Commentary

USP–NF 2024 Issue 2

February 1, 2024

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 USPNF.com at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference 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 (PF):

General Chapters
<312> Molecular weight determination for Alginates
<383> Cured Silicone Elastomers for Pharmaceutical Packaging and Manufacturing Components
<471> Oxygen Flask Combustion
<541> Titrimetry
<661> Plastic Packaging Systems and their Materials of Construction
<791> pH
<1023> Evaluation Strategy for Trace Elements in Cell Culture Media Used in The Manufacture of Recombinant Therapeutic Proteins
<1151> Pharmaceutical Dosage Forms
<1236> Solubility Measurements

Monographs
Betamethasone Valerate
Calcipotriene and Betamethasone Dipropionate Ointment
Candesartan Cilexetil and Hydrochlorothiazide Tablets
Carbomer 934P
Carbomer 940
Carbomer 941
Cinnamomum verum Bark Powder
Dextrose
Etonogestrel
Ezetimibe
Fluorouracil Injection
Ganciclovir for Injection
Gefitinib
Gefitinib Tablets
Methadone Hydrochloride Tablets
Naproxen
Naproxen Sodium
Ondansetron
Ondansetron Hydrochloride
Pentobarbital
Pimecrolimus
Plerixafor
Plerixafor Injection
Rosuvastatin Calcium
Rosuvastatin Tablets
Topiramate Extended-Release Capsules

No comments were received for the following proposals:

General Chapters
<1035> Potency Assays to Evaluate Coagulation Factor VIII and Factor IX

Monographs
Carbomer 934
Carbomer 1342
Cinnamomum verum Bark
Ergocalciferol Tablets
Liquid Glucose
Oxytetracycline Hydrochloride and Hydrocortisone Ointment
Oxytetracycline Hydrochloride and Polymyxin B Sulfate Topical Powder
Technetium TC 99M Disofenin Injection
Technetium TC 99M Red Blood Cells Injection
Technetium TC 99M Sestamibi Injection

General Chapters

General Chapter/Section(s): <312> Molecular weight determination for Alginates
Expert Committee(s): Excipients Test Method
No. of Commenters: 2

Comment Summary #1: The commenter requested correcting a typographical error in footnote 1 of the General Chapter. In the statement related to commercially available PEO/PEG standard ready kit, the commenter suggested to correct the molecular weight range from 238,000-969,000 g/mol to 23,800-969,000 g/mol.
Response: Comment incorporated.
Comment Summary #2: The commenter commented on multiple sections of the General Chapter. The comment first indicated that monographs should define the required purity of alginates and methods for verification of these but should not define or limit functionality and performance. Secondly, the comment also states, SEC/GPC technique is not recommended by the alginate manufacturers for the characterization of alginates. Moreover, it proposes that viscosity has historically been used and is already a sufficient and accepted means to differentiate alginate products. In the summary, the commenter indicated that they do not support a General Chapter on Molecular Weight Determination of Alginates and requested USP to continue dialogue with alginate manufacturers and other industry stakeholder. This is to reach a consensus on the appropriate compendial tests for the release of commercial batches versus techniques which are useful for material characterization and selection.
Response: Comments not incorporated. Methodologies included in the General Chapter are not applicable to *NF* monographs for Alginates. According to *General Notices 3.10 Applicability of Standards: "'Applicable general chapters' means gen*eral chapters numbered below 1000 or above 2000 that are made applicable to an article through reference in General Notices, a monograph, or another applicable general chapter numbered below 1000.
Regarding the development of this General Chapter, the Expert Committee considered feedback from a variety of sources, including a request from the FDA. FDA commented on the PF 45(5) revision proposal for Viscosity-Capillary Methods <911>. It indicated concerns about the use of viscosity as an indirect measurement of the polymer molecular weight. It recommended USP to develop GPC/SEC based methodologies and introduce them through the General Chapter approach.
Viscosity specification is usually utilized to differentiate the multiple types of polymers. However, establishment of standardized viscosity test is quite challenging for natural polymeric excipients such as alginates. Relative viscosities highly depend on test conditions and viscometer types.

USP is unable to source the standardized viscosity methodologies to differentiate alginate products. However, USP has been successfully working with stakeholders to develop and validate GPC/SEC method to differentiate multiple types of alginates. Thus, the USP Expert Committee recommended developing a general chapter <312>.
This General Chapter<312> has specifically been developed to help the stakeholders differentiate between different types of alginates. This chapter in no way mandates molecular weight determination as a part of material testing as per alginate NF monographs.

General Chapter/Sections:	<383> Cured Silicone Elastomers for Pharmaceutical Packaging and Manufacturing Components/Multiple sections
Expert Committee(s):	General Chapters—Packaging and Distribution
No. of Commenters:	13

General
Comment Summary #1: The commenter recommends USP to develop an informational chapter (e.g., 1383) to provide additional guidance for the IR identification of silicone elastomers and add explanation regarding compounds of concern, such as nitrosamines, latex.
Response: Comment not incorporated. Topic to be considered by the Expert Committee at a future time.
Comment Summary #2: The commenter recommends adding a risk-based approach to the chapter so as to reduce the level of testing for low-risk applications.
Response: Comment not incorporated. Such an approach would require a “low risk” application be defined and applied to all silicone components for which there is not a practical approach at this time.

Introduction
Comment Summary #3: The commenter suggests adding text that divides test into two analytical setups according to either platinum and free-radical/peroxide crosslinking.
Response: Comment incorporated.
Comment Summary #4: The commenter suggests adding “diaphragms” to the list of examples of cured silicone components.
Response: Comment incorporated

Scope
Comment Summary #5: The commenter suggests developing a separate chapter for packaging and manufacturing components instead of merging into one chapter.
Response: Comment not incorporated. To achieve the efficient use of USP chapters, tests and specification are generally the same for both packaging and manufacturing components.
Comment Summary #6: The commenter suggests including in the scope or other section that testing of the component will occur after all processing, including sterilization processes.
Response: Comment incorporated.

Biological Reactivity
Comment Summary #7: The commenter suggests the biological reactivity requirements in <383> should be aligned with <381>.
Response: Comment incorporated.

Identification: Sample Preparation-Procedure

Comment Summary #8: The commenter suggests USP to check and make sure the sample preparation and infrared spectrum noted in the chapter is correct.
Response: Comment incorporated.
Comment Summary #9: The commenter suggests making clear whether section is referring to two separate tests found in <381> (Turbidity/Opalescence test and the Color test) or if the recommended test is mistitled.
Response: Comment incorporated.
Comment Summary #10: The commenter suggests revising to make clear the purpose of the test.
Response: Comment incorporated.

Physicochemical Tests: Appearance of Solution S1
Comment Summary #11: The commenter suggests that the title reference to <381> be revised to reflect the current title.
Response: Comment incorporated.

Physicochemical Tests: Reducing Substance
Comment Summary #12: The commenters suggest there is misplaced/missing text in section and for USP review for accuracy.
Response: Comment incorporated.

Physicochemical Tests: Soluble substances
Comment Summary #13: The commenter inquired about the acceptance criteria, how it was established and adding text justifying.
Response: Comment not incorporated. The acceptance criteria in the section was adopted from the Pharm. Eur. and USP does not outline/justify acceptance criteria in a chapter.

Physicochemical Tests: Volatile matter
Comment Summary #14: The commenter suggests revising to allow more than the desired final dried weight to account for any potential loss on drying.
Response: Comment incorporated.
Comment Summary #15: The commenters suggest there is misplaced/missing text in section and for USP review for accuracy.
Response: Comment incorporated.
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Physicochemical Tests: Residual peroxide
Comment Summary #16: The commenter suggests relocating the acceptance criteria description and editing for clarity.
Response: Comment incorporated.
Comment Summary #17: The commenters suggest clarifying when the residual peroxide test applies.
Response: Comment incorporated.

Physicochemical Tests: Platinum cured
Comment Summary #18: The commenters suggest that it is not clear what should be placed in the quartz crucible and recommend revising for clarity.
Response: Comment incorporated.
Comment Summary #19: The commenter suggests relocating the acceptance criteria description and editing for clarity.
Response: Comment incorporated.

Comment Summary #20: The commenters recommend that an ICP test should be used instead of the current test.
Response: Comment not incorporated. Such a test method would be suitable. However, one has not been developed for this material and the current method.

Additional Requirement
Comment Summary #21: The commenters suggest clarifying that cured silicone elastomers for pharmaceutical packaging components are not exempt from testing per <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems.
Response: Comment not incorporated. Comment is not within the scope of the chapter.

Monograph/Section(s): <471> Oxygen Flask Combustion / Procedure
Expert Committee(s): General Chapters-Chemical Analysis Expert Committee
No. of Commenters: 1

Comment Summary #1: The commenter recommended adding to the Caution in the Introduction the following text: “or perform this test in a well-ventilated hood” to increase user safety.
Response: Comment incorporated.

Monograph/Section(s): <541> Titrimetry / Multiple Sections
Expert Committee(s): General Chapters-Chemical Analysis Expert Committee
No. of Commenters: 6

Comment Summary #1: In “Direct Titration” section, the commenter suggested to add the note “Where less than 10mL of titrant is required, a suitable microburet is to be used.
Response: Comment not incorporated. The volume of the buret is discussed further, and some clarification is added in the second paragraph in this section. See Comment #2 response.
Comment Summary #2: In “Direct Titration” section, the commenter suggested revising the volume of the added titration from 30 -100% to 20-80% of the rated capacity of the buret. In addition, the commentor wanted some clarification on the refill requirement of the buret.
Response: Comment partially incorporated. The text is revised to read as following: “To reduce uncertainty, it is considered as being good practice that the volume added is between 10% and 90% of the rated capacity of the burette. This statement does not apply for blank determination. It is not advisable to refill the buret during titration, if necessary, it is preferred to reduce the sample amount or to increase the titrant concentration.”
Comment Summary #3: The commenter stated that in “Direct Titration” section, 30-100% requirement only applies to manual titration thus a clarification is needed for this requirement.
Response: Comment incorporated. See Comment #2 response.
Comment Summary #4: The commenter stated that a blank titration is required in the current official chapter while the revised chapter text proposed a blank titration is only required when the monograph prescribes. The revised text needs more clarification.
Response: Comment incorporated. Clarification was made for blank corrections.
Comment Summary #5: The commenter recommended adding specific silver halide reference systems for calomel- and mercury-containing electrodes.
Response: Comment not incorporated. The recommendation is under “Electrodes” section in current draft.

Comment Summary #6: The commenter requested to add the statement "All acid-base reactions, however, are symmetrical. Thus, potentiometric endpoint detection may be employed in acid-base titrations and in other titrations involving symmetrical reversible reactions where an indicator is specified, unless otherwise directed in the individual monograph" at the end of the "Physical Detection" section. The commenter stated that in the absence of this statement, such replacement would require a revalidation of an entire method, and then establishing equivalency to the indicator-based compendial procedure (as per General Notices 6.30). The commenter felt that such activity would be a significant overkill in this case. The commenter believed that the presence of the readily available potentiometric option in the chapter would only improve accuracy and precision of results.
Response: Comment not incorporated. As stated in General Notice 6.30 Alternative and Harmonized Methods and Procedures An alternative method or procedure is defined as any method or procedure other than the compendial method or procedure for the article in question. The alternative method or procedure must be fully validated (see Validation of Compendial Procedures ⟨1225⟩) and must produce comparable results to the compendial method or procedure within allowable limits established on a case-by-case basis. Alternative methods or procedures can be developed for any one of several reasons not limited to simplification of sample preparation, enhanced precision and accuracy, improved (shortened) run time, or being better suited to automation than the compendial method or procedure. Only those results obtained by the methods and procedures given in the compendia are conclusive.
Comment Summary #7: The commenter stated that precipitation during titrations impact only visual endpoint detection, whereas potentiometric titration is not affected by precipitation.
Response: Comment incorporated.
Comment Summary #8: The commenter recommended adding ISO 8655-3 in the Volumetric Apparatus section to cover the requirement for piston-operated volumetric apparatus.
Response: Comment not incorporated. The volumetric apparatus requirement is covered under <31> Volumetric Apparatus as well as General Notice 8.20. We have forwarded this comment to the committee responsible for the topic of volumetric apparatus. The volumetric apparatus section is deleted from this chapter to avoid confusion.
Comment Summary #9: The commenter requested to capture modern instrumentation usage rather than historical laboratory practices.
Response: Comment not incorporated. The committee worked on a stimulus article regarding automated titration instruments. We will collect public feedback from that article and decide the next step on this topic.
Comment Summary #10: The commenter asked what type of electrode to choose since the electrode selection is removed.
Response: Comment not incorporated. This chapter is meant to be all inclusive on electrode selection. Electrode selection is based on each individual user's application.

General Chapter/Sections: <661> Plastic Packaging Systems and Their Materials of Construction/Multiple Sections
Expert Committee(s): General Chapters—Packaging and Distribution
No. of Commenters: 13

Introduction
Comment Summary #1: The commenter suggested that the addition of 21 CFR Part 174 reference, while meant to be clarifying, has the potential to add confusion as it generically refers to "indirect food additives regulations" and should be revised to clearly point to all sections of the regulation.

Response: Comment not incorporated. The Expert Committee did not identify the statement as a source of confusion.
Comment Summary #2: The commenter recommends discussing the extreme temperature areas where probes should be relocated.
Response: Comment not incorporated. Mapping process identifies extreme temperature areas, so there is no need to add such a discussion to the chapter.

Polypropylene Containers
Comment Summary #3: The commenter suggests changing “reground materials” to “regrind”.
Response: Comment incorporated.

Introduction (To be official 12/01/2025)
Comment Summary #4: The commenter suggests changing “packaging system” to “packaging component”.
Response: Comment incorporated
Comment Summary #5: The commenter suggests changing “dosage form” to “drug product”.
Response: Comment incorporated

Scope
Comment Summary #6: The commenter suggests changing “therapeutic product” to “drug product”.
Response: Comment incorporated.
Comment Summary #7: The commenter suggests clarifying the revision text that was meant to clarify how ones meets the requirement of <661.1> and <661.2>.
Response: Comment incorporated. The same text that is in <661.1> and <661.2> has been added to chapter.
Comment Summary #8: The commenter suggests adding text stating that any plastic material in a packaging system in contact with drug products shall comply with the requirements in this chapter.
Response: Comment not incorporated. The Expert Committee identified that no additional edits were necessary as the existing references to plastic materials and packaging provided sufficient information.
Comment Summary #9: The commenter suggested that most of the information discussed is informational and not directive and proposed to moved text to <1661>.
Response: Comment not incorporated. No edit was made at this time as USP has agreed with industry to not make any significant changes to the plastic packaging standards until <661.1> and <661.2> become official December 1, 2025.

Monograph/Section(s): <791> pH/Multiple sections
Expert Committee(s): General Chapters-Chemical Analysis
No. of Commenters: 1

Comment Summary #1: The commenter recommended including the word “pH” before the numeral in several instances where buffer is described as greater or lower than a numeral (e.g., “For buffer solutions greater than 11, the storage should be…”), for clarity and readability.
Response: Comment incorporated.

General Chapters/Sections: <1023> Evaluation Strategy for Trace Elements in Cell Culture Media Used in The Manufacture of Recombinant Therapeutic Proteins/Multiple Sections

Expert Committee: Biologics Monographs 2-Proteins
No. of Commenters: 5

Introduction
Comment Summary #1: The commenter suggested to add a comma between Basal cell culture media and nutrient feed in the first sentence, "Cell culture media [which includes basal cell culture media nutrient feed, and supplements (e.g. hydrolysates)] are complex mixtures…"
Response: Comment incorporated.
Comment Summary #2: The commenter suggested to replace the word "important" with desirable in this sentence, "As a result, a thorough biologic elemental monitoring program for measuring and defining acceptable trace element levels is ~~important~~ desirable to understanding their impact on recombinant protein production and product quality."
Response: Comment incorporated.

Elements of Interest
Comment Summary #3: The commenter requested to clarify what "these" is referring to in the following sentence, "All these should be considered to build comprehensive risk assessment and mitigation strategies."
Response: Comment incorporated. The sentenced was edited to define "these" by adding: "all of these supply chain risks should be considered to build comprehensive risk assessment and mitigation strategies."
Comment Summary #4: The commenter suggested to change the following sentence, "Do note that as explained in later sections of this chapter, qualification work of the analytical method should be performed to verify that the method developed produces accurate, precise, and repeatable results." To "~~Do note that as explained in later sections of the chapter~~ Qualification work of the analytical method should be performed to verify that the method developed produces accurate, precise and repeatable results **as explained later in this chapter.**
Response: Comment incorporated.
Comment Summary #5: The commenter requested to include referenced literatures that have been established to the potential cell culture roles of the elements (and update the "reference" section accordingly) in Tables 1 and 2.
Response: Comment not incorporated. The chapter provides references only to the less-commonly known cellular effects of the elements that have been reported. The effects of the majority of elements listed in Tables 1 and 2 on cell culture are known, and references are easily found in peer-reviewed literature.
Comment Summary #6: The commenter requested for clarification about the difference between Table 1 and Table 2. The commenter also suggested that Nickel should be moved to Table 1 as it is known to have an impact on product quality.
Response: Comment partially incorporated. The difference between Table 1 and Table 2 is explained in the title of each table. Table 1 is elements with known impact on cell viability and product quality. Table 2 are contaminants that may impact product quality. Nickel can have impact, but it needs to be investigated in each case as there are concentrations of Nickel that do not have impact. Because Nickel does not always have an impact on the product, it was not moved to Table 1.

Risk Assessment
Comment Summary #7: The commenter suggests to change the word through to throughout in this sentence, "In order to ensure that the critical attributes of the biological product remain consistent, a risk management process should be maintained ~~through~~ **throughout** the product

lifecycle recommended to be based on the principles of the International Council for Harmonization (ICH) guideline on Quality Risk Management (Q9) (1)."
Response: Comment incorporated.
Comment Summary #8: The commenter suggested to change this sentence:" Having an understanding of what might go wrong, what is the likelihood (probability) it will go wrong, and what are the consequences (severity) if it goes wrong can help to frame and inform the overall risk assessment. To this revised sentence: "To frame and inform the overall risk assessment, it is essential to understand what can go wrong, the probability that it will go wrong and the consequences (severity)."
Response: Comment incorporated.
Comment Summary #9: The commenter requested to cite or refer to ISO 14971 for medical device for risk management. The commenter also suggests that risk assessment should be scientifically based.
Response: Comment not incorporated. Information regarding medical device risk management may not be necessarily applicable to media. Media may not always be tested under ISO standards. The chapter states that "In order to ensure that the critical attributes of the biological product remain consistent, a risk management process should be maintained throughout the product life cycle recommended to be based on the principles of the International Council for Harmonization (ICH) guideline on Quality Risk Management (Q9) (1). The ICH Q9 guideline is cited, and this guideline states, "The evaluation of the risk to quality should be based on scientific knowledge". It does not need to be restated in the chapter that risk assessment should be scientifically based.
Comment Summary #10: The commenter suggested replacing much of the current text in the Risk Assessment section as assessment of each component of the medium can be challenging because the recipe of the medium is the property of external vendors, and the recipe is not shared with customers who purchase the medium. The commenter suggested adding details for how to monitor CQAs of the process including perfusion rate and metabolic indicators.
Response: Comment partially incorporated. The text below was added to acknowledge that the components of the medium may be proprietary and not known. The chapter is meant to be high level and the suggested language is too specific and would not apply to all applications, therefore it was not included. Text added to the chapter: "In many instances it may not be possible to assess the impact of components such as trace elements. This would require complete access to the medium formulation from a Vendor and this is typically not possible**."**
Comment Summary #11: The commenter noted that the chapter discusses that stainless steel equipment or other metal equipment could be a source of contamination. The commenter suggested to add or mention a recommendation to use single use equipment including filters, capsules for the preparation of liquid media.
Response: Comment partially incorporated. A bullet point was added to Table 3 that states to consider using single use materials when possible. The word "recommended" was not used because stainless steel may not always be a contamination risk. Also, different suppliers/manufactures do not all use single use materials.
Comment Summary #12: The commenter suggested that the total raw materials contamination concentration be less than 3% in the final liquid media. The commenter also noted that raw material contamination is very low as most raw materials are compendial grade.
Response: Comment not incorporated. The points made by the commenter are recognized throughout the chapter, including in the Case Study which was presented to discuss many of these points.
Comment Summary #13: The commenter suggested to include more details of water as a source of risk because water is a large component of media.

Response: Comment not incorporated. Media can be provided two ways, reconstituted media or dry powder that needs to be reconstituted. In the case of reconstituted media, water would be considered in the evaluation of the media as part of the media. In the case of dry powder media that needs to be reconstituted, water is not usually a source of risk because most manufacturers used purified water to reconstitute dry media.

Sample Considerations

Comment Summary #14: The commenter suggested to add a bullet point on the use of internal standards because using internal standards, for consideration of matrix effects can have a major effect on the testing.

Response: Comment not incorporated. Internal standards are already discussed in the chapter.

Comment Summary #15: The commenter suggested incorporating their preference of dilution over spiking the standard mixture.

Response: Comment not incorporated. Dilution and spiking are both options that can be used and are both discussed in the chapter.

Comment Summary #16: The commenter suggested adding a bullet point on the use of different calibration strategies to be considered for cell culture media products that have high-abundant elements, like Na, Ca, K, Mg, Fe, P and S because these elements need to be calibrated separately.

Response: Comment not incorporated. The suggested elements for calibration are not trace elements as they are abundant and are out of scope of this chapter.

Comment Summary #17: The commenter suggested adding a bullet point that regular cleaning of the device is necessary.

Response: Comment not incorporated. Cleaning practices are recognized as best practices with this technology and therefore, do not need to be discussed in this chapter.

Comment Summary #18: The commenter suggested adding a bullet point that raw materials of cell culture media products are often source for changes in element "picture".

Response: Comment not incorporated. This point was addressed by having discussions with manufacturers to share knowledge of their profiles, and raw materials are already covered in the chapter.

Comment Summary #19: The commenter suggested adding a bullet point that specific sample preparation (like Ultrasonic degradation or heat) is not absolutely necessary for cell culture media.

Response: Comment not incorporated. Table 5 provides different options for dilution and sample preparation; therefore different options of sample preparation are already covered in the chapter. Specific cases are not covered, but guidance has been given.

Analytical Techniques

Comment Summary #20: The commenter suggested including a statement that the samples stay in solution during the analysis.

Response: Comment not incorporated. Maintaining the samples in solution is best practices and is discussed in <730> *Plasma Spectrochemistry* which is cited.

Comment Summary #21: The commenter suggested to change the preparation of neat to "Use undiluted liquid sample" in Table 5.

Response: Comment incorporated.

Comment Summary #22: The commenter suggested to remove the "ed" from digested in this statement, "Dilute in appropriate solvent and heat digest~~ed~~ until clear."

Response: Comment incorporated**.**

Materials and Reagents

Comment Summary #23: The commenter suggested to add “preferably a dedicated laminar flow fume hood of polymer construction designed for trace element analysis.”
Response: Comment partially incorporated. Samples can be handled in a laminar flow fume hood, but a laminar flow fume hood is not used in every lab due to different reagent safety requirements. The words “can be” were added to the sentence about chemical fume hood. This sentence was also added to the text, “A trace element specific fume hood with a laminar flow air curtain can also be used.”
Comment Summary #24: The commenter suggested adding: “Calibration standards,” prior to “Internal standards: Certified ICP-MS grade reference materials.
Response: Comment incorporated. Text was added about calibration standards above internal standards**.**
Comment Summary #25: The commenter suggested adding the following text: “In many instances it may not be possible to assess the impact of components such as trace elements by modification of the media. This would require complete access to the medium formulation from a Vendor and this is typically not possible. In addition, the vendor may have strict limits with regards to which analytes can be measured. Close monitoring of the CQA’s of the process is strongly recommended.”
Response: Comment partially incorporated**.** It is not always possible to have complete knowledge of the media component, so text was added to the chapter, but modified to state **“**It is helpful to the success of an ICP-MS analysis to have knowledge of the specific media components and their concentrations.”
Comment Summary #26: The commenter suggested including Zn atomic mass and Selenium in Table 6.
Response: Comment incorporated.
Comment Summary #27: The commenter requested to change the isotope for Tellurium from 127 to 128 in Table 6.
Response: Comment incorporated.
Comment Summary #28: The commenter requested to align the element(s) of interest in Tables 1 and 2 with the content in Tables 6 and 7 (or clarify why the scope in Tables 6 and 7 would be broader than that in Tables 1 and 2).
Response: Comment incorporated. Antimony and Titanium have been added to Table 2. Cadmium and Selenium were added to Table 6. Cadmium was added to Table 7.

Isobaric Interferences
Comment Summary #29: The commenter suggested to add more text about interference from high concentrations of an element with a mass adjacent to an element to be quantified at trace levels should be considered, for example quantifying ^{55}Mn in the presence of high concentrations of ^{56}Fe (for example, quantification of trace Mn in ferrous sulfate, or ferric citrate).
Response: Comment not incorporated. The text in the Isobaric Interferences section sufficiently discusses interferences. More discussion would be out of the scope of this chapter.
Comment Summary #30: The commenter has suggested the following edits: “it is called a "triple quad" configuration. A **triple quad** spectrometer ~~so equipped~~ can perform a KED…”
Response: Comment incorporate**d.**

Case Study
Comment Summary #31: The commenter recommended changing the solution provided for optimization, and also recommended discussing the differences in sensitivity of different instruments.

Response: Comment not incorporated**.** The media in the Case Study was chosen because it is representative of a real, citable media. If media is used that has target concentrations that are higher, the same basic analytical strategy applies. The recommendation to discuss differences in sensitivity of instruments is not incorporated because there is not a concise way to compare sensitivities of different makes and models of spectrometers, nor will one manufacturer be endorsed over another.
Comment Summary #32: The commenter recommended revising the Case Study section to demonstrate how to achieve desirable measurement by optimizing sample preparation and method.
Response: Comment not incorporated. The point of the case study is to demonstrate that normal conditions for mass spectrometry do not apply for this type of measurement. The case study was a real-world example of a media that had been examined. The case study illustrated conditions and difficulties that will be observed by low concentrations of metals and high concentrations of salts. This case study was selected due to the unique challenges that are illustrated.
Comment Summary #33: The commenter suggested changing "is" to "are" in the sentence "The actual sodium and potassium concentrations from these two salts ~~is~~ **are** as follows".
Response: Comment incorporated.

References
Comment Summary #34: The commenter suggested revising reference #6 in the reference section to have a more consistent format with the rest of the references.
Response: Comment incorporated.

General Chapter/Sections:	<1151> Pharmaceutical Dosage Forms
Expert Committee(s):	General Chapters—Dosage Form
No. of Commenters:	5

Product Quality Tests, General
Dosage Forms, section Capsules, subsection One-piece or soft-shell capsules:
Comment Summary #1: The commenter recommends clarifying the general sentence for the interaction of shell wall and its liquid contents and its undesired interactions which may occur, as stated in the chapter.
Response: Comment not incorporated. This chapter is intended to discuss product quality tests or development of a capsule.

Water Content
Comment Summary #2: The commenter recommends adding a reference to the USP chapter on Water Activity <922> in this section.
Response: Comment incorporated.

Microbial Limits
Comment Summary #3: The commenter suggests stating that "Microbial limits is a dated terminology. Use Microbiological Examination." Also, suggesting adding a reference to USP chapter <60>.
Response: Comment incorporated.

Antimicrobial Preservative Content
Comment Summary #4: The commenter recommends adding acceptance criteria for preservative content in multidose products.

Response: Comment not incorporated. The goal of the USP chapter <1151> is to point to chapters that address topics in detail.

Injections
Table 1:
Comment Summary #5: The commenter is requesting to clarify the applicability of the excess volume recommendation for containers used to prepare a dose by withdrawal (e.g., vials) only or if ready to use injections like pre-filled syringes are also included.
Response: Comment incorporated.

General Considerations, subsection Release Profile
Comment Summary #6: The commenter suggests adding a reference to FDA Guidance on Extended Release Oral Dosage Forms: Development, Evaluation, and Application of in Vitro / in Vivo Correlations; September 1997.
Response: Comment incorporated.

Product Quality Tests, section General
Comment Summary #7: The commenter suggests revising the reference on ICH Guidance Q6A to include the full title.
Response: Comment incorporated.

Dosage Forms, subsection Suspensions
Comment Summary #8: The commenter suggests adding USP chapter <1059> as a reference.
Response: Comment incorporated.

Tablets, subsection Orally Disintegrating Tablet
Comment Summary #9: The commenter suggests deleting the word “dissolve” and revise the text to include the administration instructions.
Response: Comment incorporated.

Glossary, subsection Lipid Nanoparticle
Comment Summary #10: The commenter suggests making a note in parenthesis after Lipid nanoparticle as “not used in official titles”, since the term Lipid nanoparticle does not appear in the nonproprietary name for any FDA approved products.
Response: Comment incorporated.
Comment Summary #11: The commenter suggests removing parenthesis within “poly (ethylene glycol)” to align with NF monograph titles.
Response: Comment incorporated.

Glossary, subsection Oro-Pharyngeal
Comment Summary #12: The commenter suggests removing hyphen in Oro-pharyngeal.
Response: Comment incorporated.

General Chapter/Section(s): <1236> Solubility Measurements / Multiple Sections
Expert Committee(s): General Chapters – Physical Analysis
No. of Commenters: 3

Comment Summary #1: The commenter suggested harmonizing the concentration units in the tables for biorelevant media.

Response: Comment incorporated.
Comment Summary #2: The commenter suggested making corrections in the amount of some reagents used to prepare biorelevant media.
Response: Comment incorporated.
Comment summary #3: Under *Experimental Methods, Methods for Determination of Equilibrium Solubility, Saturation Shake-Flask Methods, Sample preparation*, the commenter suggested to state that the determination should be done in triplicate.
Response: Comment not incorporated. It is up to the user to decide the most appropriate number of replicates for their experiment.
Comment Summary #4: Under *Background, Thermodynamic Equilibrium and Solubility*, the commenter recommended adding the definition of some variables used in the equations.
Response: Comment not incorporated. The definitions are already in the text.
Comment Summary #5: Under *Background, Methods of Estimating Aqueous Solubility*, the commenter recommended to define the acronym GSE, general solubility equation.
Response: Comment not accepted, the definition of the acronym GSE is already in the text.
Comment Summary #6: Under *Background, Factors that Affect Solubility and Solubility Measurements*, *Effect of pH,* last line of the first paragraph, the commenter suggested to make the correction from pK_a (basic) to pK_b (basic). In the second equation, to make the correction to the definition of the variable K_a to acid dissociation constant.
Response: Comments incorporated.
Comment Summary #7: Under *Background, Factors that Affect Solubility and Solubility Measurements, Effect of Surface Area (Dissolution Rate*), the commenter suggested to add the definitions of the variables dC and dt.
Response: Comment not incorporated. The definitions are already located in the text.
Comment Summary #8: Under *Background, Thermodynamic Equilibrium and Solubility*, in the paragraph “This equation also shows how the total surface energy can be broken into i smaller groups each with its own surface area, Ai, and corresponding group-water interfacial tension γiV.”, the commenter suggested to add group-solvent.
Response: Comment incorporated.
Comment Summary #9: Under *Background, Thermodynamic Equilibrium and Solubility*, in the paragraph preceding the last equation, the commenter suggested change it to “For a real solution, the solute may also affect (reduce) the disorder in the solvent by inducing structure to the solvent the solvent-solvent interactions, impacting the order and stability of the solvent intermolecular structure.”
Response: Comment not incorporated. The suggested text does not provide additional clarity.

Monographs

Monograph/Section(s): Betamethasone Valerate/Multiple sections
Expert Committee: Small Molecules 5
No. of Commenters: 2

Comment Summary #1: The commenter requested that relative retention times for Betamethasone valerate related compound H and Betamethasone valerate be included in the test for *Limit of Betamethasone Valerate Related Compound H.*
Response: Comment incorporated. A note was added to the *System suitability* section indicating that the relative retention times for betamethasone valerate and betamethasone valerate related compound H are 1.0 and 1.36, respectively.

Comment Summary #2: The commenter requested that in the test for *Organic iIpurities* the limits for Betamethasone valerate related compound D (9α-bromobetamethasone 17-valerate), Betamethasone valerate related compound A (betamethasone 21-valerate) and any unspecified impurities be updated to be consistent with what is approved.
Response: Comment partially incorporated. The limit for Betamethasone valerate related compound A (betamethasone 21-valerate) is widened from NMT 0.3% to NMT 0.5% and the limit for Any unspecified impurities is widened from 0.10% to 0.1%. The limit for Betamethasone valerate related compound D (9α-bromobetamethasone 17-valerate) reflects specifications received by USP and remains as proposed at 0.10%.
Comment Summary #3: 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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Calcipotriene and Betamethasone Dipropionate Ointment/Multiple sections
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criterion in the *Definition* and in the *Assay* to be consistent with what has been approved.
Response: Comment incorporated. The acceptance criterion for calcipotriene in the Definition and in the *Assay* were revised from NLT 90.0% and NMT 110.0% to NLT 90.0% and NMT 114.0% based on data received.
Comment Summary #2: The commenter recommended revising the acceptance criteria for total betamethasone dipropionate related degradation products, 24-epi calcipotriene, and any unspecified calcipotriene related degradation product in the test for *Organic Impurities* to be consistent with what has been approved.
Response: Comment incorporated. Based on data received, the acceptance criteria for total betamethasone dipropionate related degradation products were widened from NMT 1.0% to NMT 2.5%, for 24-epi-calcipotriene from NMT 1.0% to NMT 1.6%, and for any unspecified calcipotriene related degradation product from NMT 0.5% to NMT 0.7%.
Comment Summary #3: 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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, upon receipt of data, as applicable.
EC Initiated Change #1: The reporting threshold in the test for *Organic Impurities* for Betamethasone Dipropionate was widened from 0.08% to 0.1%, based on data received.
EC Initiated Change #2: To be consistent with ICH Q3B terminology, the following changes are made. In *Table* 1 in the test for *Organic Impurities* for Betamethasone Dipropionate*,* “Any individual unspecified betamethasone dipropionate related degradation product” was revised to “Any unspecified betamethasone dipropionate related degradation product.” In *Table 2* in the test for *Organic Impurities* for Calcipotriene*,* “Any individual unspecified calcipotriene related degradation product” was revised to “Any unspecified calcipotriene related degradation product”.

Monograph/Section(s): Candesartan Cilexetil and Hydrochlorothiazide Tablets/Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 4

Comment summary #1 The commenter requested that the existing Relative standard deviation requirement of 2.0% be retained in the *Assay*.
Response: Comment not incorporated. The Expert Committee determined that the validation data supports the proposed change from NMT 2.0% to NMT 1.0% for the *Relative standard deviation* requirement in the *Assay.*
Comment summary #2: 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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors the Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #3: The commenter recommended removing Candesartan cilexetil related compound A" from the impurity table in the test for *Organic impurities* because process impurities should not be listed in a public standard for drug products and identification of an impurity by the relative retention time (RRT) is not specific, and disregarding peaks by RRTs could potentially lead to relevant coeluted degradation product peaks not being reported.
Response: Comment not incorporated. The comment is out of scope for the published proposal. The Expert Committee can consider incorporating USP's new format change for presenting relative retention times in *Organic impurities* procedures in a future revision to this monograph.
Comment summary #4: The commenter recommended including Hydrochlorothiazide dimer as a specified degradation product with an acceptance criterion of NMT 0.5% in the test for *Organic impurities*.
Response: Comment not incorporated. The comment is out of scope for the published proposal. As appropriate, the Expert Committee will consider future revisions to this monograph upon receipt of supporting information.
Expert Committee-initiated Change #1: In order to resolve discrepancies in the chemical names for USP Candesartan Cilexetil Related Compound B RS, USP Candesartan Cilexetil Related Compound D RS, and USP Candesartan Cilexetil Related Compound F RS in the monograph with the chemical names listed on the corresponding *USP Reference Standard* documentation, the chemical names listed on the current Reference Standards labels and certificates are added with an "also known as" statement.

Monograph/Section(s): Carbomer 934P
Expert Committee(s): Complex Excipients
No. of Commenters: 2

Comment Summary #1: The commenter recommended extending the official date for the omission of the monograph from August 1, 2025, to August 1, 2028.
Response: Comment partially incorporated. The official date for the omission of the monograph has been pushed back to August 1, 2026. In making this decision, the Complex Excipients Expert Committee not only assessed the potential impact of the omissions on application and nonapplication drug products, including an assessment of time necessary to switch to non-benzene containing carbomers (if necessary), but also FDA concern about the safety of drug products containing this benzene-based excipient. USP recommends that stakeholders

producing one or several drug products affected by this omission and containing benzene above the limit of detection but below 2 ppm contact FDA at CDER-benzene@fda.hhs.gov. See FDA communication titled: "FDA alerts drug manufacturers to the risk of benzene contamination in certain drugs" (content current as of 12/05/2023) for more information.
Comment Summary #2: The commenter recommends cancelling the proposal to omit the monograph because even at a high level of benzene in this excipient, a final drug product can still meet the requirement for benzene of NMT 2 ppm per *<467> Residual Solvents*.
Response: Comment not incorporated. See a response to Comment #1 above. Additionally, *<467> Residual Solvents* states that "*Class 1 residual solvents should not be used in the manufacture of drug substances, excipients, dietary ingredients, or official products because of their unacceptable toxicities or deleterious environmental effects."*

Monograph/Section(s): Carbomer 940
Expert Committee(s): Complex Excipients
No. of Commenters: 2

Comment Summary #1: The commenter suggested lowering benzene limit to NMT 2 ppm.
Response: Comment not incorporated. According to the carbomer manufacturer, lowering benzene levels to below 2 ppm in benzene-based carbomers will result in an irreversible change in physical and performance properties of these excipients. Additionally, *<467> Residual Solvents* states that "*Class 1 residual solvents should not be used in the manufacture of drug substances, excipients, dietary ingredients, or official products because of their unacceptable toxicities or deleterious environmental effects."*
Comment Summary #2: The commenter recommends cancelling the proposal to omit the monograph.
Response: Comment not incorporated. See a response to Comment #2 under Carbomer 934P.

Monograph/Section(s): Carbomer 941
Expert Committee(s): Complex Excipients
No. of Commenters: 1

Comment Summary #1: The commenter recommended extending the official date for the omission of the monograph from August 1, 2025, to August 1, 2028.
Response: Comment partially incorporated. The official date for the omission of the monograph has been pushed back to August 1, 2026. In making this decision, the Complex Excipients Expert Committee not only assessed the potential impact of the omissions on application and nonapplication drug products, including an assessment of time necessary to switch to non-benzene containing carbomers (if necessary) but also FDA concern about the safety of drug products containing this benzene-based excipient. USP recommends that stakeholders producing one or several drug products affected by this omission and containing benzene above the limit of detection but below 2 ppm contact FDA at CDER-benzene@fda.hhs.gov. See FDA communication titled: "FDA alerts drug manufacturers to the risk of benzene contamination in certain drugs" (content current as of 12/05/2023) for more information.

Monograph/Section: Cinnamomum verum Bark Powder/Specific Tests
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 1

Comment Summary #1: The commenter commented that the content requirement of volatile oil for the bark pieces and the bark powder should be different. Other pharmacopeial standards have set the volatile oil content requirement differently for the bark and bark powder with a lower content requirement for the bark powder as typical.
Response: Comment incorporated by changing volatile oil content from NLT 1.0 to NLT 0.8% for *Cinnamomum verum* Bark Powder monograph.

Monograph/Section(s): Dextrose /Chemical Information
Expert Committee(s): Simple Excipients

Expert Committee-initiated Change #1: The Expert Committee updated the chemical information for Dextrose to cover both anhydrous and monohydrate forms by adding "m=0 or 1" to the number of H_2O in the dextrose structure. Additionally, "$_D$-Glucose" was added in front of the anhydrous in the description for better clarity.

Monograph/Section(s): Etonogestrel/Multiple sections
Expert Committee: Small Molecules 5
No. of Commenters: 4

Comment summary #1: The commenter requested that in the *Assay* the *Mobile phase* be revised from methanol and water (70:30) to methanol and water (67.5:32:5) and that the *System suitability requirements* for *Relative standard deviation* be revised from NMT 0.73% to 1.0%.
Response: Comment not incorporated. The *Mobile* phase composition is consistent with the sponsor's method and is supported by validation data along with the *Relative standard deviation*.
Comment summary #2: The commenter recommended removing the "reporting thresholds" in the test for *Organic Impurities* as they will vary based on product-specific factors.
Response: Comment not incorporated. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #3: The commenter requested clarification regarding why there is a reporting threshold of 0.1% for 'etonogestrel related compound E' which is higher than the ICH Q3A reporting threshold.
Response: The reporting threshold of 0.1% for etonogestrel related compound E is consistent with the sponsor's approved specifications**.**
Comment summary #4: The commenter indicated concerns that the tests for *Assay* and *Organic Impurities* require isocratic elution which may not be the best choice to obtain good sensitivity due to the low number of theoretical plates.
Response: Comment not incorporated. The Expert Committee determined that the validation data shows adequate sensitivity.
Comment summary #5: The commenter indicted that in the test for *Organic Impurities,* the drug substance peak has strong tailing, even when the system suitability requirements are met, which may impact quantitation of potential impurities that elute just after the drug substance peak.
Response: Comment not incorporated. The Expert Committee determined that the validation data was sufficient for the FDA approved specifications submitted. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of FDA-approved specifications and supporting data.

Comment summary #6: The commenter indicted that in the test for *Organic Impurities,* allowed modification was required to achieve resolution between etonogestrel and etonogestrel related compound A. The commenter is concerned about the robustness and reproducibility of the method due to the totally porous silica stationary phase of the column.
Response: Comment not incorporated. The Expert Committee determined that the validation data was sufficient for the FDA approved specifications submitted.
Comment summary #7: The commenter indicated concern that the proposed method will not be able to separate impurities specified in the EDQM Pharmeuropa 34.2 proposal which indicates more impurities than the USP proposal. The commenter is concerned that the USP proposal's isocratic elution will not be able to adequately separate impurities.
Response: Comment not incorporated. The Expert Committee determined that the validation data was sufficient for the FDA-approved specifications submitted. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of FDA-approved specifications and supporting data.
Comment summary #8: Commenters recommended considering the EDQM Pharmeuropa 34.2 proposal, which contains an alternative HPLC method as a harmonization opportunity.
Response: Comment not incorporated. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of FDA-approved specifications and supporting data.
Comment summary #9: The commenter requested incorporating their in-house method because they are concerned that the proposed procedure is inadequate and lacks sensitivity especially regarding etonogestrel related compound E.
Response: Comment not incorporated. The Expert Committee determined that the validation data shows adequate sensitivity. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of FDA-approved specifications and supporting data.

Monograph/Section(s): Ezetimibe/Multiple sections
Expert Committee: Small Molecules 2
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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Fluorouracil Injection/Multiple sections
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment Summary #1: The commenter recommended revising the acceptance criteria for "Fluorouracil related compound A", "Fluorouracil related compound B", "Uracil", "Fluorouracil related compound E" and "any unspecified impurity" in the test for *Organic Impurities* for consistency with what have been approved.
Response: Comment incorporated. The acceptance criteria for "Fluorouracil related compound A", "Fluorouracil related compound B", "Uracil", "Fluorouracil related compound E" and "any unspecified impurity" were changed from "0.15%" to "0.2%" according to ICH.

Comment Summary #2: The commenter recommended either providing the impurity names and structures or removing the “Unidentified impurity 1” and “Unidentified impurity 2” from Table 1 in the test for *Organic Impurities*.
Response: Comment incorporated. The “Unidentified impurity 1” and “Unidentified impurity 2” with RRTs at 0.48 and 0.54 and the corresponding limits were removed from the test for Organic Impurities.
Comment Summary #3: Commenter recommended removing the “reporting threshold” as it will vary based on product-specific factors.
Response: Comment not incorporated. The new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee may consider incorporating this new approach in future revisions, as applicable.
Comment Summary #4: The commenter recommended revising the acceptance criterion for “Urea” in the “Limit of Urea” test to match with what has been approved.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.
Comment Summary #5: Commenter recommended deleting the expiration date of NMT 24 months after the date of manufacture from the *Labeling* section.
Response: Comment incorporated.
EC-initiated Change #1: The Expert Committee decided to make the following changes to the *Organic Impurities* section:

a. In the “*System suitability*” section, revise the *Relative standard deviation* from “NMT 5.0%, *Standard solution*” to “NMT 5.0% for each component, *Standard solution*” for clarity.
b. In the “*Analysis*” section, change “any other specified and unspecified impurity” to “any unspecified impurity” and change “each corresponding impurity” to “each unspecified impurity.”
c. Change the limit of “Total impurities” from “NMT 1.00%” to “NMT 1.0%”.

Monograph/Section(s): Ganciclovir for Injection/Organic Impurities
Expert Committee: Small Molecules 1
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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: The commenter recommended revising the acceptance criteria for “Total degradation products”, in the test for *Organic Impurities* to be consistent with what has been approved.
Response: Comment not incorporated. The acceptance criteria in the test for *Organic Impurities* are consistent with the approved applications which are available to USP. If necessary, the Expert Committee may consider future revisions to the monograph upon the receipt of supporting data.

Monograph/Section(s): Gefitinib/ Organic Impurities
Expert Committee: Small Molecules 3

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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Expert Committee-initiated Change #1: To harmonize the Gefitinib and Gefitinib Tablets monographs, the relative retention time for dichloroaniline is revised from 0.73 to 0.7. This change is based on comments received for the Gefitinib Tablets monograph.

Monograph/Section(s): Gefitinib Tablets/Organic Impurities
Expert Committee: Small Molecules 3
No. of Commenters: 2

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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: Commenter requests the relative retention time for dichloroaniline be revised to 0.7 from 0.73 in the test for *Organic Impurities*.
Response: Comment incorporated

Monograph/Section(s): Methadone Hydrochloride Tablets/Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment summary #1: The commenter recommended that USP work with approved manufacturers to ensure that marketed products will be able to meet the requirements in the proposed monograph to avoid a drug shortage.
Response: Comment Incorporated. The acceptance criteria for “Any individual degradation product” and “Total degradation products” are widened from NMT 0.10% to NMT 0.2% and from NMT 0.5% to NMT 1.2% respectively to accommodate other FDA-approved products.
Comment summary #2: 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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #3: The commenter recommended revising the acceptance criteria for “Any individual degradation product” and “Total degradation products” in the test for *Organic Impurities* to be consistent with what has been approved.
Response: Comment Incorporated. The acceptance criteria for “Any individual degradation product” and “Total degradation products” are widened from NMT 0.10% to NMT 0.2% and from NMT 0.5% to NMT 1.2% respectively to accommodate other FDA-approved products.

Comment summary #4: The commenter indicated that their products meet the current *USP* monograph and will also meet the proposed monograph updates outlined in *PF* 47(4), except that their in-house method used an L1 column instead of an L7 column.
Response: Comment not incorporated. The use of alternate procedures is discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures.

Monograph/Section(s): Naproxen/Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 4

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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: The commenter recommended revising the acceptance criteria for "Naproxen related compound K", "Naproxen related compound A", "Any unspecified impurity" and "Total impurities" in the test for *Organic Impurities* to be consistent with what has been approved.
Response: Comment not incorporated. The acceptance criteria in the test for *Organic Impurities* are consistent with the approved applications which are available to USP. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #3: The commenter requested that the concentration of the *System suitability solution* in the test for *Enantiomeric purity* be revised to equal the *Sample solution* concentration of 50µg/mL of Naproxen to have an appropriate comparison between components at same level of response in the *Identification B* test.
Response: Comment not incorporated. The Expert committee determined that the proposed concentration works for the intended use based on the available supporting data.
Comment summary #4: The commenter suggested revising concentrations of the components in the *System suitability solution* from 25 µg/mL each to 50 µg/mL of USP Naproxen RS and 1.25 µg/mL of USP Naproxen Related Compound G RS in the test for Enantiomeric purity.
Response: Comment not incorporated. The procedure is based on the validation data and is currently harmonized with the *European Pharmacopeia* (EP) procedure. This change would require additional supporting data and would result in the procedure no longer being harmonized with the EP procedure.
Comment summary #5: The commenter indicated that in the test for *Organic Impurities* the resolution between components is close to the system suitability acceptance criteria. The commenter requested additional information be included in the monograph for taking specific precautions if needed for complying with the resolution criteria.
Response: Comment not incorporated. USP does not typically include language for taking precautions to meet system suitability without supporting data to indicate a specific issue. The monograph does include the "(See Chromatography <621>, System Suitability)" statement that delineates adjustments as described in <621>.
Comment summary #6: The commenter requested that the test for *Optical Rotation* not be removed from the monograph.
Response: Comment not incorporated. The Expert Committee determined that the removal of the *Optical Rotation* test is justified scientifically because the addition of the *Enantiomeric purity* test together with other tests is adequate to establish the quality of the drug substance.

Monograph/Section(s): Naproxen Sodium/Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 4

Comment summary #1: The commenter requested adding an *Identification* test for the chemical identification of sodium.
Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.
Comment summary #2: 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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #3: The commenter recommended revising the *Acceptance criteria* for "Naproxen related compound A", in the test for *Organic Impurities* to be consistent with what has been approved.
Response: Comment not incorporated. The *Acceptance criteria* in the test for *Organic Impurities* are consistent with the approved applications that are available to USP. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #4: The commenter indicated that in the test for *Organic impurities* the resolution between components is close to the *System suitability* acceptance criteria. The commenter requested additional information be included in the monograph for taking specific precautions if needed for complying with the resolution criteria.
Response: Comment not incorporated. USP does not typically include language for taking precautions to meet system suitability without supporting data to indicate a specific issue. The monograph does include the "(See Chromatography <621>, System Suitability)" statement that delineates adjustments as described in <621>.
Comment summary #5: The commenter requested revising the acceptance criteria for "Any unspecified Impurity" in the test for *Organic Impurities* per ICH Q3A considering the highest strength of naproxen sodium currently under approval in US, i.e. NAPRELAN® 750 mg and two tablets per day and total 1500 mg.
Response: Comment not incorporated. The acceptance criteria for "Any unspecified Impurity" is consistent with those that have been approved.
Comment summary #6: The commenter requests to replace the test for *Organic impurities* with their alternative method which they feel is superior as it offers additional controls and quantitates more impurities than the PF proposal.
Response: Comment not incorporated. Use of alternate procedures is discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures.
Comment summary #7: The commenter requested additional preparation instructions or an alternate preparation technique for the Sample solution in the test for *Enantiomeric purity* indicating that the extraction procedure may be difficult to verify and may introduce significant variability.
Response: Comment not incorporated. Use of alternate sample preparation techniques are discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures. USP does not have any additional information regarding the sample preparation instructions which are based on the enantiomeric purity procedure from EP and the validation data.

Monograph/Section(s): Ondansetron/Multiple sections
Expert Committee: Small Molecules 3
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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: The commenter recommends revising the "Any unspecified impurity" limit in the test for *Organic Impurities* to be consistent with ICH Q3A Identification Threshold.
Response: Comment not incorporated. The current USP monograph acceptance criterion is retained for "Any unspecified impurity." The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Expert Committee-initiated Change #1: The *Labeling* statement, **"**Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled." is revised to remove the phrase "to ensure acceptable levels of bacterial endotoxins, it is so labeled" because the phrase inappropriately suggests that measures taken to ensure sterility also ensure acceptable levels of bacterial endotoxins.
Expert Committee-initiated Change #2: In the *Assay,* in the *Solution A* preparation, the spelling of Sodium 1-heptanesulfonate is corrected and the hyperlink for monobasic sodium phosphate anhydrous is corrected to link to the sodium salt instead of the potassium salt.

Monograph/Section(s): Ondansetron Hydrochloride/Multiple sections
Expert Committee: Small Molecules 3
No. of Commenters: 2

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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: The commenter recommends revising the "Any unspecified impurity" limit in the test for *Organic Impurities* to be consistent with ICH Q3A Identification Threshold.
Response: Comment not incorporated. The current USP monograph acceptance criterion for "Any unspecified impurity" is consistent with the sponsor's current approved acceptance criteria. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #3: The commenter observed in the test for *Organic Impurities* the ondansetron related compound G peak is merging with Ondansetron from the *System suitability solution*. The commenter indicated that the other system suitability requirements for the *Sensitivity solution* and % RSD for *Standard solution* are achieved.
Response: Comment not incorporated. The Expert committee determined that the validation data shows sufficient resolution.
Expert Committee-initiated Change #1: The *Labeling s*tatement, "Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels

of bacterial endotoxins, it is so labeled," is revised to remove the phrase "to ensure acceptable levels of bacterial endotoxins, it is so labeled" because the phrase inappropriately suggests that measures taken to ensure sterility also ensure acceptable levels of bacterial endotoxins.
Expert Committee-initiated Change #2: In the test *Assay,* in the *Solution A* preparation, the spelling of Sodium 1-heptanesulfonate is corrected and the hyperlink for monobasic sodium phosphate anhydrous is corrected to link to the sodium salt instead of the potassium salt.

Monograph/Section(s): Pentobarbital/Multiple sections
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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: The commenter requested in the test for *Organic Impurities, to* add a system suitability resolution requirement of NLT 2.0 between the peaks due to Pentobarbital Ethyl analog and Pentobarbital similar to the EP monograph.
Response: Comment not incorporated. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #3: The commenter recommended revising the limit for "Any unspecified impurity" to NMT 0.10% to be in line with ICH Q3A guidelines in the test for *Organic Impurities*.
Response: Comment not incorporated. The acceptance criteria were not revised as part of this proposal and are already official. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #4: The commenter recommended changing the name for 'pentobarbital imino analog' (6-imino-5-ethyl-5-(1methylbutyl)barbituric acid) to 'pentobarbital amino analog' [6-amino-5-ethyl-5-(pentan-2-yl) pyrimidine-2,4(3H,5H)-dione], to be consistent with the EP monograph and the name and structure presented in SciFinder.
Response: Comment not incorporated. The Expert Committee determined either name is appropriate. USP typically only includes a single name for tautomers; the proposed "imino" name reflects the submission and is retained.

Monograph/Section(s): Pimecrolimus/Multiple sections
Expert Committee: Small Molecules 1
No. of Commenters: 5

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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #2: Commenter stated that the main peak (Pimecrolimus) is observed at 36.72 minutes instead of at 27 minutes when they analyzed the sample of Pimecrolimus by the *Organic Impurities* test method described in the proposal.
Response: Comment not incorporated. Retention times listed in the Briefing are for information only.

Comment summary #3: The commenter observed that at a column temperature of 60º, there is a coelution of two peaks (one is unknown, and one is a pimecrolimus triene analog) and recommended increasing the column temperature from 60º to 65º to separate the two peaks.
Response: Comment not incorporated. Increasing the column temperature from 60º to 65º is permitted under *<621> Chromatography, Liquid Chromatography: Gradient Elution.*
Comment summary #4: The commenter recommended that the sum of the peak responses for Pimecrolimus, Pimecrolimus Form B and Pimecrolimus Form C be used in the calculation for the RSD system suitability requirement.
Response: Comment not incorporated. The tautomers, if present, are used in the acceptance criteria calculations for the *Assay* and *Organic Impurities* test. However, only the Pimecrolimus peak is used to establish system suitability, since the tautomers may not be present.
Comment summary #5: The commenter requested to add the structural formula for the impurity Pimecrolimus Triene Analog.
Response: Comment not incorporated. The full chemical name is included in the *<11> USP Reference Standards* section as part of the USP Pimecrolimus System Suitability Mixture RS. It is not current practice to add the structure to the monograph.
Comment summary #6: The commenter requested to add the chromatogram of USP Pimecrolimus System Suitability Mixture RS to correctly identify Pimecrolimus Triene Analog.
Response: Comment not incorporated. Chromatograms are not included in USP monographs. A typical chromatogram may be included with the USP Pimecrolimus System Suitability Mixture RS certificate.
Comment summary #7: The commenter indicated that the solubility information for Pimecrolimus in the Briefing is incorrect.
Response: Comment not incorporated. The statement in the Briefing is incorrect, however the information in the Briefing section of *PF* is for informational purposes only and is not included in the monograph. The correct solubility information for Pimecrolimus is as follows: “Pimecrolimus is freely soluble in methylethylketone, methylisobutylketone, dichloromethane and tetrahydrofuran, soluble in acetone, methanol, ethanol, acetonitrile and toluene, sparingly soluble in isopropanol and practically insoluble in water.”
Comment summary #8: The commenter requested to change the solvent used in the test for optical rotation chloroform to DMSO because chloroform has acute toxicity, is an irritant and has health hazards.
Response: Comment not incorporated. Changing the solvent from chloroform to DMSM would require changing the acceptance criteria. The procedure and acceptance criteria for specific optical rotation using chloroform is consistent with the sponsor’s approved application. If necessary, the Expert Committee will consider a future revision using an alternative solvent to the monograph upon the receipt of supporting data.
Expert Committee-initiated Change #1: In the test for *Organic Impurities*, the *Sensitivity solution*, *Signal-to-noise* requirement in the *System suitability* section, and the reporting threshold are removed.

Monograph/Section(s): Plerixafor/Multiple sections
Expert Committee: Small Molecules 2
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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific

factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Expert Committee-initiated Change #1: The *Labeling* statement, “Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms to ensure acceptable levels of bacterial endotoxins, it is so labeled,” is revised to remove the phrase “to ensure acceptable levels of bacterial endotoxins, it is so labeled” because the phrase inappropriately suggests that measures taken to ensure sterility also ensure acceptable levels of bacterial endotoxins.

Monograph/Section(s): Plerixafor Injection/Multiple sections
Expert Committee: Small Molecules 2
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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Rosuvastatin Calcium/Multiple sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment summary #1: The commenter recommended adding a test for the quantitative measurement of calcium content as any variation in the calcium content will affect the molecular weight.
Response: Comment not incorporated. The comment is out of scope for the published proposal. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment summary #2: 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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.
Comment summary #3: The commenter indicated that in the test for *Organic Impurities* the hyperlink for USP Rosuvastatin System Suitability Mixture RS did not appear to be working.
Response: Comment incorporated. The issue with the link in *PF* has been corrected and users can access the USP Rosuvastatin System Suitability Mixture RS certificate which includes an example chromatogram.
Expert Committee-initiated Change #1: The proposed change to delete “solvent-free” from the *Definition* and the *Assay* is not approved and “solvent-free” will be retained.

Monograph/Section(s): Rosuvastatin Tablets/Multiple sections
Expert Committee: Small Molecules 2
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. A new USP general chapter, ⟨477⟩ User-Determined Reporting Thresholds, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

Monograph/Section(s): Topiramate Extended-Release Capsules /Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 5

Comment Summary #1: The commenters requested revisions to *Identification A* regarding sample preparation, solvent composition, and the flexibility to use <197A>.
Response: Comment partially incorporated. The Expert Committee determined that spectral agreement was only needed for specific bands and that the option to use <197A> was appropriate. The Expert Committee will consider further revisions to the monograph upon the receipt of supporting data.
Comment Summary #2: The commenter requested flexibility in the *Assay* regarding the shaking and sonication times**.**
Response: Comment partially incorporated. The Expert Committee revised the *Sample solution* preparation in the *Assay* to be more flexible by replacing "shaking at about 10 min intervals for NLT 60 min" with "shaking for NLT 10 m in".
Comment Summary #3: The commenter requested replacing the proposed *Diluent* in the *Assay* with their in-house solvent composition of methanol and water (50:50).
Response: Comment not incorporated. The Expert Committee found the current solvent composition to be consistent with the validated procedure. The Expert Committee will consider further revision to the monograph upon the receipt of supporting data. The use of alternate procedures is discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures.
Comment Summary #4: The commenter requested flexibility in the *Assay* by adding a second procedure.
Response: Comment not incorporated. USP monographs do not typically include multiple tests for *Assay*. An alternative sample preparation can be considered in a future revision upon the receipt of supporting data. Use of alternate procedures is discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures.
Comment Summary #5: The commenters requested the addition of their in-house procedures to the test for *Dissolution*. A commenter indicated that the test for *Dissolution* is not suitable for their product. Another commentor indicated that their procedure is more sensitive, precise, and robust.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monograph upon the receipt of supporting data.
Comment Summary #6: The commenter requested revising the pore size of the filter referenced in the test for *Dissolution* from 0.45 µm to 0.2 µm.
Response: Comment partially incorporated. The *Sample solution* in the test for *Dissolution* is revised to reference the use of a suitable filter of 0.45-µm or finer pore size**.**
Comment Summary #7: The commenter requested revising the *Buffer* in the test for *Dissolution* from pH 7.2 Buffer to pH 6.8 Buffer for improved discrimination.
Response: Comment not incorporated. The dissolution parameters are consistent with the sponsor's FDA-approved submission. An additional dissolution test can be considered upon receipt of FDA-approved specifications.
Comment Summary #8: The commenter requested the option to use suitable sinkers in the test for *Dissolution*.

Response: Comment incorporated.
Comment Summary #9: The commenters requested replacing the procedure in the *Limit of Sulfamate and Sulfate* with different procedures. A commenter indicated that the procedure is not suitable for their product. Another commenter indicated a preference for an isocratic procedure for flexibility and to avoid the need for conductivity instrumentation.
Response: The Expert Committee found that the sponsor's validated procedure is suitable for its use and inclusion in the public standard. The Expert Committee will consider future revisions upon the receipt of supporting data. Use of alternate procedures is discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures.
Comment Summary #10: The commenter observed retention times in the test for the *Limit of Sulfamate and Sulfate* which were not consistent those proposed.
Response: Comment not incorporated. The Expert Committee found that the sponsor's validated procedure is suitable for its use and inclusion in the public standard. The Expert Committee will consider future revisions upon the receipt of supporting data. Use of alternate procedures is discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures.
Comment Summary #11: The commenters requested removing the test for the *Limit of D-Fructose*. A commenter indicated that it could be controlled, if present, as an unspecified impurity with a limit of NMT 0.2%.
Response: Comment incorporated. The Expert Committee determined that D-Fructose is sufficiently controlled in the drug substance. The test for the *Limit of D-Fructose* is removed, the related footnote in *Table 3* is revised, and USP Fructose RS is removed from the *USP Reference Standards <11>* section.
Comment Summary #12: The commenter indicated that they were unable to successfully execute the procedure for *Organic Impurities*.
Response: Comment not incorporated. USP did not receive similar comments from other stakeholders nor encounter issues within our laboratories. The Expert Committee found that the sponsor's validated procedure is suitable for its use and inclusion in the public standard. The Expert Committee will consider future revisions upon the receipt of supporting data.
Comment Summary #13: The commenter requested the inclusion of centrifugation in the preparation of the *Sample solution* within the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee found that the sponsor's validated procedure is suitable for its use and inclusion in the public standard. The Expert Committee will consider future revisions upon the receipt of supporting data. Use of alternate procedures is discussed in *General Notices* 6.30. Alternative and Harmonized Methods and Procedures.
Comment Summary #14: The commenter requested widening the limit of Topiramate related compound A in the test for *Organic Impurities* from NMT 0.3% to NMT 0.5% for consistency with the limits in the Topiramate Tablets and Topiramate Capsules monographs as well as their in-house specifications.
Response: Comment not incorporated. The specifications in the monograph reflect FDA-approved requirements. The Expert Committee will consider future revisions to the monograph upon the receipt of supporting data.
Comment Summary #15: The commenter requested adding another procedure to the test for *Organic Impurities*. The commenter indicated that their procedure is more sensitive.
Response: Comment not incorporated. The Expert Committee finds the current procedure to be suitable for its use and inclusion in the public standard. The Expert Committee will consider future revision to the monograph upon the receipt of supporting data. The use of alternate procedures is discussed in *General Notices* 6.30 Alternative and Harmonized Methods and Procedures.