designated by the FDA unless otherwise specified in the applicable monograph.”

This revision was initially proposed in 2017 after the U.S. Food and Drug Administration’s (FDA) issuance of its final guidance, *Nonproprietary Naming of Biological Products* in January 2017. The final guidance indicated FDA’s thinking that biological products licensed under the Public Health Service Act (PHS Act) bear a nonproprietary name that includes an FDA-designated suffix. This guidance also referenced FDA’s intent to continue its practice of designating the names of biological products with a prefix, where necessary. In 2019, FDA issued an additional draft guidance document, *Nonproprietary Naming of Biological Products: Update*.

To understand the impact of this revision, USP has held ongoing scientific engagements, conducted two Comment rounds in *Pharmacopeial Forum*, and hosted a stakeholder roundtable. The proposal received varied stakeholder comments expressing both support and opposition.

The purpose of this revision is to clarify the continued application of USP public quality standards to biologic products that may be assigned an FDA-designated prefix and/or suffix, including originator biological products, related biological products, biosimilar products, and interchangeable products and is not intended to comment on FDA’s biological product naming policy. This revision will help provide clarity to stakeholders with respect to FDA’s naming convention and official titles of USP monograph standards.

Section 2.20 Official Articles:

Comment Summary #1: Commenters indicated disagreement with FDA's guidance, *Nonproprietary Naming of Biological Products* but expressed appreciation for USP's proposal to minimize confusion.

Response: Comment partially incorporated. The Council of Experts determined the revision is necessary to clarify the continued application of USP public quality standards to biological products and to prevent confusion and potential compliance issues for industry.

Comment Summary #2: Commenters suggested not to align USP naming of biological products regulated under the Public Health Service Act with the FDA guidance, *Nonproprietary Naming of Biological Products*.

Response: Comment not incorporated. The Council of Experts determined the revision is necessary to clarify the continued application of USP public quality standards to biological products and to prevent confusion and potential compliance issues for industry.

Comment Summary #3: The commenter suggested that USP monographs for biological products are not beneficial to public health and may impede or delay innovation.

Response: Comment not incorporated. The Council of Experts determined the revision is necessary to clarify the continued application of USP public quality standards to biological products and to prevent confusion and potential compliance issues for industry.

Comment Summary #4: Commenters requested cancellation of the proposed revision because they do not support the use of prefixes and/or suffixes for biological products regulated under the Public Health Service Act, per the FDA guidance, *Nonproprietary Naming of Biological Products*.

Response: Comment not incorporated. The Council of Experts determined the revision is necessary to clarify the continued application of USP public quality standards to biological products and to prevent confusion and potential compliance issues for industry.

Reagents

Reagent: Methanol
Expert Committee: USP Headquarters
No. of Commenters: 1

Comment Summary #1: The commenter requested clarity on the definition of "Anhydrous Application" stated in the text.

Response: Comment incorporated. USP changed the wording of the heading from "For Anhydrous Applications" to "Applications Requiring Anhydrous Methanol".

Reagent: 0.1 N Sodium Hydroxide VS
Expert Committee: USP Headquarters
No. of Commenters: 1

Comment Summary #1: The commenter noted that the standardization procedure listed in the text is for potentiometric endpoint not for visual endpoint.

Response: Comment incorporated. USP updated the section title to read “Standardization with potentiometric endpoint”.

General Chapters

General Chapter/Sections: <206> Aluminum

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 5

Comment Summary #1: For procedures describing ICP-OES, commenter recommended,

- a. including some text to describe the instrument qualification process before testing (e.g., calibration procedure, criteria, etc.).
- b. including additional concentrations over the working range of the standardization solutions to help the reader demonstrate linearity before continuing the procedure.

Response:

- a. Comment not incorporated. ICP-OES Instrument qualification is covered in chapter <730>.
- b. Comment not incorporated. It has been established in the literature as well as empirical evidence that the use of three standards in ICP-OES is the optimal number of standards for the technique. Adding more levels can in many cases provide false interpretation of the linearity of the analysis. Please see the following reference from Internationally recognized expert in Atomic Spectroscopy (1) Boumans, P.W.J.M., Inductively Coupled Plasma Emission Spectroscopy, Part I, John Wiley and Sons, 1987, p. 18ff.
2) (https://www.perkinelmer.com/CMSResources/Images/46-74353FAR_LinearRangeStudyoftheOptimaSimultaneousICP-OES.PDF)

REQUIREMENTS FOR PROCEDURE VALIDATION

Comment Summary #1: In the SPECIFICITY subsection, commenter recommended including a list of some components that could be responsible for interfering with assessing the element.

Response: Comment not incorporated. This chapter is intended for use for any material and any potential interference must be therefore evaluated on a case-by-case basis. As such, it is not possible for USP to generalize the list of interferences.

Comment Summary #2: Commenter recommended tightening ranges for the acceptance criteria for ACCURACY, PRECISION, and INTERMEDIATE PRECISION.

Response: Comment not incorporated. The acceptance criteria presented have been shown to be adequate for the purpose (ppb concentrations), in particular at working ranges close to LOD and LOQ.

Comment Summary #3: Commenter recommended that the proposed ICP-MS and ICP-OES procedures, that are the same procedures as those currently in <233>, are not to be added to the six element-specific chapters as this approach will not benefit excipient monographs for following reasons:

- a) The addition of the ICP-MS and ICP-OES procedures, which are already described in <233>, is redundant. Even if the ICP-MS and ICP-OES procedures are added to the element-specific chapters they will be still considered as alternative procedures because they are not referenced in excipient monographs and cannot be used without being validated.

Response: Comment not incorporated. The procedures in these element specific chapters modernize these chapters by including instrumental procedures and make the stakeholders aware of the availability of these procedures as an alternative along with validation requirements necessary for their use as an alternative . This addition would also allow one to directly reference these procedures in future monographs.

Alternate procedures should be validated and show comparable results per GNs section 6.30 *Alternative and Harmonized Methods and Procedures*. In this case, the required validation criteria is set forth in the element specific chapters. Users are not required to use ICP – OES/MS based procedures but may choose to as long as they meet the validation requirements. Inclusion of these procedures in element specific chapters eliminates the potential for redundant testing.

Comment Summary #4: Commenter stated that users can use the procedures listed in <233> per General Notices section 6.30. *Alternative and Harmonized Methods and Procedures* if they prefer using ICP-MS and ICP-OES technology for analysis of elemental impurities.

Response: Comment not incorporated. The procedures in these element specific chapters are included to inform the stakeholders of the availability of these procedures as an alternative and provide validation requirements necessary for their use as an alternative. Alternative procedures should be validated per General Notices section 6.30 *Alternative and Harmonized Methods and Procedures*. In this case, the required validation criteria is set forth in the element specific chapters. Users are not required to use ICP – OES/MS based procedures but may choose to as long as they meet the validation requirements. Inclusion of these procedures in element specific chapters eliminates the potential for redundant testing.

Comment Summary #5: Commenter stated that because the limits for elemental impurities in excipient monographs are associated with the existing wet chemistry procedures, the methodology and the existing limits cannot be changed unless validation and sample evaluation work are conducted and demonstrate that the current and any alternative procedures produce comparable results. There may be some cases in which the current limits have to be revised to reflect results obtained by ICP-MS and ICP-OES technology.

Response: Comment not incorporated. These procedures are stand-alone procedures and not referenced in monographs. If a user decides to go with the instrumental procedure and fails to meet the limits given in the monograph, they may reach out to USP with data and request a change in monograph limits.

PROCEDURES

Comment Summary #1: The name for some procedures is not included in the text of all six chapters as is done for other Procedures. Therefore, the commenter recommended adding a line in each chapter as suggested below:

<206> Aluminum -- Procedure 1: Atomic Absorption Spectroscopy

<211> Arsenic – Procedure 1: Colorimetry

Procedure 2: Colorimetry

<241> Iron – Procedure 1: Chemical method

<251> Lead – Procedure 1: Chemical method

<261> Mercury – Procedure 1: Titration

Procedure 2: Atomic Absorption Spectroscopy

Procedure 3: Atomic Absorption Spectroscopy

<291> Selenium – Procedure 1: Spectroscopy

Response: Comment incorporated. The name of the procedures has been added for all six chapters for consistency.

Comment Summary #2: ICP Procedures -Standardization

Standardization solution 1, Standardization solution 2, and Blank

In all six chapters, the order of the text may lead users to run the standards and blank in the order given. Some software will not allow this and the blank needs to be run first. Therefore, suggest change to:

Blank, Standardization solution 1, and Standardization solution 2

Response: Comment not incorporated. The format reflects the standard convention used by USP. The specific analysis sequence should be that used in the validation of the method.

REQUIREMENTS FOR PROCEDURE VALIDATION:

Comment Summary #1: Commenter requested clarification as to why the sentence "*The following validation requirements do not apply when the monograph prescribes Procedure 2 or Procedure 3,*" cannot apply to ICP validation. The listed validation requirements are a suitable approach to validating the ICP methods and are not out of alignment with General Notices or <1225> *Validation of Compendial Procedures*, therefore, suggest delete sentence and replace with wording clear for the intent.

Response: Comment incorporated. Section has been revised to provide greater clarity. The validation requirements section was revised to clarify that the criteria are applicable for primary and alternative methods.

Comment Summary #2: Commenter expressed that a switch from an existing wet chemistry sample preparation procedures to one that uses ICP-OES or ICP-MS with complete digestion may lead to varying results as is common when comparing results generated from different procedural approaches as is the case at times when comparing results from leaching methods to results from total digestion methods. Commenter recommended considering this variance/bias in results based on the procedures used and provide comments on potential method-to-method variability when these ICP-OES and ICP-MS procedures are included in General Chapters that allow the flexibility of multiple test method approaches.

Response: Comment not incorporated. These procedures are stand-alone procedures and not referenced in monographs. If a user decides to go with the instrumental procedure and fails to meet the limits given in the monograph, they may reach out to USP with data and request a change in monograph limits.

General Chapter/Sections: <211> Arsenic

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 5

Please see [commentary for <206>](#) for comments related to all six of the elemental chapters.

Comment Summary #1: The proposed procedures are exclusively ICP-AES and ICP-OES or ICP-MS, hence, well-known and already established procedures such AAS (e.g., with flame, graphite furnace or hydride generation) are not mentioned, even as a possible alternative. Commenter recommended introducing following statement from chapter <233> in chapters <211> Arsenic, <241> Iron, <251> Lead and <261> Mercury. This should make possible the determination of those elements by means of other analytical procedures (when fit for purpose), e.g., AAS:

“Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use”.

Response: Comment incorporated. Introductory statement is included.

General Chapter/Sections: <241> Iron

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 5

Please see [commentary for <206>](#) for comments related to all six of the elemental chapters.

Comment Summary #1: The proposed procedures are exclusively ICP-AES and ICP-OES or ICP-MS, hence, well-known and already established procedures such AAS (e.g., with flame, graphite furnace or hydride generation) are not mentioned, even as a possible alternative. Commenter recommended introducing following statement from chapter <233> in chapters <211> Arsenic, <241> Iron, <251> Lead and <261> Mercury. This should make possible the determination of those elements by means of other analytical procedures (when fit for purpose), e.g., AAS:

“Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use”.

Response: Comment incorporated.

General Chapter/Sections: <251> Lead

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 5

[Please see commentary for <206>](#) for comments related to all six of the elemental chapters.

Comment Summary #1: The proposed procedures are exclusively ICP-AES and ICP-OES or ICP-MS, hence, well-known and already established procedures such AAS (e.g., with flame,

graphite furnace or hydride generation) are not mentioned, even as a possible alternative. Commenter recommended introducing following statement from chapter <233> in chapters <211> Arsenic, <241> Iron, <251> Lead and <261> Mercury. This should make possible the determination of those elements by means of other analytical procedures (when fit for purpose), e.g., AAS:

“Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use”.

Response: Comment incorporated. Introductory statement is included.

General Chapter/Sections: <261> Mercury

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 5

Please see [commentary for <206>](#) for comments related to all six of the elemental chapters.

Comment Summary #1: The proposed procedures are exclusively ICP-AES and ICP-OES or ICP-MS, hence, well-known and already established procedures such AAS (e.g., with flame, graphite furnace or hydride generation) are not mentioned, even as a possible alternative. We would like to recommend introducing following statement from chapter <233> in chapters <211> Arsenic, <241> Iron, <251> Lead and <261> Mercury. This should make possible the determination of those elements by means of other analytical procedures (when fit for purpose), e.g., AAS:

“Any alternative procedure that has been validated and meets the acceptance criteria that follow is considered to be suitable for use”.

Response: Comment incorporated. Introductory statement is included.

General Chapter/Sections: <291> Selenium

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 5

Please see [commentary for <206>](#) for comments related to all six of the elemental chapters.

Comment Summary #1: Commenter recommended omission of this chapter due to USP’s decision to remove all tests for elements that are part of USP <232>/ICH Q3D elemental impurities list from drug substance monographs.

Response: Comment not incorporated. There may be other potential users of chapter <291> therefore, USP intends to evaluate the impact of omitting this chapter before reaching a decision on its omission.

General Chapter/Sections: <771> Ophthalmic Products – Quality Tests / Multiple Sections

Expert Committee: General Chapters – Dosage Forms

No. of Commenters: 5

Comment Summary #1: The commenter suggested that all the arrows in Figure 1 should be pointing inward to the area of the eye rather than outward to the label.

Response: Comment incorporated.

Comment Summary #2: Under OPTHALMIC DOSAGE FORMS, last sentence, the commenter suggested changing from “For multidose products, a suitable antimicrobial preservative or packaging system is required to maintain sterility over the shelf life of the product.” to “For multidose products, a suitable antimicrobial preservative or packaging system is required to maintain antimicrobial effectiveness over the shelf life of the product.”

Response: Comment incorporated.

Comment Summary #3: Under “Solutions”, first sentence, the commenter suggested changing from “Included in this section are those solid products that, when reconstituted according to instructions in the labeling, result in a solution.” to “Included in this section are solutions and those solid products that, when reconstituted according to instructions in the labeling, result in a solution.”

Response: Comment incorporated.

Comment Summary #4: Under “Suspensions”, first sentence, the commenter suggested changing from “Included in this section are those solid products that, when reconstituted according to instructions in the labeling, result in a suspension.” to “Included in this section are suspensions and those solid products that, when reconstituted according to instructions in the labeling, result in a suspension.”

Response: Comment incorporated.

Comment Summary #5: Under “Inserts”, third sentence, the commenter suggested changing from “Inserts can be classified as erodible (soluble) or nonerodable (insoluble).” to “Inserts can be classified as erodible (soluble, biodegradable) or nonerodable (insoluble, nonbiodegradable).”

Response: Comment incorporated. The text was modified to be in accordance with the information in the USP General Chapter <1151> *Pharmaceutical Dosage Forms*.

Comment Summary #6: Under ANTIMICROBIAL PRESERVATIVES, last sentence, the commenter suggested changing from “Acceptance criteria for antimicrobial preservative content in multiple-unit products should be established.” to “Acceptance criteria for antimicrobial preservative content in multi-dose products should be established.”

Response: Comment incorporated.

Comment Summary #7: Under CONTAINER-CLOSURE INTEGRITY, last sentence, the commenter suggested changing from “Validation of container integrity must demonstrate no penetration of microbial contamination or of chemical or physical impurities (see Package Integrity Evaluation—Sterile Products <1207>).” to “Validation of container integrity must demonstrate no penetration of microbial contamination or of chemical or physical impurities prior to opening (see Package Integrity Evaluation—Sterile Products <1207>).”

Response: Comment not incorporated. The topic is covered by the USP General Chapter <1207> *Package Integrity Evaluation – Sterile Products*.

Comment Summary #8: Under VISCOSITY, first sentence, the commenter suggested changing from “An increase in viscosity increases the residence time of a formulation in the eye.” to “An increase in viscosity increases the residence time of a formulation on or in the eye.”

Response: Comment not incorporated. The text was modified to better describe the drug products.

Comment Summary #9: The commenter proposed adding additional thresholds for reporting, identifying and qualifying leachables for topical ophthalmic drug products into <771>, in accordance with perspectives provided by FDA during various workshops.

Response: Comment not incorporated. The FDA has not published a formal guidance document establishing the thresholds for leachables and extractables for ophthalmic products. USP intends to update the chapter to reflect these thresholds after such publication by FDA.

Comment Summary # 10: Commenter requested clarification regarding the tests and acceptance criteria for a packaging system to maintain sterility over the shelf life of the product.

Response: Comment not incorporated. Both whole product and package system are tested. This information is included in the section *Container Closure Integrity*.

Comment Summary #11: Under *Universal Tests, Identification*, it is stated that the most widely used identification methods are HPLC <621> and TLC <201>. The commenter suggested updating the text to cover more state of art procedures.

Response: Comment incorporated. All the references of analytical procedures were removed to allow for the use of any appropriate and validated analytical technique.

Comment Summary #12: In the Introduction, Figure 1, the commenter suggested adding the word “route” after each entry. The commenter indicated the figure is intended to portray some of the routes of administration to the eye. However, because the term “route” is not consistently used, it appears as if some of the entries (i.e., Sub-Tenon, Superior rectus, Inferior rectus muscle) are intended to portray the anatomy of the eye. The word “muscle” should either be added after “superior rectus” or deleted from the “inferior rectus” entry. The commenter also suggested considering pointing the arrows at the injection site rather than away from the injection site.

Response: Comments incorporated.

Comment Summary #13: Under *Suspensions*, Paragraph 2, final sentence, the commenter suggested the following editorial change: The drug particle size is often reduced to levels of <10 µm in an attempt to avoid excessive lacrimation is desirable to reduce irritation. While lacrimation typically results from irritation of the eye, the goal is to reduce irritation whether or not lacrimation occurs.

Response: Comment incorporated. The text was simplified.

Comment Summary #14: The commenter suggested to add the words “lacrimal punctum” to the arrow in the Figure 2. This would be consistent with the Figure 1 entries.

Response: Comment incorporated.

Comment Summary #15: Under *Drug Product Quality*, introductory paragraph, sentence 1, item 2, the commenter suggested changing “e.g., dissolution or drug release...” To “i.e., dissolution or drug release...”

Response: Comment incorporated.

Comment Summary #16: Under *Universal Tests, pH*, Sentence 4 – the commenter noted that the acceptance criteria for pH is a range, not a single value. The acceptable range should be based upon drug product stability data but may not always reflect maximum product stability because there may be other factors to consider such as patient acceptability. The commenter suggested the following editorial changes: “The pH value range of the formulation should be the one where the drug product is the most stable based on drug product stability data.”

Response: Comment incorporated.

Comment Summary #17: Under *Antimicrobial Preservatives*, Sentence 1, item 2, the commenter recommended that item 2 be revised. It is the radiopharmaceutical drug product that would contain a radionuclide, not the antimicrobial agent. Item 2 should read: The substance antimicrobial agent radiopharmaceutical drug product contains a radionuclide with a physical half-life of <24 h.”

Response: Comment incorporated.

Comment Summary #18: Under *Container-Closure Integrity*, Sentence 1, the commenter suggested the following editorial changes: “The packaging system should be closed or sealed in such a manner as to prevent contamination or loss of contents and should provide evidence of being incorporate a tamper evident design.”

Response: Comment incorporated.

Comment Summary #19: Under *Specific Tests, Resuspendability/Redispersibility*, the commenter recommended adding the following text as the final sentence in this subsection to be consistent with expectation that an applicant provide a one-time quantitative demonstration of dose homogeneity: “Quantitative demonstration of the active ingredient’s redispersibility during product development is also recommended.”

Response: Comment incorporated.

General Chapter/Sections: <857> Ultraviolet-Visible Spectroscopy /Multiple Sections

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 14

GENERAL COMMENTS/INTRODUCTION

Comment Summary #1: The commenter requested clarification for the rationale replacing “cell” with “cuvette” throughout the chapter.

Response: Comment incorporated. With increasing use of UV-Vis with biosystems, the terminology use was changed to avoid the overlap of terms in disciplines (e.g., biological cell vs. sample cell).

Comment Summary #2: The commenter requested further clarification as to whether the plate readers with monochromators could be used, as multichannel plate reader (which are excluded from the scope of the chapter) is a plate reader that has a specific wavelength selection and do not have a monochromator detector.

Response: Comment partially incorporated. The EC revised the entry to incorporate additional text in the introduction to clarify the exclusion: " Chromatographic detectors and any type of multichannel plate reader systems (i.e., filter or monochromator systems) are specifically excluded from this chapter."

PRINCIPLES OF MEASUREMENT

Comment Summary #1: The commenter stated that the equation that describes the incident and transmitted radiation is incorrect and suggested it should be established at the same wavelength.

Response: Comment not incorporated. The commenter did not correctly identify the designation of the variables. The "naught" variable designation is intended to refer to the radiation intensity, not the radiation wavelength variable. It denotes the difference between incident radiation and transmitted radiation, not the wavelength.

Comment Summary #2: The commenter suggested including content for cuvettes handling and cuvette verification procedures.

Response: Comment not incorporated. The EC, stating that precautions and additional analytical considerations are included in Chapter <1857>, determined that there is no need for such added text.

QUALIFICATION OF UV-VIS SPECTROMETERS

Comment Summary #1: The commenter, referring to the Control of Wavelengths and Absorbance, requested that the precision acceptance criteria for be revised to percent relative standard deviation (%RSD) instead of standard deviation.

Response: Comment not incorporated. The EC, noting that USP Chapter <1225> states that the evaluation of precision can be reported by calculating "...statistically valid estimates of standard deviation or relative standard deviation", determined that the current text is suitable.

Comment Summary #2: The commenter requested clarification regarding the removal the reference to deuterium lines and xenon line in the text and Table 2 of the proposed revision.

Response: Comment incorporated. The EC determined that the removal of the deuterium line reference in the text for wavelength accuracy was an editorial error, and the deleted text has been reinstated. The appropriate xenon line for wavelength accuracy was included in the body text and Table 2 of the balloted document.

Comment Summary #3: The commenter, referring to Control of wavelengths subsection, noted that the language under the control of wavelengths in the body text, Table 1 and Table 3 exhibit discrepancies. Hence, the commenter requested that USP address this discrepancy by aligning

the statement under Table 3 with the wavelength ranges in Table 1, to clarify the operational range that can be claimed on the system.

Response: Comment incorporated. The text before Table 1 was revised to clarify the requirement stating that “the wavelengths selected for qualification must bracket the intended range for use.”

Comment Summary #4: The commenter, stating that diode array instruments it is not clear how many replicates are needed to assess accuracy, requested clarification.

Response: Comment incorporated. The EC revised the entry to include, “For diode array instruments, only one wavelength accuracy measurement is required (no replicate measurements are required), and no precision determination needs to be performed, due to the non-mechanical design of the monochromator.”

Comment Summary #5: The commenter, referring to Establishment of acceptance limits (absorbance) -choice if standard stating that the temperature controls may be important when measuring standards, noted that is provided.

Response: Comment not incorporated. The EC determined that the current text is suitable, noting that the discussion on the impact of temperature on the measurement is discussed in Chapter <1857> and a reference was provided under the Control of Absorbance section.

Comment Summary #6: The commenter requested that the Control of Absorbance using metal-on-fused-silica and neutral density glass should be listed as alternatives for qualification as these reference materials may be challenging to acquire.

Response: Comment not incorporated. The chapter indicates that the listed entries in Table 4 are provided as options and are not requirements.

Comment Summary #7: The commenter requested an additional reference material of nicotinic acid at a level of 36 mg/L be included for Control of Absorbance at 1 – 3 AU.

Response: Comment incorporated. The reference material has been included in Table 4 and in the text under Control of Absorbance.

Comment Summary #8: The commenter, noting that the neutral density glass filters in the range of 0-1 AU had been removed from Table 4, requested adding them again.

Response: Comment incorporated. The EC, noting that the neutral density glass filters were inadvertently removed, re-added those entries to the Table 4.

Comment Summary #9: The commenter expressed concern over the use of certified nicotinic acid solutions to qualify the Control of Absorbance at 213 and 261 nm with certified set of sealed nicotinic acid standards (with concentrations from 6 mg/L to 48 mg/L to cover our intended absorbance working range 0 – 2 A. The commenter expressed the inability to meet the requirements, even while assessing the impact of the spectral bandwidth and temperature of the measurement.

Response: Comment not incorporated. The EC noting that the use of certified nicotinic acid is well established standard used for the control of absorbance at 213 nm and 261 nm, determined that the current content is suitable.

Comment Summary #10: The commenter, referring to Control of wavelength – Wavelength precision, which requires the standard deviation of the mean value of the six wavelength measurements, indicated that the terms “standard deviation of the mean” is confusing and requested replacing it with “standard deviation”.

Response: Comment incorporated. The EC revised the text.

Comment Summary #11: The commenter, referring to the control of absorbance section, noted that the new absorbance precision specifications represent tighter specifications due to the increased number of significant figures in the specification and requested to revert to previous specifications. Another commenter referring to the same topic requested a justification for establishing tighter acceptance limits.

Response: Comment not incorporated. The EC, noting that the UV-Vis spectrometers intended for compendial applications must meet these requirements, determined that the specifications are suitable. The EC also noted that for at least the last 20 years, numerous manufacturers of UV-Vis spectrometers have typically met these updated specifications indicated in the chapter.

Comment Summary #12: The commenter, referring to the Estimation of the Limit of Stray Light Section, requested adding “while doing this measurement with Acetone, “Air” or “Empty cuvette” should be used as reference” reasoning that “Air” is the “Appropriate” reference for Acetone measurement.

Response: Comment incorporated. The EC revised the entry to state: “If measurements are being performed in the 250–330 nm region, on a spectrometer using individual sources for the UV and visible regions of the spectrum, then an additional PQ verification using acetone should be performed, using air as reference.”

Comment Summary #13: The commenter, referring to Table 5 in the Estimation of Stray Light section, requested that the EC reexamine the necessity of 4 standards for verification of stray light under the rationale that the 190nm to 330nm spectral range is enough as most of the UV applications falls under UV region.

Response: Comment not incorporated. The EC, stating that the selection of materials listed are options for Estimation of the Limit of Stray Light based on the spectrum region of interest, and not all are required, determined that the entries are suitable.

Comment Summary #14: The commenter, referring the Table 5 in the Estimation of Stray Light section, suggest revising the header of the table to add “for Procedure B” at the end and remove “For procedure B” from the first row of Column 1 and 2. Additionally, the commenter suggested that the table be moved after Procedure B subsection.

Response: Comment not incorporated. The EC, stating that the materials listed in the table are options applicable for Estimation of the Limit of Stray light by both Procedure A and Procedure B, determined that the current Table 5 content is suitable.

Comment Summary #15: The commenter suggested including a spectral range assessment for Estimation of the Limit of Stray Light above 400 nm.

Response: Comment not incorporated. The EC, stating that there are no available standard procedures for Estimation of the Limit of Stray Light above 400 nm, and are not currently required by any pharmacopeia, determined that the current text is suitable.

Comment Summary #16: The commenter, referring to Estimation of the Limit of Stray Light, recommended adding that getting absorbance maxima of greater than 2 (or transmittance of less than 1%) is important (Irrespective of its wavelength) reasoning that this peak value may change due to resolution selection of the instrument.

Response: Comment not incorporated. The EC, stating that the wavelengths listed in Table 5 are recommended, and the acceptance criteria for Procedure B includes a maximum absorbance of greater than 2.0 AU, determined that the current text is suitable.

Comment Summary #17: The commenter, referring to Table 5 in Estimation of the Limit of Stray Light - measurement of stray light with Aqueous sodium iodide or potassium iodide (10 g/L)- requested that recommended the spectral range should be changed to 200 nm to 270 nm reasoning that the peak value is expected near 220 which may shift depending on the resolution selection of the instrument.

Response: Comment not incorporated. The EC, stating that 210 nm is acceptable lower wavelength limit for the specified range determined that the current content is suitable.

Comment Summary #18: The commenter, noting that a sentence has been added in the Performance Qualification section about trending and statistical evaluation as being necessary, requested additional clarification on requirements for the statistical evaluation.

Response: Comment partially incorporated. The EC added language that includes a recommendation for statistical evaluation and trend analysis that can used to confirm ongoing fitness for purpose but is not a requirement.

Comment Summary #19: The commenter, referring to the second paragraph of the Performance Qualification section, recommended an alternative verbiage.

Response: Comment partially incorporated in line with response to Comment 18.

General Chapter/Sections: <781> Optical Rotation /Multiple Sections

Expert Committee: General Chapters–Physical Analysis

No. of Commenters: 10

GENERAL COMMENTS

Comment Summary #1: The commenter requested to revise the measurement temperature from 25°C to 20°C.

Response: Comment not incorporated. Monograph requirements are established upon a measurement temperature of 25°C. To change this requirement, USP must acquire data to

revise individual monographs accordingly. USP intends to review this revision process and consider this work for the future.

INTRODUCTION

Comment Summary #1: The commenter recommended simplifying and clarifying the equations for specific rotation such that there is a distinction between the calculation for a neat liquid and a solution, and the circumstance in which density should be applied.

Response: Comment not incorporated. The text was revised to include three equations, one for a neat, undiluted liquid, one for a sample solution where the concentration is reported in g/mL, and another for a sample solution where the concentration is reported in g/g.

Comment Summary #2: The commenter suggested describing the formal units for optical rotation.

Response: Comment not incorporated. The units of optical rotation are included as $(^\circ)\text{mL}\cdot\text{dm}^{-1}\cdot\text{g}^{-1}$, which is typically expressed as $(^\circ)$.

Comment Summary #3: The commenter suggested that the notation for specific rotation should include the dependence on both the wavelength and temperature.

Response: Comment incorporated. Text to clarify the dependence of specific rotation on temperature is included, such that the notation is described accurately.

QUALIFICATION OF POLARIMETERS

Comment Summary #1: The commenter suggested that traceability of a temperature reading device, per general notices 6.80.30, should claim traceability to a metrological institute, e.g. NIST or equivalent.

Response: Comment not incorporated. The existing language in the Operational Qualification/Temperature Control section states: “The OQ of a polarimeter’s temperature control is performed by demonstrating that the operating temperature is within $\pm 0.5^\circ\text{C}$ to a temperature recorded on a temperature reading device that is traceable to a National Institute of Standards and Technology (NIST) standard or equivalent (see General Notices, 6.80.30. Temperature Reading Devices).”

Comment Summary #2: The commenter indicated that the Operational Qualification of the wavelength accuracy and bandwidth was inadequate, as the procedure proposed is also impacted by other conditions as temperature, path length, and light emission intensity. In addition, the commenter indicated that the procedure requirements may not be applicable to polarimeters employing atomic emission lamps.

Response: Comment incorporated. The section has been revised such that the wavelength and the bandwidth of the polarimeter is reported for polarimeters employing bandpass filters, whereas polarimeters employing alternative sources only need report the source wavelength.

Comment Summary #3: The commenter suggested that the wording stating the “wavelength accuracy and bandwidth of the light source” is misleading, as the wavelength accuracy and bandwidth are dependent on the interference filters.

Response: Comment incorporated. The section has been revised such that the wavelength and the bandwidth of the polarimeter is reported for polarimeters employing bandpass filters.

Comment Summary #4: The commenter requested the minimum Operational Qualification of Optical Rotation accuracy of $\pm 0.005^\circ$ be implemented, or at least an accuracy of $\pm 0.01^\circ$ for the entire measuring range of the polarimeter.

Response: Comment not incorporated. Not all polarimeters manufactured and currently used in industry report optical rotation to the third decimal place. The European Pharmacopeia (Ph.Eur.) also requires an operational accuracy of 0.01° . The requirement is harmonized with the Ph.Eur., where the accuracy of the optical rotation is qualified using a certified reference material with a stated expanded uncertainty $\pm 0.01^\circ$ or better.

Comment Summary #5: The commenter suggested removing the Wavelength Accuracy and Bandwidth section, as the procedure for Accuracy of Optical Rotation implies wavelength accuracy.

Response: Comment partially incorporated. The section for Wavelength Accuracy and Bandwidth simply requires reported the determined operating wavelength and bandwidth.

Comment Summary #6: The commenter suggested an accuracy of $\pm 0.005^\circ$ is excessive for the reference material because the polarimeter is only capable of reporting a result of $\pm 0.01^\circ$, and the NIST Sucrose SRM reports an uncertainty of $\pm 0.007^\circ$.

Response: Comment incorporated. The section has been revised such that the optical rotation is qualified using a certified reference material with a stated expanded uncertainty $\pm 0.01^\circ$ or better. This adjustment allows for the use of the NIST Sucrose SRM.

Comment Summary #7: The commenter requested a modified limit for the certified optical rotation reference material of $\pm 0.010^\circ$.

Response: Comment partially incorporated. The section has been revised such that the optical rotation is qualified using a certified reference material with a stated expanded uncertainty $\pm 0.01^\circ$ or better.

Comment Summary #8: The commenter suggested the proposed repeatability requirement does not allow for instances where the polarimeter manufacturer does not provide repeatability specifications.

Response: Comment not incorporated. The EC has concluded that repeatability and precision requirements are available for polarimeters currently in market.

PROCEDURES

Comment Summary #1: The commenter suggested that the specific size of the measurement cell could be variable as long as the % volume is appropriate for the sample size being measured. A 2.0 or 5.0-dm measurement cell could also be appropriate.

Response: Comment not incorporated. USP monograph requirements are established on the 1.0-dm cells.

Comment Summary #2: The commenter suggested that the difference between the USP and Ph. Eur. operating temperatures of 25°C and 20°C, respectively, is double the work for companies, and requests the USP harmonize with the Ph.Eur.

Response: Comment not incorporated. USP monograph requirements are established at 25°C. USP will engage in harmonization efforts, but each monograph requirements would need to be revised, as well. To change this requirement, USP would require validated results. USP invites sponsors to submit validation package for monographs for harmonizing the operating temperature to 20°C.

General Chapter/Sections: <1857> Ultraviolet-Visible Spectroscopy – Theory and Practice
/Multiple Sections

Expert Committee: General Chapters–Chemical Analysis

No. of Commenters: 8

THEORY

Comment Summary #1: Several commenters, referring to the first and second sentence of the second paragraph of the “Theory” section, commented that they contained an error using the term “chromosomes” instead of “chromophores”.

Response: Comment incorporated. The text has been revised.

Comment Summary #2: The commenter requested a rationale for removing the Derivative Spectroscopy section.

Response: Comment not incorporated. The EC, stating that only two known USP monographs employ the use of UV-Vis first derivative spectroscopy and that the deleted content in this section did not support these monograph procedures, determined that the deletion was appropriate. The EC further noted that the content of this section is widely available in textbooks.

UV-VIS SPECTROMETERS

Comment Summary #1: The commenter, referring to the first sentence of the first paragraph of Spectral Bandwidth—Effect on Resolution and Signal-to-Noise Ratio section, recommended revising the sentence “to read “Spectral bandwidth (SBW) is important to ensure adequate peak resolution.”

Response: Comment incorporated.

Comment Summary #2: The commenter, referring to the sentence “If access to a variable-bandwidth instrument is available, then the optimum setting can be defined as the largest bandwidth at which no significant reduction in peak intensity is observed”, recommended revising it to replace “the largest bandwidth” with “the narrowest bandwidth”.

Response: Comment partially incorporated. The EC revised the entry to replace the “largest bandwidth” with “narrowest slit width”.

Comment Summary #3: The commenter, referring to the sentence “Custom-built systems do not have additional shuttering, stray light filtering, and other capabilities that are found in

commercially designed spectrometers” in the Alternative UV-Vis Detector Spectrometer Configurations section, suggested revising the sentence to “Custom-built systems may not have additional shuttering, stray light filtering, and other capabilities that are found in commercially designed spectrometers,” reasoning that these capabilities are often built into custom systems.

Response: Comment incorporated. The EC revised the text .

Comment Summary #4: The commenter, referring to the excerpt starting with the second sentence until the end of last paragraph of Optimum Working Photometric Range subsection, recommended revising the entry to: “The use of shorter path length cuvettes may be successful to reduce a measured solution absorbance when ratio dilution with solvent is not possible. Ratio dilution with solvent may increase error associated with the measurement or alter the solution chemistry of the sample,” reasoning that it is common practice to perform ratio dilution, especially if other size cuvettes are not readily available.

Response: Comment not incorporated. The EC determined that the current text is suitable, stating that while it is understood ratio dilution is common practice, the intention of <1857> is to provide best practices, and that the best practice here is to use shorter pathlength cuvettes as opposed to performing ratio dilutions.

ANALYTICAL CONSIDERATIONS

Comment Summary #1: The commenter noting that a section titled “Temperature Coefficients and Effects” has been added on the temperature dependence of absorbance due to variations in sample concentration, stated that it is unclear on whether the additional temperature monitoring is required for qualification or not. Further, the commenter noted that USP <857> has no further information on limits for temperature control and most UVs have no way of adjusting temperature so this would be based on room temperature only, which will be very hard to control when a qualification is happening. The commenter requested a reference table for standard accuracy at different temperatures should be included, reasoning that actual implementation needs further clarification.

Response: Comment not incorporated. The EC determined that the current text is suitable, stating that USP <1857> does not provide mandatory requirements for temperature control, but gives to the reader additional information and best practices on temperature control need when measuring liquid reference materials at higher concentrations.

Comment Summary #2: The commenter, referring to the third column header of Table 2 - 190L1-noted that it is unclear why “190” was included and recommended either removing “190” or clarifying why it is necessary, possibly as a footnote to Table 2.

Response: Comment incorporated. The text has been revised.

Comment Summary #3: The commenter, referring to the first sentence of the Sample-Based Factors section and some other places noting that “Spectrophotometry” has been replaced with “spectroscopy” in the proposed text, suggested revising the sentence to replace UV-Vis spectroscopy with UV-Vis spectrometry. The commenter provided as rationale that “spectroscopy” refers to the theoretical study whereas “spectrometry” is the method used to acquire quantitative measurement of the spectrum.

Response: Comment incorporated.

Comment Summary #4: The commenter, referring to a new added paragraph in Solution Preparation subsection of Sampling Factors section and stating that the added section appears to be redundant and unnecessary, recommended that this paragraph be removed.

Response: Comment not incorporated. The EC determined that the current text is suitable, stating that redundancy in communicating best practices and providing information is valuable to reinforce particularly important messages.

Comment Summary #5: The commenter, referring to entries “It is preferable to use a single cuvette for all measurements of both the reference and samples, and where possible, never move the cuvette if you can move the solution” in the third paragraph and “whenever possible, measure standards and samples at the same time and under the same conditions to minimize the potential for bias in the fourth paragraph of the “CUVETTE” section,” stated that these two statements are opposite and asked for clarification.

Response: Comment not incorporated. The EC determined that the current text is suitable, noting that both measurement procedures, using single cuvette or two cuvettes, are discussed in the chapter and analytical considerations for both are discussed.

Comment Summary #6: The commenter, referring to the last paragraph of “CUVETTES” section, suggested revising the sentence to replace “spectroscopic” term with “spectrometric” term. The commenter’s rationale was to align with the expected update to replace “spectrophotometry” with to “spectrometry” in the rest of the text.

Response: Comment incorporated.

Monographs

Monograph/Section: Amantadine Hydrochloride Tablets/Multiple Sections

Expert Committee: Small Molecules 1

No. of Commenters: 2

Comment Summary #1: The commenter noted their approved dissolution method and/or tolerances are different from what is proposed in the monograph.

Response: Comment not incorporated. The commenter did not provide data to support their comment. As appropriate, a second dissolution test can be added in the future upon receipt of the supporting data.

Comment Summary #2: The commenter recommended removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of any reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

EC-initiated Change #1: Change from “Any individual unspecified degradation product” to “Any unspecified degradation product” in the *Organic Impurities* test to be consistent with ICH terminology.

Monograph/Section(s): Amiloride Hydrochloride Tablets /Organic impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of any reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #2: The commenter recommended tightening the limits for Amiloride acid, Amiloride methyl ester, and 5-Hydroxyamiloride hydrochloride to align with ICH Q3B guidelines

Response: Comment not incorporated. The limit of NMT 1.0% for each of those specified impurities is consistent with what has been approved by the US FDA. The EC will consider future revisions to the monograph upon receipt of supporting data.

Comment Summary #3: The commenter noted the impurity of “Chloropyrazine methyl carboxylate” was misspelled as “Amiloride ethyl ester.” The commenter recommended changing the text to “Amiloride methyl ester”.

Response: Comment partially incorporated. “Amiloride ethyl ester” has been replaced by “Amiloride related compound A” to be consistent with current naming practice. The corresponding footnote reflects the correct chemical structure.

Comment Summary #4: The commenter suggested revising “Any other unknown impurity” to “Any unspecified degradation product” to align with ICH Q3B guidelines.

Response: Comment not incorporated. The “any other unknown impurity” of NMT 0.5% limit is consistent with what has been approved by the US FDA. The EC will consider future revisions to the monograph upon receipt of supporting data.

Monograph/Section: Argatroban Injection/Multiple Sections

Expert Committee: Small Molecules 2

No. of Commenters: 3

Comment Summary #1: The commenter recommended that USP work with the approved manufacturers to ensure that the marketed products will be able to meet the requirements in the proposed monograph to avoid a drug shortage.

Response: Comment incorporated. USP reached out to approved manufacturers. The EC evaluated the information received and made additional changes to this monograph as summarized below. The EC will consider future revisions to the monograph upon receipt of additional supporting data.

Comment Summary #2: The commenter recommended that this monograph be developed in conjunction with a monograph for Argatroban in Sodium Chloride Injection.

Response: Comment not incorporated. This comment was outside of the scope of this specific standard, however, we note that a monograph proposal for Argatroban in Sodium Chloride Injection was developed and published in PF46(1).

Comment Summary #3: The commenter recommended revising the proposed *Definition* to accommodate other FDA approved products.

Response: Comment incorporated. The *Definition* was revised by not specifying water as an inactive ingredient and removing “in Water for Injection.” (Please also see the additional change listed in EC-initiated Change #1.)

Comment Summary #4: The commenter recommended revising the acceptance criteria for Dehydroargatroban and Total degradation products in the test for *Organic Impurities* to accommodate other FDA-approved applications.

Response: Comment incorporated. The acceptance criterion for Dehydroargatroban was widened from NMT 0.3% to NMT 1.5%, and a footnote was added to Table 2 for Total degradation products to exclude Dehydroargatroban in the Total degradation products.

Comment Summary #5: The commenter recommended removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #6: The commenter recommended adopting flexible approach and revising the acceptance criterion for *pH* in the Specific Tests section to accommodate other FDA-approved applications.

Response: Comment incorporated. Based on information received by USP from manufacturers, the acceptance criterion for the test of *pH* was revised from 6-8 to 6-8.5 including an additional note “this pH test is applicable to formulations which contain sorbitol.”

Comment Summary #7: The commenter indicated that it’s not suitable to include the test for *Osmolality and Osmolarity* <785> in this monograph as a public standard and recommended deleting it.

Response: Comment incorporated.

Comment Summary #8: The commenter commented that the acceptance criteria are not included in *Bacterial Endotoxins Test* <85> in the Specific Tests section.

Response: Comment not incorporated. The monograph refers to the general chapter *Bacterial Endotoxin Test* <85> for the requirements; no change is needed.

EC-initiated Change #1: The term “argatroban” was revised to “Argatroban” in the first sentence of the *Definition* to be consistent with the current USP practice.

Monograph/Sections: Candesartan Cilexetil/ Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

EC-initiated Change #1: To align the chemical information between the monograph and the associated labels and certificates of reference standards, alternative chemical names were included for USP Candesartan Cilexetil Related Compound A RS, USP Candesartan Cilexetil Related Compound B RS, USP Candesartan Cilexetil Related Compound D RS and USP Candesartan Cilexetil Related Compound F RS in the section *USP Reference Standards <11>*.

Monograph/Sections: Candesartan Cilexetil Tablets/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to do further stakeholder engagement is needed. USP intends to do further stakeholder engagement on this issue.

Comment Summary #2: The commenter indicated that process impurities should not be listed in a public standard for drug products and recommended the removal of one of the process impurities, Candesartan cilexetil related compound A from Table 3

Response: Comment not incorporated. The designation of process impurities included Table 3 and the associated footnote are part of the official text outside of the scope of the proposed revisions. The EC will consider future revisions to this monograph upon receipt of supporting information.

EC-initiated Change #1: To align the chemical information between the monograph and the associated labels and certificates of reference standards, alternative chemical names were included for USP Candesartan Cilexetil Related Compound A RS, USP Candesartan Cilexetil Related Compound B RS, USP Candesartan Cilexetil Related Compound D RS and USP Candesartan Cilexetil Related Compound F RS in the section *USP Reference Standards <11>*.

Monograph/Sections: Chlordiazepoxide and Amitriptyline Hydrochloride Tablets/Organic Impurities

Expert Committee: Small Molecules 4

No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #2: The commenter requested changing the acceptance criterion for 2-Amino-5-chlorobenzophenone from what was proposed for consistency with what has been approved.

Response: Comment incorporated by retaining the currently official acceptance criterion for 2-Amino-5-chlorobenzophenone.

Comment Summary #3: The commenters requested revising several of the acceptance criteria, removing the reference to cyclobenzaprine, and replacing the proposed analytical procedure with a different analytical procedure which is more robust.

Response: Comment partially incorporated by retaining the currently official test for Organic Impurities instead of using the proposed procedure. The EC will consider future revisions to the monograph.

EC-initiated Change #1: The relative retention times for Chlordiazepoxide and Amitriptyline are explicitly stated within the *System suitability* section of the revised Assay.

EC-initiated Change #2: The references to USP Amitriptyline Related Compound A RS, USP Amitriptyline Related Compound B RS, USP Cyclobenzaprine Hydrochloride RS, and USP Nortriptyline Hydrochloride RS are removed from the USP Reference Standards <11> section as they are no longer needed.

Monograph/Sections: Chlordiazepoxide Hydrochloride Capsules/Organic Impurities

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to do further stakeholder engagement on this issue.

Comment Summary #2: The commenter requested changing the acceptance criterion for 2-Amino-5-chlorobenzophenone from what was proposed for consistency with what has been approved.

Response: Comment incorporated by retaining the currently official acceptance criterion for 2-Amino-5-chlorobenzophenone.

EC-initiated Change: The reference to USP Chlordiazepoxide Related Compound A RS is removed from the *Sensitivity solution* and the *Signal-to-noise ratio* requirement.

Monograph/Section(s): Colistin Sulfate/Organic Impurities

Expert Committee: Biologics Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as ICH Q3A limits (including reporting threshold) will vary based on product-specific factors because of the different Maximum Daily Doses (MDD) for different products using the drug substance.

Response: Comment not incorporated. Colistin Sulfate as a fermentation product is out of the scope of ICH Q3A.

Monograph/Section(s): Cranberry Fruit Juice and Cranberry Fruit Juice Concentrate / Identification, Composition and Specific Tests

Expert Committee: Botanical Dietary Supplements and Herbal Medicines

Number of Commenters: 9

Identification

Comment Summary #1: The commenter asked if USP plans to include pictures of the reference profile under *Identification B. HPTLC for Articles of Botanical Origin <203>* and *Identification C. HPLC Profile of Flavonoids*. It could be helpful to see a characterized profile to interpret acceptance.

Response: Comment incorporated. The HPLC chromatograms of the *USP Cranberry Fruit Juice Dry Extract RS* will be provided in this reference material's corresponding CoA. HPTLC images of the *USP Cranberry Fruit Juice Dry Extract RS* will be available in the Supporting Information of the Dietary Supplements Compendium (DSC), which is an online publication.

Comment Summary #2: The commenter indicated that some peak descriptions under *Identification C. HPLC Profile of Flavonoids* are rather empirical (without scale / unit) as 'no peak', 'minor', etc. Is it possible to describe some scaled specifications (e.g., ratio between peaks, or peak % on total area basis calculation)?

Response: Comment not incorporated. The area ratio of peonidins (Σ peonidin-3-O-galactoside and peonidin-3-O-arabinose) and cyanidins (Σ cyanidin-3-O-galactoside and cyanidin-3-O-arabinoside) (ranging between 0.5 and 1.9), was proposed in the monograph; area ratios between other compounds largely varied and thus could not be proposed as characteristic ratios.

Comment Summary #3: The commenter asked to confirm that the acceptance criteria under *Identification B. HPTLC for Articles of Botanical Origin <203>* correctly specifies that there should not be any band of procyanidin B2/B1 because cranberry juice is a source of that procyanidin.

Response: Comment not incorporated. Although procyanidin B2 and B1 could be minor components in Cranberry Fruit Juice, these bands are not detected by HPTLC under the conditions proposed in the monograph. Detection of these bands could indicate adulteration with grape seed extract.

Comment Summary #4: Regarding authenticity, the commenter proposed that the monograph include reference to the utility of MALDI-TOF MS (Feliciano et al., 2012 and AOAC Official First Action Status-in press), an advanced analytic platform for identification of A-type proanthocyanidins (PACs) in Cranberry. The DMAC method cannot differentiate Cranberry (PACs) from those of potential adulterants (i.e., grape seed extract and peanut skin).

Response: Comment not incorporated. USP is currently evaluating MALDI-TOF MS and other HR-MS techniques for PAC characterization and detection of adulteration for a possible new USP General Chapter and future monograph modernization. The commenter's recommendation will be considered as this chapter is developed.

Comment Summary #5: The commenter suggested that another authenticity method is needed since DMAC (4-dimethylaminocinnamaldehyde) does not distinguish the type of PACs (A vs. B-type) from different plant sources. MALDI-TOF should be included or referenced as the method for authenticity testing in any product in which PAC content is of interest.

Response: Comment not incorporated. USP is currently evaluating MALDI-TOF MS and other HR-MS techniques for PAC characterization and detection of adulteration for a possible new USP General Chapter and future monograph modernization. The commenter's recommendation will be considered as this chapter is developed.

Comment Summary #6: The commenter indicated that under *Identification B. HPTLC for Articles of Botanical Origin <203>*, different amounts of the supernatant of Standard solution C (1.5 mL) and Sample solutions (150 µL for Cranberry Fruit Juice Concentrate and 1 mL for Cranberry Fruit Juice) are put on the cartridges and asked if the same volume of Standard solution C (1.5 mL) could be used in both cases to avoid mistakes in the procedure.

Response: Comment not incorporated. The sample preparation concentration and the amount of sample loaded on the cartridges depend on the ingredient type because the concentration of polyphenols differs considerably among the different ingredients. These volumes are based on optimization and validation.

Comment Summary #7: Under *Identification B. HPTLC for Articles of Botanical Origin <203>*, the commenter indicated that the precondition with SPE cartridge, according to L1 definition, the diameter should be 1.5 to 10 mm. The diameter of the Phenomenex cartridge is 55 mm thus, in our opinion should be L2 type.

Response: Comment incorporated. It was confirmed that the SPE cartridge corresponds to L2 according to our USP Chromatography Column database.

Comment Summary #8: The commenter stated that in some places under *Identification B. HPTLC for Articles of Botanical Origin <203>*, the term "orange-brick band" in contrast to "brick-orange band" was used?

Response: Comment incorporated. The color of the band was changed to brick-orange where applicable.

Comment Summary #9: Under *Identification B. HPTLC for Articles of Botanical Origin <203>*, the commenter asked if the term "below" instead of "before" was correct in the following statement: "The occurrence of a yellow-green band near the sample application and **before** cyanidin-3-O-glucoside might indicate the presence of peanut skin extract."

Response: Comment incorporated. The statement was corrected as follows: "The occurrence of a yellow-green band between the sample application and cyanidin-3-O-glucoside might indicate the presence of peanut skin extract."

Composition

Comment Summary #1: Under *Composition. Content of Dextrose and Fructose*, for the HPLC determination of dextrose and fructose, the commenter suggested that due to the known thermosensitivity of RI detectors, a fixed column temperature (instead of ambient temperature) should be proposed. It is also recommended to keep the connection between the column and the detector as short as possible.

Response: Comment incorporated. RI detectors usually require 5°C above room temperature; therefore, a temperature of 30°C has been incorporated.

Comment Summary #2: The commenter indicated no description/acceptance of organic acids in juice. It is recommended to use the same as for concentrate.

Response: Comment not incorporated Both monographs, Cranberry Fruit Juice and Cranberry Fruit Juice Concentrate include organic acid content specifications.

Comment Summary #3: The commenter suggested that the monograph for Cranberry Fruit Juice be revised to include a method for quantification of proanthocyanidins.

Response: Comment not incorporated. The commenter did not provide data to support the inclusion of such a method. USP will consider introducing limits for PAC content in this monograph upon receiving supporting information.

Comment Summary #4: The commenter inquired why is there no quantitation (by DMAC) of proanthocyanidins in Cranberry Fruit Juice.

Response: Comment not incorporated. The commenter did not provide data to support quantitation (by DMAC) of proanthocyanidins (PACs) in Cranberry Fruit Juice. USP will consider introducing limits for PAC content in this monograph upon receiving supporting information.

Comment Summary #5: The commenter stated that for Cranberry Fruit Juice Concentrate, the DMAC test under *Composition. Content of Proanthocyanidins*, the acceptance NLT 0.6% looks too high, suggesting a lower limit of 0.5% instead.

Response: Comment not incorporated. The data received for Cranberry Fruit Juice Concentrate for Dietary Supplements support a specification that is not lower than 0.6% PACs. Further revisions may be considered upon receipt of supporting data.

Comment Summary #6: The commenter proposed that to consider the solids content, which can differ (notably for concentrate), the %PAC calculation based on the DMAC test should be done on a dry matter basis (or solid content basis based on RI analysis) instead of % calculation on the raw material basis

Response: Comment not incorporated. The %PAC calculation in Cranberry Fruit Juice Concentrate is expressed in % w/w, so the weight of the material (instead of the solid content) is accounted for.

Specific tests

Comment Summary #1: The commenter stated that the solids content is defined as $7.5 \pm 0.5\%$ for Cranberry Fruit Juice and $50 \pm 0.5\%$ for Cranberry Fruit Juice Concentrate, requesting an increase in both ranges.

Response: Comment not incorporated. The specifications and CoAs received from different manufacturers support a limit of soluble solids of $7.5 \pm 0.5\%$ and $50 \pm 0.5\%$ for Cranberry Fruit Juice and Cranberry Fruit Juice Concentrate, respectively.

Monograph/Sections: Choline Bitartrate/Multiple Sections

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 0

EC-initiated Change #1: The EC decided to add an additional note to the *Related Compounds* procedure to help users distinguish, identify, and address artifact and impurity peaks in the HPLC-CAD chromatograms.

EC-initiated Change #2: Instructions for the *Standard response line* in the test procedure for the *Limit of Total Amines* contain error in representation of the accurate cumulative concentrations after each addition of the *Standard solution*, which should be calculated by taking into account the accurate total volume of the solution in the vessel. Instructions to calculate the correct and accurate cumulative concentrations have been added to the text.

Monograph/Section: Doxycycline/Multiple Sections

Expert Committee: Small Molecules 1

No. of Commenters: 3

Comment Summary #1: The commenter requested removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #2: The commenter requested including <197K> in *Identification A* and allowing the flexibility of using either <197A> or <197K> as in the Doxycycline Hyclate monograph.

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

Comment Summary #3: The commenter recommended using the same USP standard of doxycycline, in the tests for *Assay* and *Organic Impurities* in both Doxycycline and Doxycycline Hyclate monographs.

Response: Comment not incorporated. Based on the supporting data, the EC determined the use of USP Doxycycline Monohydrate RS is suitable for the tests in Doxycycline monograph.

Comment Summary #4: The commenter indicated there are slight differences in the relative retention times and relative response factors for *Organic Impurities* test between Doxycycline and Doxycycline Hyclate monographs and recommended using the same values of relative retention times and relative response factors in both monographs.

Response: Comment not incorporated. The EC determined the relative retention times and relative response factors are consistent with the validation data.

Monograph/Section(s): Enzacamene/Organic Impurities

Expert Committee: Small Molecules 3

No. of Commenters: 0

EC-initiated Change #1: Change from “Any individual unspecified impurity” to “Any unspecified impurity” in Table 2 of the *Organic Impurities section* to be consistent with ICH terminology.

Monograph/Section: Etravirine/ Organic Impurities

Expert of Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Monograph/Section: Etravirine Tablets/ Organic Impurities

Expert of Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to do further stakeholder engagement on this issue

Monograph/Sections: Fluticasone Propionate/Impurities

Expert Committee: Small Molecules Monographs 5

No. of Commenters: 3

Comment Summary #1: The commenter recommended revising the limit for any unspecified impurity in the test for *Organic Impurities* to be consistent with ICH Q3A guidelines.

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

Comment Summary #2: The commenter requested removing the “reporting threshold” in the test for *Organic Impurities*.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement.

Comment Summary #3: The commenter recommended replacing fluticasone propionate with fluticasone propionate related compound D in the preparation of the *Sensitivity solution* in the test for *Organic Impurities* to avoid possible interference resulting from system carryover from previous injections of higher concentration sample solutions.

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

Comment Summary #4: The commenter recommended decreasing the concentration of the *Sensitivity stock solution* to permit a different final dilution in the preparation of the *Sensitivity solution* in the test for *Organic Impurities*.

Response: Comment not incorporated. USP *General Notices and Requirements* permits changes in solution preparations, as discussed in Section 6.50.20.1. *Adjustments to Solutions*, provided that the change does not increase the error of the measurement.

Comment Summary #5: The commenter recommended adding a Residue on Ignition test with appropriate limits to control inorganic impurities.

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

Monograph/Section(s): Fosamprenavir Calcium/Multiple sections

Expert Committee: Small Molecules 1

No. of Commenters: 2

Comment Summary #1: The commenter recommended a change in reagent form used to prepare the Buffer in the Assay section.

Response: Comment not incorporated. The EC determined that the preparation listed matches what is in the submission the developed monograph is based off. Further revisions will be considered upon receipt of supporting data.

Comment Summary #2: The commenter recommended revising the Assay calculation to include the correction for water.

Response: Comment not incorporated. The EC determined that the calculation is calculated against the USP RS that is already corrected for water and assigned a value.

Comment Summary #3: The commenter recommended the *Standard solution* in the *Organic Impurities* test be identical to that in the Assay.

Response: Comment not incorporated. The EC determined that the concentration in the *Standard solution* for the *Organic Impurities* test is based on the unspecified impurity level to evaluate response.

Comment Summary #4: The commenter noted that two different impurities in Table 1 and Table 3 are given the same name of Fosamprenavir pyrophosphate and recommended the name(s) be changed so they are different.

Response: Comment incorporated. One of the impurities is a dimer and the name was corrected accordingly, Fosamprenavir pyrophosphate appears in Table 1 and Bisfosamprenavir pyrophosphate appears in Table 3.

Comment Summary #5: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

EC-initiated Change #1: Change from the “Any individual unspecified impurity” to “Any unspecified impurity” in Table 1 and Table 3 of the *Organic Impurities* section to be consistent with ICH terminology.

Monograph/Sections: Latanoprost/Organic Impurities

Expert Committee: Small Molecules 3

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #2: The commenter recommended revising the limit of “Any unspecified impurity” from 0.1% to 0.10% to be in line with ICH Q3A.

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

Monograph/Section(s): Menthol/Assay and Related Compounds
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 5

Comment Summary #1: The commenter proposed implementation of an internal standard in Assay and Related Compounds.

Response: The proposed revision included an internal standard.

Comment Summary #2: The commenter proposed determining %RSD based on ratio of $A_{\text{menthol}}/A_{\text{internal standard}}$ in System suitability

Response: Comment not incorporated. The proposed revision included an internal standard and determination of %RSD using the ratio of $A_{\text{menthol}}/A_{\text{internal standard}}$ in System suitability; no additional revision was needed.

Comment Summary #3: The commenter asked whether it is possible to perform GC using helium as the carrier gas if the conditions are appropriately converted.

Response: Comment not incorporated. The proposed GC system using helium as a carrier gas exhibited poor peak response.

Comment Summary #4: The commenter proposed indicating relative retention time (RRT) for the internal standard in Assay, and also asked the “Related compounds” section can be placed before “Limit of nonvolatile residue”.

Response: Comment incorporated to include RRT of internal standard (0.27). No need to replace the sections as the current order of the sections is aligned with USP style.

Comment Summary #5: The commenter questioned whether the proposed Assay method works because the test by commenter’s lab using the proposed method found two out of specifications among 16 runs.

Response: Comment not incorporated. After examining experimental details and data, no issues were found in the method. No further actions are required.

Monograph/Section: Molindone Hydrochloride/Organic Impurities
Expert Committee: Small Molecules 4
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement.

Monograph/Sections: Naloxone Hydrochloride/Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 3

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement.

Comment Summary #2: The commenters indicated that the acceptance criteria for all specified impurities and Total impurities are different from what have been approved by the FDA.

Response: Comment partially incorporated. There are five specified impurities included in Table 3. USP received information from manufacturers for four specified impurities and Total impurities with higher approved limits. The acceptance criteria were widened from NMT 0.10% to NMT 0.15% for each of these four specified impurities (10 α -Hydroxynaloxone, Noroxymorphone, 10 β -Hydroxynaloxone and 2,2'-Bisnaloxone) and from NMT 0.5% to NMT 0.8% for Total impurities.

Comment Summary #3: The commenter indicated that their specification includes an additional specified impurity “10-Ketonaloxone” with an acceptance criterion at NMT 0.15% and a wider acceptance criterion for Total impurities at NMT 1.0%.

Response: Comment not incorporated. Based on the available information, the EC determined that it’s not necessary to add the specified impurity “10-Ketonaloxone” to Table 3 and the revised acceptance criterion for Total impurities at NMT 0.8% is adequate.

Monograph/Section(s): Pramipexole Dihydrochloride/Limit of Pramipexole Related Compound D

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested that USP not change the reference standard concentrations in the procedure for the Limit of Pramipexole Related Compound D, as they believe that the USP Pramipexole Related Compound D RS was always a dihydrochloride sale.

Response: Comment not incorporated. USP Pramipexole Related Compound D RS has changed salt forms over time, necessitating the updates to the test.

Monograph/Sections: Primidone Tablets/Organic Impurities

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the “reporting threshold” as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Monograph/Section: Propionic Acid / Organic Impurities

Expert Committee: Simple Excipients

No. of Commenters: 1

Comment Summary #1: The commenter suggested changing the “NMT 0.15%” requirement for any unidentified individual impurity to “NMT 0.2%” with supporting data.

Response: Comment incorporated. The available data supported this change.

Monograph/Sections: Propranolol Hydrochloride Injection/Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Monograph/Section(s): Rivaroxaban/Multiple Sections

Expert Committee: Small Molecules 2

No. of Commenters: 6

Comment Summary #1: The commenter recommended harmonizing the *Enantiomeric Purity* test procedure with the corresponding test in the *European Pharmacopeia 10.7* monograph for Rivaroxaban and including a limit of NMT 0.5% for *the Rivaroxaban R Isomer*.

Response: Comment not incorporated. The EC determined that the proposed procedure and the acceptance criterion are consistent with a US FDA approved application.

Comment Summary #2: The commenter recommended harmonizing the *Identification test B* with the corresponding test in the *European Pharmacopeia 10.7* monograph and include the reference to the *Enantiomeric Purity* test instead of the *Assay* test for the retention time agreement.

Response: Comment not incorporated. The EC determined that the proposed *Identification test B* is consistent with an FDA approved application and will consider a future revision as appropriate.

Comment Summary #3: The commenter recommended harmonizing the acceptance criterion for *Water Determination <921>, Method I, Method Ic* with the corresponding limit of NMT 0.5% in the *European Pharmacopeia* monograph.

Response: Comment not incorporated. The EC determined that the proposed acceptance criterion for water determination is consistent with an FDA approved application.

Comment Summary #4: The commenter indicated that the proposed procedures for *Organic Impurities* and the *Enantiomeric Purity* tests are not suitable for their drug substance because the in-house impurities are either coeluting or closely eluting and one of in-house impurities is not soluble in the diluent.

Response: Comment not incorporated. The EC will consider future revision to the monograph upon receiving the necessary supporting information.

Comment Summary #5: The commenter indicated that the *Injection volume* under the *Assay* and *Organic Impurities* test procedures is below the suggested injection precision of the general analytical instruments.

Response: Comment not incorporated. The EC determined that the proposed *Injection volume* is consistent with validation data and is suitable for its intended use.

Comment Summary #6: The commenter indicated that the peak response of rivaroxaban is low due to the proposed low *Injection volume* in the tests for *Assay* and *Organic Impurities*.

Response: Comment not incorporated. The EC determined that the proposed *Injection volume* is consistent with validation data and is suitable for its intended use.

Comment Summary #7: The commenter requested replacing the proposed procedures for *Assay* and *Organic Impurities* tests with their in-house test procedures as they are fully validated and are specific for all known impurities for rivaroxaban.

Response: Comment not incorporated. The EC determined that the proposed methods are consistent with validation data and are suitable for their intended use.

Comment Summary #8: The commenter requested removing the reporting threshold from the *Organic Impurities* test as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #9: The commenter requested replacing the proposed procedures for *Assay* and *Organic Impurities* tests with their in-house test procedures as they provide higher peak response due to larger injection volume.

Response: Comment not incorporated. The proposed methods are fully validated and are consistent with a US FDA approved application.

Comment Summary #10: The commenter requested replacing the proposed Enantiomeric purity test procedure with their in-house test procedure for better resolution.

Response: Comment not incorporated. The proposed method is fully validated and is consistent with a US FDA approved application.

Monograph/Section: Saquinavir Mesylate/Organic Impurities

Expert Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from

monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Monograph/Section(s): Siler Root/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

Comment Summary: The commenter indicated that the USP convention is not to italicize the botanical family name, the Siler Root family monographs should be corrected in this regard.

Response: Comment incorporated. The monographs of Siler Root, Siler Root Powder and Siler Root Dry Extract are corrected consistent with the USP convention.

Monograph/Section(s): Siler Root Powder/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

Comment Summary: The commenter indicated that the USP convention is not to italicize the botanical family name, the Siler Root monograph should be corrected in this regard.

Response: Comment incorporated. The monographs of Siler Root, Siler Root Powder and Siler Root Dry Extract are corrected consistent with the USP convention.

Monograph/Section(s): Siler Root Dry Extract/Multiple Sections
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

Comment Summary #1: The commenter indicated that the USP convention is not to italicize the botanical family name, the Siler Root monograph should be corrected in this regard.

Response: Comment incorporated. The monographs of Siler Root, Siler Root Powder and Siler Root Dry Extract are corrected consistent with the USP convention.

Monograph/Section(s): Sodium Propionate / Organic Impurities
Expert Committee: Simple Excipients
No. of Commenters: 0

EC-initiated Change #1: A note of “The peak eluting at RRT 0.3 is sodium ion peak. This peak, and the peaks eluting before it, are exclusive from integration. These peaks are not from organic impurities of sodium propionate” was added in the *Analysis* section of the test to offer clarity.

Monograph/Sections: *Streptococcus thermophilus*
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1

Comment Summary # 1: The commentor questioned the basis for providing *Food Chemical Codex* (FCC) as a source method for testing *Listeria*.

Response: Comment not incorporated. The EC concluded that referencing *FCC* is acceptable, noting that *FCC* is an official publication of USP and the method for *Listeria* in *FCC* is based on AOAC Official Method 999.06 *Listeria* in Foods. *USP-NF* does not currently have a method to test *Listeria* and efforts are underway to revise <2022> *Microbiological Procedures for the Absence of Specified Microorganisms- Nutritional and Dietary Supplements*, to include testing method for *Listeria* and other pathogens.

Comment Summary #2: The commentor requested justification for the wide differences among the sample test quantities in the test for *Contaminants, Contaminant microorganisms*.

Response: The monograph references <64> *Probiotic tests* for specified microorganisms which in turn references <2022> *Microbiological Procedures for the Absence of Specified Microorganisms- Nutritional and Dietary Supplements*, that has a requirement for testing 10g of samples. The different sample quantities required in the monograph is based on the sponsor provided documents. Per *General Notices and Requirements, 3.10. Applicability of Standards*, “Where the requirements of a monograph differ from the requirements specified in these General Notices or an applicable general chapter, the monograph requirements apply and supersede the requirements of the General Notices or applicable general chapters, whether or not the monograph explicitly states the difference”.

Monograph/Section: Tamsulosin Hydrochloride Capsules/Organic Impurities

Expert Committee: Small Molecules 3

No. of Commenters: 1

Comment Summary #1: The commenter requested removing the ‘reporting threshold’ because it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #2: The commenter requested removing “methoxy tamsulosin”, “ethoxyphenoxy ethyl bromide”, and “desethoxy tamsulosin” from Table 13 in the Organic Impurities section as they are sufficiently controlled in the drug substance.

Response: Comment incorporated. The impurities were moved to the System suitability section where a ‘Note’ was included with associated relative retention times.

Comment Summary #3: The commenter requested aligning the acceptance criteria for ‘Any unspecified impurities’ with ICH Q3B.

Response: Comment incorporated. The criterion for ‘Any unspecified impurities’ was changed from NMT 0.6% to NMT 0.63%. This is based on the following calculation: 0.005 mg (5ug [identification threshold]) /0.8 mg (MDD) = 0.00625 x 100 = 0.63%.

Comment Summary #4: The commenter requested widening the acceptance criteria for ‘Total impurities’ for consistency with what has been approved.

Response: Comment incorporated. The criterion for 'Total impurities' was changed from NMT 0.9% to NMT 2.0% consistent with a US FDA approved application.

Monograph/Sections: Tiotropium Bromide/Multiple sections

Expert Committee: Small Molecules Monographs 5

No. of Commenters: 5

Comment Summary #1: The commenter recommended revising the second of three chemical names proposed in the *Chemical Information* to align the usage of alpha- and beta- with current chemical nomenclature conventions.

Response: Comment partially incorporated. The second chemical name, which is based on an older chemical nomenclature scheme, is not included in the monograph.

Comment Summary #2: The commenter requested removing the "reporting threshold" in the test for *Organic Impurities*.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that before the removal of reporting thresholds from monographs can occur, further stakeholder engagement is needed. USP intends to conduct further stakeholder engagement on this issue.

Comment Summary #3: The commenters recommended not proceeding with the proposed LC-MS test for the *Limit of Tiotropium Related Compound G and Tiotropium Related Compound H*, citing tailing of the tiotropium peak that leads to an elevated baseline and potentially interferes with the accurate quantitation of tiotropium related compound G. A commenter also suggested that the analytical method may suffer from poor precision.

Response: Comment not incorporated. The analytical method satisfied all validation requirements for accuracy and precision over the range of 25% to 150% of the impurity acceptance criterion, i.e., NMT 0.10% each of tiotropium related compound G and tiotropium related compound H. Additionally, the compendial test procedure permits users to optimize method performance for their instrumentation. The EC will consider future revisions to the monograph upon receipt of the necessary supporting data.

Comment Summary #4: The commenters requested revising the acceptance criteria for *Water Determination* to accommodate both the anhydrous and monohydrate forms of tiotropium bromide.

Response: Comment incorporated. The acceptance criteria for *Water Determination* were widened from the range 2.6%-3.4% to the limit NMT 4.0%, thereby accommodating both the anhydrous and monohydrate forms of tiotropium bromide.

EC-initiated Change #1: The UNII codes for tiotropium bromide (anhydrous) and for tiotropium bromide monohydrate are added to the *Chemical Information* in the monograph.

Monograph/Sections: Zinc Acetate /Multiple Sections

Expert Committee: Small Molecules 2

No. of Commenters: 2

Comment Summary #1: The commenter recommended USP to tighten the acceptance criteria for 'Arsenic' and 'Lead' to be consistent with ICH Q3D guidelines.

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

Comment Summary #2: The commenter recommended USP to include tests for 'Aluminum' and 'Iron' with acceptance criteria consistent with what have been approved by the FDA and recommend USP to contact the FDA approved applicants to obtain the relevant information.

Response: Comment partially incorporated. USP was not able to obtain any additional supporting information from FDA approved applicants. The EC will consider future revisions to the monograph upon the receipt of supporting data.