



Commentary

USP–NF 2023 Issue 3

June 1, 2023

In accordance with USP’s *Rules and Procedures of the Council of Experts (“Rules”)*, and except as provided in Section 9.02 *Accelerated Revision Processes*, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary (USP–NF)* for public review and comment in the *Pharmacopeial Forum (PF)*, USP’s free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee (EC) deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status, a summary of comments received and the appropriate Expert Committee’s responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of USP.NF.com at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees’ responses to public comments on proposed revisions. If there is a difference or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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

General Chapters

[<314> Molecular Weight Determination for Copolymers Containing Alkyl Methacrylate or Alkyl Acrylate](#)
[<670> Auxiliary Packaging Components](#)
[<831> Refractive Index](#)
[<901> Detection of Asbestos in Pharmaceutical Talc](#)
[<1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products](#)
[<1079.3> Monitoring Devices - Time, Temperature, and Humidity](#)
[<1094> Capsules – Dissolution Testing and Related Quality Attributes](#)
[<1504> Quality Attributes of Starting Materials for the Chemical Synthesis of Therapeutic Peptides](#)
[<1567> Pyrrolizidine Alkaloids as Contaminants](#)
[<1604> Presentation of Aerodynamic Particle Size Distribution \(APSD\) Measurement Data for Orally Inhaled Products](#)
[<1724> Semisolid Drug Products – Performance Tests](#)
[<1901> Theory and Practice for Asbestos Detection in Pharmaceutical Talc](#)
[<1912> Measurement of Yield Stress of Semisolids](#)

Monographs

[Acetazolamide Extended-Release Capsules](#)
[Betamethasone Acetate](#)
[Bivalirudin](#)
[Bromelain](#)
[Calcium Pantothenate](#)
[Carbamazepine](#)
[Cefoperazone Sodium](#)
[Cetostearyl Alcohol](#)
[Cisplatin Injection](#)
[Clobazam](#)
[Cranberry Fruit Juice Dry Extract](#)
[Cranberry Fruit Juice Dry Extract Capsules](#)
[Cromolyn Sodium](#)
[Cyanocobalamin](#)
[Dapaqliflozin Propanediol](#)
[Dimethyl Fumarate](#)
[Dimethyl Fumarate Delayed-Release Capsules](#)
[Flurbiprofen](#)
[Gabapentin Compounded Cream](#)
[Glucagon](#)
[Inositol Niacinate](#)
[Isopropyl Alcohol](#)
[Lactobacillus Reuteri](#)
[Lactobacillus Rhamnosus](#)
[Morphine Sulfate](#)
[Nadolol](#)
[Oxycodone Hydrochloride Tablets](#)

[Pantoprazole Sodium](#)
[Sucralose](#)
[Sulbactam Sodium](#)
[Talc](#)
[Terbutaline Sulfate](#)
[Terbutaline Sulfate Injection](#)

No comments were received for the following proposals:

General Chapters

<581> Vitamin D Assay
<1118> Monitoring Devices—Time, Temperature, and Humidity

Monographs

Bivalirudin for Injection
Candelilla Wax
Dalteparin Sodium
Flurbiprofen Tablets
Gramicidin
L-Alpha-Glycerolphosphorylcholine
Methylprednisolone
Pummelo Peel
Pummelo Peel Flavonoids Dry Extract
Pummelo Peel Powder
Sodium Fluoride F 18 Injection
Spironolactone and Hydrochlorothiazide Tablets

General Chapter/Section(s):	<314> Molecular Weight Determination for Copolymers Containing Alkyl Methacrylate or Alkyl Acrylate/ Multiple sections
Expert Committee:	Excipients Test Methods
No. of Commenters:	2

Comment Summary #1: The commenter recommended changing the text “The following procedures are used to” to “The following gel permeation chromatography (GPC)/size exclusion chromatography (SEC) procedures are used to” in the introduction section.

Response: Comment incorporated. The Expert Committee agreed that this change offers more clarity to users.

Comment Summary #2: The commenter recommended revising the filtering instruction of the solutions to be more general in *APPARENT WEIGHT-AVERAGE MOLECULAR WEIGHT AND POLYDISPERSITY*.

Response: Comment incorporated. The “using a glass syringe through a PTFE filter of 1-µm pore size” was changed to “using a suitable syringe compatible with tetrahydrofuran through a suitable filter of 1-µm pore size” and the detailed information was moved to a footnote.

Comment Summary #3: The commenter recommended changing the term “polydispersity” to “polydispersity index (PDI)” in the *Analysis* section of *APPARENT WEIGHT-AVERAGE MOLECULAR WEIGHT AND POLYDISPERSITY*.

Response: Comment not incorporated. “Polydispersity” is a term consistently used in the *USP-NF*.

Comment Summary #4: The commenter indicated that the sample interacts with the material of the brand of columns mentioned in the Briefing and there are differences in results between the USP method versus their method. The commenter suggested that USP revise this chapter or withdraws this chapter.

Response: Comment not incorporated. The manufacturer of the columns identified that normally in theory, no such chances of interaction occur. The USP method was successfully validated, and accuracy passed the requirement in the validation. The commenter obtained comparable results (within 8%) with those obtained in *USP* using the USP method, which indicates good reproducibility of the USP method. The commenter’s method was not validated.

General Chapter/Section(s): <670> Auxiliary Packaging Components
Expert Committee: General Chapters—Packaging and Distribution
No. of Commenters: 5

Pharmaceutical Coil (Residual hydrogen peroxide concentration)

Comment Summary #1: The commenter recommends clarifying that the percentage of hydrogen peroxide is expressed as weight per weight.

Response: Comment incorporated.

Comment Summary #2: The commenter suggests that the hydrogen peroxide calculation is inaccurate due to potential erroring the 0.017 factor.

Response: Comment incorporated.

Activated Charcoal (Identification)

Comment Summary #3: The commenter suggests revising the text under *Identification* to specify the gas environment.

Response: Comment incorporated.

Activated Charcoal (Inorganic Impurities)

Comment Summary #4: The commenter suggests revising the criteria under *Inorganic Impurities* to include ppm.

Response: Comment not incorporated. Other acceptance criteria in the chapter is in “mg/kg” so this comment was not incorporated to maintain chapter’s alignment.

Activated Charcoal (Loss on Drying)

Comment Summary #5: The commenter suggests expanding the temperature range for drying to 105-120.

Response: Comment incorporated.

Comment Summary #6: The commenter suggests revising the limit to “NMT 5%” based on carbon batch data.

Response: Comment incorporated.

Activated Charcoal (Absorption Capacity)

Comment Summary #7: The commenter suggests revising the limit to “NMT 21%” based on carbon batch data.

Response: Comment incorporated.

Activated Charcoal (Water Extractables)

Comment Summary #8: The commenter suggests revising the limit to “NMT 5%.”

Response: Comment incorporated.

Odor Adsorbent-Activated Charcoal

Comment Summary #9: The commenter suggests revising the limit to “NMT 40%.”

Response: Comment incorporated.

General Chapter/Section(s): <831> Refractive Index/ Multiple Sections
Expert Committee: General Chapters-Physical Analysis (Solution Subcommittee)

No. of Commenters: 7

Comment Summary #1: The commenter wanted to change the phrase “pharmaceutical materials” to “matter” in the first sentence in the chapter.

Response: Comment not incorporated. The scope of *USP-NF* is pharmaceutical materials.

Comment Summary #2: The commenter recommended that an example be given for pure water measured at 25° instead of 20° in the *Introduction* section to be consistent with the *Measurement Procedure* requirement that samples are measured at 25°.

Response: Comment not incorporated. Pure water is used as an example to explain the meaning of refractive index. The text doesn’t indicate all sample measurement should be conducted at 20°.

Comment Summary #3: The commenter suggested to add “C” for temperature to clarify the unit is Celsius.

Response: Comment not incorporated. Per *USP General Notice 8.180 Temperatures*, the temperatures in *USP-NF* are expressed in centigrade (Celsius) degrees.

Comment Summary #4: The commenter recommended more flexibility be provided on the operational qualification requirement to allow for demonstration of compliance according to specific application and users requirements.

Response: Comment not incorporated. The current operation qualification requirement is consistent with what commercially available apparatus can achieve. The chapter text used general wording to avoid excluding other instruments.

Comment Summary #5: The commenter asked the following questions regarding operational qualification. Is the accuracy of the device ± 0.001 the true requirement? Is user standardization required with water prior to any testing? Are other scales (e.g., brix scale, ISUM scale) acceptable?

Response: The accuracy is the accuracy for certified reference materials (CRMs), not for instruments. This is a broad range to allow users using inexpensive CRMs for their application. The accuracy depends on specific applications. Other scales are not needed based on the purpose of this chapter. However, users can use other scales if appropriately justified.

Comment Summary #6: The commenter made the following revision suggestions for second sentence under Operational Qualification: “*The apparatus should provide refractive index*”

readings to ± 0.0001 , and it should provide a means of operation at the prescribed temperature, with readings accurate to a resolution in temperature of at least $\pm 0.1^\circ\text{C}$ ". The underlined words are added as recommendation by the commenter.

Response: Comment not incorporated. This is not resolution; it is an accuracy requirement. Celsius is default in *USP-NF* as explained in previous comment response; and therefore "C" is not needed.

Comment Summary #7: One commenter stated that the OQ requirement for the instrument to operate at the prescribed temperature, with readings accurate to at least $\pm 0.1^\circ$ is not in line with current manufacturing tolerances. For example, a representative operating manual listed a temperature measurement accuracy of 0.3°C , and water baths often have uncertainty of 0.2°C . The other commenter recommended to change the temperature accuracy from $\pm 0.1^\circ$ to $\pm 0.05^\circ$ for operational qualification.

Response: Comment not incorporated. Most suppliers have 20° as default temperature. The requirement of $\pm 0.1^\circ$ is achievable. Other accuracy could be appropriate for other specific applications. In such cases, it is up to the user to demonstrate suitability.

Comment Summary #8: The commenter stated the reference material must always have a better uncertainty than the instrument itself.

Response: Comment not incorporated. The choice of certified reference materials depends on the user's intended use. Users could be more strict or accurate in choosing reference material if their specific application requires.

Comment Summary #9: The commenter recommended that the text mention names of certified reference material for verification of the accuracy of the refractometer.

Response: Comment not incorporated. There are plenty of certified reference materials to be used. Users can choose any given reference material for their application so long as it meets the stated accuracy.

Comment Summary #10: Instead of using expanded uncertainty of the reference material plus the accuracy specification of the instrument, the commenter recommended that the text add ± 0.0001 to the expanded uncertainty of the reference material value as a specification under accuracy check.

Response: Comment not incorporated. The value of ± 0.0001 mentioned in the text is the readability of the apparatus not the accuracy or uncertainty of the reference material.

Comment Summary #11: The commenter recommended that repeatability cover the full operational range of the instrument.

Response: Comment not incorporated. There is no need to cover the full operational range. It is up to the user to conduct repeatability based on their intended use.

Comment Summary #12: The commenter asked if statistic tools can be used in assessing repeatability. The commenter suggested to add language to discuss the linearity of the inheritance properties of a grating/prism.

Response: Comment not incorporated. Current language in the chapter is clear and basic for repeatability. Linearity is not covered and should be checked with the instrument supplier (if needed).

Comment Summary #13: The commenter disagreed with the following sentence: "The result should be equal to or less than the stated repeatability performance specification of the instrument (as provided by the manufacturer)." The commenter concluded that the repeatability has in fact no meaning. The commenter gave an example of a manufacturer's repeatability specification set as 0.1, then this check of the repeatability would be passed. The repeatability must be at least the same as accuracy.

Response: Comment not incorporated. Repeatability is critical. There is an uncertainty limit of ± 0.001 for reference materials stated in other section in the chapter.

Comment Summary #14: The commenter stated that the two stages of PQ evaluation may not be needed and recommended to add more flexibility.

Response: Comment not incorporated. The chapter explains PQ as a check point in addition to calibration. PQ depends on specific applications.

Comment Summary #15: The commenter suggested to include the option to use distilled water as an alternative to certified reference material for daily control of equipment. The commenter also advised to add “well-defined” before reference material for clarity.

Response: Comment not incorporated. The chapter text doesn’t exclude the use of distilled water as reference material. “Suitable” and “well-defined” are redundant so there is no change in wording in the sentence.

Comment Summary #16: The commenter recommended to verify the temperature at the place of measurement, which is the interface between sample and measuring prism (measuring prism surface). This is different from the sample temperature.

Response: Comment not incorporated. The commercially available instruments could work differently concerning temperatures. The chapter text does not specify one single way to handle it.

Comment Summary #17: The commenter stated that allowable tolerance should be defined for measurement temperature criteria of 25° under *Measurement Procedures*.

Response: Comment not incorporated. The temperature tolerance is discussed in the OQ section in the chapter.

General Chapter/Section(s): <901> Detection of Asbestos in Pharmaceutical Talc/
Multiple sections

Expert Committee: Excipients Test Methods

No. of Commenters: 14

Comment Summary #1: Commenters recommended an extra or a longer time for implementation (i.e., ~3 years), as X-ray diffraction (XRD) and Polarized Light Microscopy (PLM) are not commonly used for routine release testing.

Response: Comment partially incorporated. The Expert Committee approved an official date of December 1, 2023, for the two general chapters <901> and <1901>, while the Expert Committee also approved an extended official date of December 1, 2025, for the *USP* Talc monograph, with changes to be published in USP–NF 2023 Issue 3. The additional two years are intended to provide the time needed by manufacturers and users to implement the test methods and make necessary changes.

Though chapter <901> will become official before the *USP* Talc monograph becomes official, the chapter will only apply when revisions to the *USP* Talc monograph (which references chapter <901>) becomes official and the chapter <1901> is for informational purpose only. The earlier official date for both chapters will help stakeholders in the adoption of the of the *USP* Talc monograph revisions that will become official later.

Please see [Compendial Notice](#) published on the USP web site on May 26, 2023.

Comment Summary #2: Commenters recommended retaining "suppliers" to perform the asbestos testing, as indicated in the original note of the Talc monograph.

Response: Comment not incorporated. Based on the discussions of the Expert Committee and the FDA’s input, both suppliers and end users need to certify to the FDA that their products comply with the compendial standard and cGMP requirements. They may have third parties (such as contract laboratories) test for asbestos if they do not have the capability to perform the asbestos tests.

Comment Summary #3: Commenters recommended the following:

- a. changing the format of microbial limits according to the current USP style, such as changing from “NMT 100 cfu/g” to “NMT 10² cfu/g”, etc.
- b. changing the limit for Talc intended for topical administration from “Total combined molds and yeasts count: NMT 50 cfu/g” to “Total combined molds and yeasts count: NMT 10¹ cfu/g”

Response: Comment a was incorporated, but comment b was not incorporated. The updated texts are shown as below:

- Intended for topical administration
 - Total aerobic microbial count: NMT 10² cfu/g
 - Total combined molds and yeasts count: NMT 5 x 10¹ cfu/g
- Intended for oral administration
 - Total aerobic microbial count: NMT 10³ cfu/g
 - Total combined molds and yeasts count: NMT 10² cfu/g

According to general chapter <1111> *MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE*, for pharmaceutical substance, the total combined molds and yeasts count is NMT 10² cfu/g. Additionally, the commenter did not provide data to support the limit change to “NMT 10¹ cfu/g”. Therefore, comment b is not incorporated.

Comment Summary #4: The commenter is willing to implement the proposed changes/update in the *Definition*, *Limit of Calcium*, and *Labeling* sections.

Response: Comment noted

Comment Summary #5: Commenters recommended providing reference standards in order to validate the methods according to general chapters <1225> and <1226>.

Response: Comment partially incorporated. Due to the challenges of handling asbestos and developing physical reference standards, USP included 5 representative XRD diffractograms and 85 PLM images in chapter <1901> as references.

Comment Summary #6: Commenters recommended only performing the X-ray Diffraction (XRD) test to be consistent with the *European Pharmacopeia* (EP), as the Talc monograph is a PDG harmonized monograph.

Response: Comment not incorporated. As explained in the *Stimuli* article “[Modernization of Asbestos Testing in USP Talc—Part 2](#)” published in *PF* 46(5), both XRD and PLM are mandatory for asbestos testing in pharmaceutical talc. The asbestos testing is currently a non-harmonized attribute in the Pharmacopeial Discussion Group (PDG) harmonized Talc monograph, however, EP is also planning to align with the XRD and PLM testing procedures proposed in the USP chapters <901> and <1901>. Therefore, both XRD and PLM procedures will be implemented by EP as well. Additionally, contract labs are available for testing if pharmaceutical manufacturers do not have the capability to perform the tests.

Comment Summary #7: The commenter stated the following:

“This method has been well-tested. Many laboratories have participated in establishing quantitative measures of reliability. The detection limit is robust and equivalent to methods based on electron microscopy. The including of a wet sieving method enhances the possibility of detecting asbestos given that its high tensile strength and resistance to grinding leaves long fibers intact. The method can be applied to raw materials or to materials that have been concentrated by heavy liquids. Of particular importance is the inclusion of criteria by which asbestiform amphibole can be discriminated from non-asbestiform habits of the same mineral. This is an excellent method and a significant advance for screening talc for the presence of asbestos.”

Response: Comment noted.

Commentary for USP–NF 2023, Issue 3

Comment Summary #8: The commenter provided the following comment:

No testing institution which would be able to carry out the proposed tests is found in Japan, in terms of wet sieving pretreatment, appropriate analytical equipment, and experienced analyst. It is difficult for both excipient manufacturers and pharmaceutical manufacturers to conduct the tests in Japan.

Response: Comment not incorporated. In the USA, contract laboratories are available for testing if stakeholders do not have the capability to perform the tests. To protect public health, the committee identified the importance of testing asbestos in pharmaceutical talc.

Comment Summary #9: The commenter recommended the following regarding wet sieving:

- a. The wet sieve preparation should be optional.
- b. Should provide some flexibility in the sieve size used and allow for use of disposable screening materials which would remove or reduce the possibility of transfer of material from sample to sample.
- c. If, after sieving, the mass of material remaining on the sieve is less than 0.01% of the initial sample, the protocol should end. If less than 0.01% remains, the result is certain to be lower than the stated limit of detection and quantification (0.01%).

Response: Comment a: Not incorporated. Based on the round robin study results, the wet sieving procedure is mandatory to achieve the desired detection limit (0.01%). According to [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#), alternative method or procedure can be used. However, they 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.

Comment b: Partially incorporated. Sieves should be cleaned and maintained in accordance with manufacturers recommendations and/or instructions. Step #9 was added to <901> for this procedure. Flexibility of using sieve size should follow [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#).

Comment c: Not incorporated. According to the testing procedure in <901>, sieving should be continued until a minimum of 5 mg of material remaining on the sieved is collected. However, it may stop earlier if asbestos is detected. Validation is needed if an alternative method is used.

Comment Summary #10: The commenter recommended the following regarding PLM:

- a. The mass of sample placed on slides is stated to be 1-2 mg. In practice, 0.5 mg will produce a more optimal loading of particulate.
- b. If amphibole asbestos is determined by PLM, the option for energy dispersive x-ray spectroscopy (EDS) analysis should be mandatory to confirm the PLM finding.
- c. The *Reporting Results* section could be edited for clarity, particularly at numbers 3 & 4.

Response: Comment a: Partially incorporated. According to [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#), alternative method or procedure (such as use of 0.5 mg sample) can be used. However, they 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.

Comment b: Not incorporated. Energy dispersive x-ray spectroscopy (EDS) is not within the scope for PLM. A lab may employ it as an optional procedure.

Comment c: Incorporated. The #3 and #4 in *Reporting Results* are edited to be more explicit. See <901> which will be available on the *USP-NF* platform from June 1, 2023, and become official on December 1, 2023.

Comment Summary #11: The commenter stated the following:

- a. "In the <901>, *Procedure 2: Polarized Light Microscopy*" subsection "*Sample Analysis*", in addition to the examples of morphology identified ("straight, curved, bundle, wavy, splayed ends, etc.") the term "polyfilamentous" should also be listed.
- b. The commenter expressed support for USP referring to the glossary section of EPA 600/R-93/116 in defining the term asbestiform.

Response: Comment a: incorporated by adding "polyfilamentous" to the text. Comment b noted.

Comment Summary #12: The commenter stated the following:

- a. The commenter is supportive of the proposed method <901> and supporting information in chapter <1901>. Most notably, they commend the incorporation of the EPA 600/R-93/116 definition for asbestiform into the USP protocol for measurement of asbestos in talc. They are pleased to see that the panel has addressed FDA's request for modernizing the test method.
- b. The proposed USP method for measuring asbestos in talc for pharmaceutical applications should be considered by the FDA for the measurement of asbestos in talc for cosmetic applications and other related uses of talc. The commenter expressed it would be prudent for the USP to recommend that the FDA instruct the Interagency Working Group on Asbestos in Consumer Products (IWGACP) to incorporate this proposed USP Detection of Asbestos in Pharmaceutical Talc method, when determination of asbestos is required in all talc applications including cosmetics. There is no rational scientific reason for having different test protocols for each application of talc.

Response: Comment a noted and incorporated. Comment b noted and feedback was shared with the FDA on this topic.

Comment Summary #13: The commenter provided several comments on the XRD instrument conditions and parameters under *Procedure 1: X-ray Diffraction* in the general chapter <901>.

Response: Comments incorporated because those additional conditions and parameters also apply to XRD analysis. See general chapter <901> which will be available on the *USP-NF* platform on June 1, 2023, and become official on December 1, 2023.

Comment Summary #14: The commenter made the following comments on <901>:

- a. For clarity, the commenter suggested including a statement in <901> that there is no level of asbestos that is recognized as safe and that the limits are based on limits of detection, not toxicological limits.
- b. Recommended a reference to *(1901) Theory and Practice of Asbestos Detection in Pharmaceutical Talc* be added to the *Limit of Detection* and *Quantification* subsections under *Procedure 1: X-Ray Diffraction* and *Procedure 2: Polarized Light Microscopy*. This would provide the reader with additional context and clarity.

Response: Comment a: Partially incorporated. The Expert Committee agreed to add a note at the end of "Reporting Results" for both XRD and PLM as follows:

- "[Note: The limits are based on limits of detection.]

Comment b: Incorporated. The Expert Committee agreed to add a reference to <1901> in the *Limit of Detection and Quantification* subsections of both XRD and PLM sections in <901>.

Comment Summary #15: The commenter suggested including a table to summarize the scope, features, and advantages/disadvantages of each technique in chapter <1901>. The table would help highlight and clarify why and how the different techniques are complementary to each other.

Response: Comment incorporated. See *Table 1* in chapter <1901>.

Comment Summary #16: The commenter recommended using categorized subsections and subtitles (e.g., "Purpose", "Scope", "Table of characteristic peaks", "Table of samples", and "Instrument calibration/qualification") in <1901>. This would enhance clarity and readability.

Response: Comment not incorporated. There are already subsections in the XRD and PLM sections of chapter <1901>.

Comment Summary #17: The commenter recommended spelling out “National Institute of Standards and Technology (NIST) or NIST-traceable Standards should be used for all types of asbestos...” in the Standards and Calibration section of chapter <1901>.

Response: Comment incorporated.

Comment Summary #18: The commenter recommended adding references and original sources in the *Appendix* of chapter <1901>. Original sources of data would be helpful if any update is published, or data verification is needed.

Response: Comment incorporated. International Centre for Diffraction Data (ICDD) was spelled out and included as reference #18. The hyperlink to the ICDD website was also included.

General Chapter/Section(s): <1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products
Expert Committee: General Chapters—Packaging and Distribution
No. of Commenters: 2

Table 1

Comment Summary #1: The commenter recommends adding a mitigation strategy: Route qualification or Shipping Lane Assessment.

Response: Comment not incorporated. The comment was considered, and the committee did not identify this as necessary to address in the table as it is out of scope.

Comment Summary #2: Because a monitoring device failure won't lead to cold/hot areas but to uncaptured excursions, the commenter recommends adding an effect: uncaptured excursions.

Response: Comment not incorporated. The comment was considered, and the committee did not identify this as necessary to address in the table as it is out of scope.

4.4.2 (Qualification)

Comment Summary #3: The commenter suggests that if three replicate tests covering each season are made in a qualified environmental (climate) chamber under the same controlled conditions, the three results will be identical. Thus, it is being suggested that a second and third test is not necessary.

Response: Comment incorporated.

General Chapter/Section(s): <1079.3> Monitoring Devices - Time, Temperature, and Humidity
Expert Committee: General Chapters—Packaging and Distribution
No. of Commenters: 5

General

Comment Summary #1: The commenter recommends clarifying that the resolution of measuring equipment should be commensurate with the measurement task to be performed.

Response: Comment incorporated.

Comment Summary #2: The commenter recommends adding a statement about how monitoring equipment communicates the observations.

Response: Comment incorporated.

Introduction

Comment Summary #3: The commenter suggests including a statement regarding the impact of pressure due to air transport.

Response: Comment incorporated.

Alcohol and Mercury Thermometers

Comment Summary #4: The commenter suggests specifying the temperature should be in Celsius.

Response: Comment not incorporated. See General Notices section **8.180. Temperatures**

Electronic Temperature-Data Loggers

Comment Summary #5: The commenter suggests referencing the section on Relative Humidity Measurement Technologies.

Response: Comment incorporated.

Infrared Devices

Comment Summary #6: The commenter suggests revising text to mention that infrared readers can also produce digital temperature values.

Response: Comment incorporated.

Electronic Temperature-Data Loggers

Comment Summary #7: The commenter suggests that recorders need to record complete shipment data from start button to stop button or end of shipment designation vs time it departed and arrived.

Response: Comment not incorporated. The subcommittee does not see value in revising the chapter to address this comment.

Radio Frequency Data Loggers

Comment Summary #8: The commenter suggests editing to discuss other transmission technologies.

Response: Comment incorporated.

Comment Summary #9: The commenter recommends mentioning calibration and testing of chemical temperature threshold indicators.

Response: Comment incorporated.

Ascending-Temperature Threshold Indicators

Comment Summary #10: The commenter recommends stating that ascending-temperature threshold indicator should be stored at temperature below threshold.

Response: Comment incorporated.

Descending-Temperature Threshold Indicators

Comment Summary #11: The commenter recommends stating that descending-temperature threshold indicator should be stored at temperature below threshold.

Response: Comment incorporated.

Calibration of Temperature and Humidity Monitoring Devices

Comment Summary #12: The commenter recommends discussing time in the section.

Response: Comment incorporated.

Comment Summary #13: The commenter recommends mentioning that calibrating a sensor isn't adequate to ensure proper functionality.

Response: Comment incorporated.

Comment Summary #14: The commenter recommends discussing the potential of time drift and the need for accuracy being checked.

Response: Comment incorporated.

Comment Summary #15: The commenter suggests that sample testing is acceptable for electronic indicators.

Response: Comment not incorporated. Electronic devices can be calibrated but not single-use time temperature indicators.

General Chapter/Section(s): <1094> Capsules – Dissolution Testing and Related Quality Attributes/ Multiple sections

Expert Committee: General Chapters – Dosage Forms

No. of Commenters: 4

Comment Summary #1: The commenter suggested to provide examples of potential tests that could be used to access the mechanical properties of capsules.

Response: This suggestion will be addressed in future revisions of the chapter.

Comment Summary #2: The commenter indicated that considering the difference in dissolution lag time between HPMC and gelatin, it may be worth pointing out that in vivo when gelatin capsules are dosed with room temperature water then the dissolution of the capsules is typically slower than in vitro experiments at 37°C and so often the difference observed between hypromellose and gelatin is not relevant.

Response: Comment not incorporated. The comment was considered, and the committee identified that the information provided in the chapter is appropriate.

Comment Summary #3: The commenter said that they had a positive experience using size exclusion chromatography with multi-angle light scattering (SEC-MALS) in quantitation of the gelatin crosslinking.

Response: The commenter was asked to provide additional information about the use of this technique for this particular application. This comment may be addressed in a future revision of the chapter.

Comment Summary #4: Under 3.2.3 *Use of Enzymes*, the commenter suggested that the length of pre-treatment is a method development parameter and should be justified for the individual product/method.

Response: Comment not incorporated. The committee identified that the existing text allows for other approaches.

Comment Summary #5: The commenter suggested adding more details on how to force the development of cross-linking in gelatin capsules.

Response: Comment incorporated. A reference to a paper that describes procedures to promote the cross-linking in gelatin capsules was added to the chapter text.

Comment Summary #6: The commenter suggested to further elaborate the failure in the dissolution test that is not related to crosslinking (e.g., granule ageing/change in porosity) during stability studies.

Response: Comment not incorporated. The committee identified that the existing text of the chapter provides a sufficient discussion of this topic.

Comment Summary #7: Under 3.2.3. *Use of Enzymes*, the commenter suggests using any combination of enzyme and buffer that fits the product to simulate physiological conditions.

Response: Comment not incorporated. The enzyme is selected according to the pH of the dissolution medium to provide conditions for its optimal activity. The use of enzymes in the dissolution test of gelatin capsules is to digest the cross-linked gelatin capsules and not simulate physiological conditions.

Comment Summary #8: Under 1.1 *Types of Capsules*, the commenter suggested modifying the text to provide additional information and clarity.

Response: Comment incorporated.

Comments Summary #9: Under 2. *Cross-linking in Gelatin Capsules*, the commenter suggested modifying the text to clarify that the presence of cross-linking can be evidenced either visually or experimentally.

Response: Comment incorporated.

Comment Summary #10: Under 2. *Cross-linking in Gelatin Capsules*, the commenter suggested to include a full description of capsule switching test.

Response: Comment incorporated.

Comment Summary #11: In section 6.4 *Overall Potential Capsule Defect Assessment*, the commenter recommended clarifying that the functionality of the capsules as a delivery system is affected by the manufacturing process.

Response: Comment incorporated.

Comment Summary #12: Under *Dissolution Procedure Development*, several instrumental techniques about detecting cross-linking are listed, the commenter suggested to include additional information on how these techniques can be used.

Response: Comment not incorporated. It may be addressed in a future revision of the chapter.

Comment Summary #13: Under *Cleaning Considerations*, the commenter suggested replacing validated with qualified or verified.

Response: Comment incorporated.

General Chapter/Section(s): <1504> Quality Attributes of Starting Materials for the Chemical Synthesis of Therapeutic Peptides

Expert Committee: Biologics Monographs 1 – Peptides and Oligonucleotides

No. of Commenters: 5

General

Comment Summary #1: The commenter suggested replacing “HPLC” with “LC”.

Response: Comment not incorporated. The committee did not identify additional concerns with using “HPLC.”

Comment Summary #2: The commenter suggested revising “fragments” to “peptide fragments.”

Response: Comment not incorporated. The committee did not identify additional concerns with the terminology, as the context of this chapter is about peptide starting materials.

Comment Summary #3: The commenter suggested including a definition for “peptide” and a general description of “peptide fragment” in the text.

Response: Comment not incorporated. The committee did not identify additional concerns with the terminology, as this is a chapter about peptide starting materials, not peptide drug substances or products. The peptide definition is covered in the General Chapter <1503>.

Comment Summary #4: The commenter suggested clarifying the synthesis methods, the size of the synthetic therapeutic peptides and providing justified specifications for starting materials.

Response: Comment not incorporated. The committee identified that these topics are referenced in further detail in General Chapter <1503>.

Scope

Comment Summary #5: The commenter requested to clarify the market products and developing products.

Response: Comment partially incorporated. The text was changed from “This general chapter is intended to provide guidance” to “This general chapter is intended to provide recommendations.” This chapter is intended for the starting materials for all synthetic therapeutic peptides.

Comment Summary #6: The commenter recommended replacing “minimum quality attributes” with either “suitable quality attributes” or “appropriate quality attributes.”

Response: Comment not incorporated. The chapter’s intention was to provide recommendations on the minimum quality attributes, not to provide requirements.

Comment Summary #7: The commenter suggested including “amino acid solid supports/derivatized resins” in portions of the text listing examples of starting materials.

Response: Comment partially incorporated. The text “including resin-bound AAD” was added for clarity.

Introduction

Comment Summary #8: The commenter proposed to add “Amino acid solid supports/derivatized resins, while outside the scope of this chapter, are considered starting materials by regulatory agencies and have their own set of critical quality attributes.” for clarity.

Response: Comment not incorporated. Resin that is bound with amino acid or amino acid derivatives is included in protected amino acid derivatives.

Comment Summary #9: The commenter suggested clarifying that GMPs are applied when the production of the API begins.

Response: Comment not incorporated. The committee did not identify the need for additional explanation, based on the acceptance of the fact that the point when the API production begins is the point when GMP is applied.

Supplier Qualification and Evaluation of Synthetic Route

Comment Summary #10: The commenter recommended deleting the sentence of “It is recognized that having detailed information on the manufacturing process of the starting material may not always be possible due to restrictions on intellectual property.”

Response: Comment partially incorporated. This sentence was revised to “Starting material manufacturers are required to provide sufficient information to support regulatory submissions. Publicly available, published synthetic routes for the manufacture of starting materials can be used as supportive information.”

Comment Summary #11: The commenter stated that the second class of impurities is missing.

Response: Comment not incorporated. The second class of impurities is in the PF proposal.

AAD-Related Impurities Originated from Amino Acids

Comment Summary #12: The commenter requested to consider the storage and potential degradation products for starting materials.

Response: Comment not incorporated. Impurities generated during storage and degradation are discussed in AAD-Related Impurities Originating from the AAD Manufacturing Process section.

Comment Summary #13: The commenter requested to clarify in the *Amino Acid Enantiomers* section, whether USP recommends that the optical impurity level of 0.1% to 0.5% in amino acids prior to their Fmoc protection as industry standards.

Response: Comment not incorporated. The mentioned optical impurity level is the optical purity of the commercially available amino acids.

Comment Summary #14: The commenter suggested adding Isoleucine and Leucine substitution example in the *Foreign Amino Acids* section.

Response: Comment incorporated. The sentence of “In particular, contamination with isomeric impurities such as isoleucine in leucine is especially challenging” at the end of the *Foreign Amino Acid* section was added.

Comment Summary #15: The commenter suggested revising the context “the accuracy of this method is generally limited to a standard deviation (SD) of 0.1%” to either “The accuracy of this method is generally limited to a limit of quantitation of 0.1%” or “The precision of the method is limited to a standard deviation (SD) of 0.1%” in the Control of Critical Impurities section.

Response: Comment not incorporated. Accuracy is the intended parameter.

AAD-Related Impurities Originated from the AAD Manufacturing Process

Comment Summary #16: The commenter suggested moving Unprotected Amino Acids section to AAD-Related Impurities Originated from Amino Acids section.

Response: Comment not incorporated. Unprotected amino acids are the impurities generated during the AAD production and storage, which should belong to AAD-Related Impurities Originated from the AAD Manufacturing Process.

Non-AAD Impurities

Comment Summary #17: The commenter suggested revising “genotoxic impurities” to “mutagenic impurities” to be consistent with ICH M7.

Response: Comment not incorporated. ICH M7 also talks about genotoxic impurities. The broader term of genotoxic is preferred here.

Comment Summary #18: The commenter suggested including that the knowledge of purge and downstream process control can be used to understand which residual solvents and reagent used in SM synthesis are of concern, and it would be expected that chromatography steps may eliminate any risks of residual solvents and reagents used in the preparation of starting materials unless disruptive to the synthesis.

Response: Comment not incorporated. No revisions are needed because the Expert Committee agreed the chapter provides sufficient content regarding the residual solvent and reagent.

Comment Summary #19: The commenter proposed to limit the benzene-free to alcohols only.

Response: Comment not incorporated. Alcohol is not the only solvent that potentially could contain benzene.

Comment Summary #20: The commenter suggested clarifying that the benzene-free solvents are used in the synthesis of therapeutic peptides and whether the recommendation of certifying benzene-free solvents is applied to solid phase peptide synthesis (SPPS).

Response: Comment partially incorporated. The sentence of “For this reason, it is recommended that manufacturers of all solvents used should certify that the solvents are benzene-free.” was revised to “For this reason, the manufacturers of all solvents should limit the content of benzene unless they can certify solvents are benzene-free.”.

Comment Summary #21: The commenter proposed to remove 5.0 in the BSE/TSE-Free Starting Materials section.

Response: Comment incorporated. 5.0 was deleted.

Comment Summary #22: The commenter noted that the parent peptide is likely to contain primary or secondary amine functionality and therefore scavenges any nitrosating agents. Also, the size of the nitroso-peptide makes it unlikely to be a nitrosamine in the cohort of concern.

Response: Comment not incorporated. It is part of the risk assessment.

Comment Summary #23: The commenter noted that it’s important to consider the maximum daily dose of API to understand risk to the patient. Many peptide products are very low dose and risk versus solvents, PMIs and EIs may not be relevant and not need control in the starting materials as they can’t exceed the permitted daily dose for the patient.

Response: Comment not incorporated. It is part of the risk assessment.

Conclusion and Recommendation for AAD Specifications

Comment Summary #24: The commented stated that the quality attribute after assay by titration is missing.

Response: Comment not incorporated. The last quality attribute is in the PF proposal.

Comment Summary #25: The commenter suggested removing “by titration” and using either “Assay” or “Purity”.

Response: Comment partially incorporated. The context of “Assay by titration” was revised to “Assay (e.g., by titration)”.

Comment Summary #26: The commenter suggested adding a brief explanation and/or some examples to other components for clarity.

Response: Comment incorporated. The context of “Other component” was changed to “Other components as necessary”. The sentence of “Other impurities (not related) and components are included in the specification based on their potential effect on the API manufacturing process and the quality of the final API.” to “Other impurities (not related) and potential components are included in the specification based on their potential effect on the API manufacturing process and the quality of the final API.”.

Comment Summary #27: The commenter suggested including purity and water as quality attributes.

Response: Comment not incorporated. Purity is not necessary. Water is considered within other components.

Comment Summary #28: The commenter suggested reducing the importance of batch data in specification setting.

Response: Comment not incorporated. Historic batch data are used.

Comment Summary #29: The commented pointed out that the term “unidentified impurities” is unclear and could be inferred as either “unspecified” impurities or “new” impurities.

Response: Comment incorporated. The context of “unidentified impurities” was changed to “unspecified impurities”.

General Chapter/Section(s):	<1567> Pyrrolizidine Alkaloids as Contaminants/ Multiple Sections
Expert Committee:	Botanical Dietary Supplements & Herbal Medicines
No. of Commenters:	2

1. Introduction

EC-initiated change #1: The Expert Committee suggested revising the text containing food and food ingredients to botanical drugs, herbal medicines, botanical dietary ingredients, and supplements to align with the scope of the chapter. Members also suggested deleting the reference of an EFSA study conducted on European population to focus on U.S. requirements.

2.2 Stability of PAs

EC-initiated change #2: The Expert Committee recommended revising the section by deleting specific studies to provide more clarity to the topic.

3.1 Dietary Exposure to PAs

EC-initiated change #3: Several changes were proposed by the Expert Committee to this section including deleting the subsections 3.1, 3.2, and 3.3. These changes were proposed to align the chapter with botanical drugs, herbal medicines, botanical dietary ingredients, and botanical dietary supplements and to remove the references related to food, feed, and animal products.

4.2 Chronic Toxicity

EC-initiated change #4: The Expert Committee recommended deleting the text referencing studies by NTP and IARC related to carcinogenicity as these studies were done in rats and mice and tumorigenicity has not been observed in humans and no epidemiological studies or long-term data were available.

5. PAs Recommended for Monitoring in Food in Europe

EC-initiated change #5: The Expert Committee suggested revising the section to delete the specific reference of studies by several organizations in animal derived food and recommended revising the title of *Table 1* to "List of PAs selected for monitoring botanical drugs, botanical dietary ingredients, and botanical dietary supplements.

6. Regulatory and Proposed Tolerable Daily Intake Levels

EC-initiated change #6: The Expert Committee recommended removing the text related to risk assessment studies performed by EFSA in Europe and proposed deleting the tolerable daily intake level text as these levels are indicated in *Table 2*.

7. Relative Potencies of PAs

EC-initiated change #7: The Expert Committee suggested deleting several texts in the section related to risk assessment based on REP factors as these texts did not align with the scope of the chapter.

8. Analytical Methods and Challenges

EC-initiated change #8: The Expert Committee suggested making changes to this section by

deleting the text referencing analytical data on food and feed. The members also recommended adding a sentence regarding the challenges associated with analytical methods for the quantitation of PAs and challenges related to the availability of reference standards.

9. Recommendations/Next steps

EC-initiated change #9: The Expert Committee suggested several changes to the section. Recommended changing the title to conclusion, adding a text for manufacturers to evaluate the levels of PAs in their product arising from the plant itself, or from contamination from external sources.

General Chapter/Section(s):	<1604> Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled Products
Expert Committee:	General Chapters–Dosage Forms
No. of Commenters:	2

Comment Summary #1: The commenter requested changing the chapter title as follows as these are combination products containing both a drug and device constituent part:

“Presentation of Aerodynamic Particle Size Distribution (APSD) Measurement Data for Orally Inhaled **Drug** Products”.

This change would make the Chapter consistent with draft Guidances for MDIs and DPIs.

Response: Comment incorporated. The expert committee made a change to the title with a note that the terminology would be changed in other chapters during the revision process. The JS commented that removing the word “drug” may open the chapter up to covering other products that are not drug related (like e-cigarettes). If this terminology is changed would the terminology need to be changed in other chapters immediately or could it be aligned during the revision process.

Comment Summary # 2: The commenter suggested revising the sentence in the *Introduction* section as follows to clarify that the delivered mass does not include drug deposited in the patient interface:

“This mass includes both (and is the sum of) the sized and non-sized fraction **sampled from deposited on components after** the patient interface (e.g., the inhaler mouthpiece) (see Figure 1).”

Response: Comment incorporated. The JS also altered *Figure 1* to remove inhaler and mouthpiece and change to all “adapter”. The adapter could be shaded to show it is separate.

Comment Summary #3: The commenter proposed replacing the word, “sampled” with “emitted” in the following sentence for clarity and make the same change throughout the chapter:

“This mass includes both (and is the sum of) the sized and non-sized fraction sampled/ emitted from the patient interface ...”

Response: Comment incorporated.

Comment Summary #4: The commenter suggested replacing the term “patient interface” with “on the mouthpiece” as this term is ambiguous and should be removed.

Response: Comment incorporated.

Comment Summary #5: The commenter suggested including “nasal aerosols” in the following sentence.

“Therefore, this chapter may not be appropriate for nasal spray or nasal powder drug products.”

Response: Comment not incorporated. Almost all the size distribution from these products is

contained in droplets greater than the upper limit of size resolution of cascade impactors.

Comment Summary #6: The commenter proposed modifying the following sentence as below since the monograph scope is data presentation, not sample analysis, or method development. Therefore, remove text relating to the specifics of the methodology and add reference to <601 for methodology.

“For determination of aerodynamic particle size distribution, the number of actuations should be minimized but sufficient to allow quantification of drug deposited on the stage with lowest deposition without overloading the stage with highest deposition, and for details on performing the measurement, see <601>.”

Response: Comment incorporated.

Comment Summary #7: The commenter requested revising the following sentence to remove redundant wording from:

“This chapter presents two pharmacopeial approaches that may be used evaluate the data obtained from CI analysis data, ...”

To

“This chapter presents two pharmacopeial approaches that may be used to evaluate CI analysis data, ...”

Response: Comment incorporated.

Comment Summary #8: The commenter recommended revising the following sentence for better flow and better description of what is to be done from:

“Assessment of the deposition profile by stage grouping of the delivered mass of drug product per actuation from the inhaler mouthpiece.”

To

“Assessment of the deposition profile of the delivered mass of drug product per actuation from the inhaler mouthpiece by grouping CI stages”.

Response: Comment incorporated.

Comment Summary #9: The commenter suggested to reword the sentence as follows for clarity.

“It might be appropriate to use ~~one or more approaches~~ more than one approach.”

Response: Comment incorporated.

Choice of CI and Sampling Flow Rate for The APSD Measurement

Comment Summary #10: The commenter suggested revising the sentence as follows for clarity:

“The effective cut-off diameters that define the aerodynamic diameters associated with the sizing components at the flow rate at ~~which the CI is operated~~ CI operational flow rate differ between impactor type [e.g., NGI versus the Andersen Cascade Impactor (ACI)].”

Response: Comment incorporated.

Comment Summary #11: The commenter recommended adding the underlined text in the following sentence for clarity and completeness:

“However, when inhalers with different flow resistances are compared, measurements should be made at the same pressure differential, which will require operating at different flow rates. For some passive inhalation systems (e.g., breath-actuated DPIs), it is difficult to make meaningful comparisons of aerosol metrics such as FPD, FPF, or MMAD between a measurement collected on an NGI vs. those collected using an ACI due to the differences in the two impactors internal volumes. The difference in internal

volume alters the initial acceleration and aerosolization of particles emitted from the inhaler early in the profile before the peak flow rate is achieved. Additionally, the NGI and ACI differ because of different ECDs per stage, further prohibiting a direct comparison between the two impactors.”

Response: Comment incorporated.

Approaches for Pharmacopeial APSD Data Presentation

Comment Summary #12: The commenter requested clarifying what "such losses" refers to in the following sentence. If it refers to limit for wall losses per section C.1.2. of USP <601>, then should be specified. Otherwise, please define to prevent confusion.

“However, where **such losses** are known to be ≤5% of the total delivered drug mass into the impactor, the procedure may be simplified by assaying only drug on the collection plates.

Response: Comment incorporated. Replaced “such losses” with “losses due to internal non-sizing components (also commonly referred to as wall losses)”

Deposition Profile Section:

Comment Summary #13: The commenter suggested modifying the sentence as follows for clarity:

“Do not include the mass of the drug substance recovered from the interior walls of the CI, as the aerodynamic particle size of such deposits do not equate with the size ranges associated with each of the impaction stages is undefined.”

Response: Comment incorporated.

Multiple Determinations

Comment Summary #14: The commenter recommended revising the following sentence as follows since it is common practice to report replicate runs as N=# of runs:

“It is also recommended that when presenting data based on multiple determinations that the sample size be noted (i.e., N=X, where X is the number of samples).”

Response: Comment incorporated.

Comment Summary #15: The commenter suggested replacing the word “train” with “apparatus” in the following sentence as it is more common.

“Construct a graph with the average mass of drug substance per actuation as the ordinate and the collection site within the sampling **train apparatus** as the abscissa;...”

Response: Comment incorporated.

The APSD: Sized Deposition Profile

Comment Summary #16: The commenter suggested revising the “Note” by adding the underlined wording as follows:

“[Note: Some distributions may not conform to the illustration in Figure 5, which is specific to an NGI, due to differences in the configuration of the CI used to make the measurements.]

Response: Comment partially incorporated. Note revised as follows to provide additional clarity.

“[Note: Some distributions may not conform to the illustration in Figure 5, which is specific to an NGI]”

Comment Summary #17: The commenter recommended revising the following sentence for clarity from

“In Contrast, when the PS is used with the NGI, mass on the initial stage 1 does ...”

To

“In Contrast, when the PS is used with the NGI, mass on the initial stage 1 (S1) does ...”

Response: Comment incorporated.

Stage Groupings

Stage Grouping of the Deposition Data

Comment Summary #18: The commenter recommended revising the sentence as follows as it is more common to use “sampling apparatus”.

“For quality control purposes, the mass deposition data from both non-sizing and sizing components of the ~~sampling –train apparatus~~”

Response: Comment incorporated.

Comment Summary #19: The commenter noted that Groups 2-4, “coarse”, “fine” and “extra-fine” refer to the “particle fraction of the dose” and suggested replacing “dose” with “mass”, as the number of actuations collected during testing using the cascade impactor are typically larger than the typical patient dose. Use of “mass” would be a more accurate term to define the number of particles collected from each stage of the impactor.

Response: Comment incorporated.

Comment Summary #20: The commenter suggested revising the following sentence for clarity from:

“The groups for the purpose of the chapter can be defined, for example, in terms of four relative categories:”

To

“In the illustration provided for this chapter, the groups have been defined in terms of four relative categories:”

Response: Comment incorporated.

Sized Fraction

Comment Summary #21: The commenter requested revising the following sentence as follows to avoid misinterpretation of word “diameter” by changing it to “aerodynamic diameter”:

*“The $FPD < X \mu m$, where X is an **aerodynamic diameter** within the range of the cut-off diameters for the impactor in use at the relevant flow rate, can be estimated from the raw distribution in several ways.”*

Response: Comment incorporated.

Comment Summary #22: The commenter suggested creating a new section for the MMAD calculations as it is currently discussed under the Section “**Sized Fractions**” although MMAD is not a sized fraction.

Response: Comment partially incorporated. Following wording added for clarification: “Relevant to, and associated with the sized fractions, is a measure of the central point of the APSD: the mass median aerodynamic diameter (MMAD).”

Comment Summary #23: The commenter suggested to Change m_0 to m_p (for preseparator) in Table 2B (and all NGI tables) to avoid confusion with a Stage 0 that does not exist in the NGI) since Stage 0 does not exist in NGI.

Response: Comment incorporated.

Comment Summary #24: The commenter requested defining F_2 and F_3 in the equation to indicate that F_2 and F_3 are the cumulative dose up to stage 2 and 3, respectively.

Response: Comment incorporated.

Comment Summary #25: The commenter requested clarification on what is meant by, “approximately linear” in the following sentence.

“For best results, the CDP should be approximately linear in the region for the estimation.”

Response: Comment not incorporated. For best results, the CDP should be approximately linear in the region for the estimation, recognizing that the degree of linearity of the CDP is a task that requires the tester’s judgement to assess and may vary from one product to another.

Figures

Comment Summary #26: The commenter requested separating “Inhaler and Mouthpiece” from the sizing components in Figures as they are not part of the aerosol sampling system.

Response: Comment incorporated.

Figure 1

Comment Summary #27: The commenter requested revising the *Figure 1* caption as follows as it is more common to use “sampling apparatus” as opposed to “sampling train”:

“**Figure 1.** CI sizing and non-sizing components of the **sampling train apparatus** used for determination of APSD for OIPs.” Therefore, we suggest revising the caption as follows: “Figure 1. CI sizing and non-sizing components of a **sampling apparatus** used for determination of APSD for OIPs.”

Response: Comment incorporated.

Comment Summary #28: The commenter requested changing the wording in *Figure 1*, box in lower right corner, from:

“The stage numbering conforms to that for the NGI; other numbering applies for the various configurations of the ACI.”

To

“The stage layout/numbering depicted for Sizing Components, conforms to that for the NGI” as it better describes what is depicted in the figure.

Response: Comment incorporated.

Comment Summary #29: The commenter requested presenting impactor stages in one row in Figure 1, if possible, for better readability.

Response: Comment not incorporated. The figure is presented in this specific way for better readability.

Figures 2 – 4

Comment Summary #30: The commenter indicated that the deposition on the adapter is here

added to the deposition in the mouthpiece and suggested changing it to add the deposition on the adapter to the deposition in the induction port, especially since adapter deposition is part of the calculation of mass balance and the fact that the drug already have left the device.

Response: Comment incorporated. Figures revised.

Figure 5

Comment Summary #31: The commenter requested revising the Y-axis label units from “mass/actuation” to “ $\mu\text{g}/\text{actuation}$ ” as this would be consistent with the units in *Figures 2, 3, and 4*.

Response: Comment incorporated. JS changed “mass per actuation” to “ $\mu\text{g}/\text{actuation}$.” Noted that the measurement is not always micrograms, can be milligrams. Replaced “mass” in figures 2-5 with “micrograms” to read “(e.g., micrograms per actuation)”

Comment Summary #32: The commenter suggested revising the sentence as follows because it is common practice to report replicate runs as N=# of runs.

“Figure 5. Differential mass-weighted APSD profile (NGI with PS at 30L/min) based on a sample size of **N=X**.”

Response: Comment incorporated.

Comment Summary #33: The commenter requested correcting *Figure 5*, if needed, as the x-scale in this figure seems more linear than logarithmic.

Response: Comment incorporated. *Figure 5* was revised. The following note has also been added to the chapter for clarification.

“[NOTE—All figures in this Chapter are for illustrative purposes.]”

Figure 6

Comment Summary #34: The commenter suggested revising the content of the box under “Non-Sizing Components” to replace “Induction port with Induction port and Adapter” for clarity.

Response: Comment incorporated.

Comment Summary #35: The commenter requested clarifying the *Figure 6* caption. Caption says “Measure of spread*. *=GSD only if APSD is unimodal and log-normal”. Should any measure of spread be used if this is not the case? If so, what measure?

Response: Comment not incorporated as the appropriateness of a spread factor will have to be determined by the person reviewing the data (e.g., to inspect if the size distribution is not unimodal)

Figure 7

Comment Summary #36: The commenter suggested revising the caption of this figure from:

“Curve fitting of cumulative mass-weighted deposition data to generate APSD as a CDP.”

To

“Curve fitting using a Morgan-Mercer-Flodin model for the cumulative mass-weighted deposition data to generate APSD (see “Sized Fraction” section, below)”

Response: Comment not incorporated. The Figure is provided as a general representation of the use of a CDP and not meant to restrict the user to the Morgan-Mercer-Flodin approach.

Comment Summary #38: The commenter noted that the X-axis is labeled as being on a Log10 scale. However, the axis does not appear to follow a Log10 scale. Therefore, suggest revising the scale to be Log10 or revising the X-axis label.

Response: Comment incorporated. *Figure 7* is a representation of the curve, but not the actual curve scale. It would be hard with the graphic package available to convert to the actual scale. Added “representation” to figure caption for clarification.

General Chapter/Section(s): <1901> Theory and Practice for Asbestos Detection in Pharmaceutical Talc/ Multiple sections
Expert Committee: Excipients Test Methods
No. of Commenters: 14

Comment Summary #1: Commenters recommended an extra or a longer time for implementation (i.e. ~3 years), as X-ray diffraction (XRD) and Polarized Light Microscopy (PLM) are not commonly used for routine release testing.

Response: Comment partially incorporated. The Expert Committee approved an official date of December 1, 2023, for the two general chapters <901> and <1901>, while the Expert Committee also approved an extended official date of December 1, 2025, for the *USP* Talc monograph, with changes to be published in USP–NF 2023 Issue 3. The additional two years are intended to provide the time needed by manufacturers and users to implement the test methods and make necessary changes.

Though chapter <901> has been approved for an official date earlier than the *USP* Talc monograph's anticipated official date, the chapter's requirements referencing the Talc monograph will only apply upon the latter's official date. Please also note that Chapter <1901> is for informational purposes only. The earlier official date for both chapters will help stakeholders in the adoption of the of the *USP* Talc monograph revisions that are anticipated to become official at the later 2025 date.

Please see [Compendial Notice](#) published on the USP web site on May 26, 2023.

Comment Summary #2: Commenters recommended retaining "suppliers" to perform the asbestos testing, as indicated in the original note of the Talc monograph.

Response: Comment not incorporated. Based on the discussions of the Expert Committee and the FDA's input, both suppliers and end users need to certify to the FDA that their products comply with the compendial standard and cGMP requirements. They may have third parties (such as contract laboratories) test for asbestos if they do not have the capability to perform the asbestos tests.

Comment Summary #3: Commenters recommended the following:

- a. changing the format of microbial limits according to the current USP style, such as changing from “NMT 100 cfu/g” to “NMT 10² cfu/g”, etc.
- b. changing the limit for Talc intended for topical administration from “Total combined molds and yeasts count: NMT 50 cfu/g” to “Total combined molds and yeasts count: NMT 10¹ cfu/g”

Response: Comment a incorporated, but comment b not incorporated. The updated texts are shown as below:

- Intended for topical administration
 - Total aerobic microbial count: NMT 10² cfu/g
 - Total combined molds and yeasts count: NMT 5 x 10¹ cfu/g
- Intended for oral administration
 - Total aerobic microbial count: NMT 10³ cfu/g
 - Total combined molds and yeasts count: NMT 10² cfu/g

According to general chapter <1111> *MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE*, for pharmaceutical substance, the total combined molds and yeasts count is NMT 10^2 cfu/g. Additionally, the commenter did not provide data to support the limit change to “NMT 10^1 cfu/g”. Therefore, this comment #b is not incorporated.

Comment Summary #4: The commenter is willing to implement the proposed changes/update in the *Definition, Limit of Calcium, and Labeling* sections.

Response: Comment noted.

Comment Summary #5: Commenters recommended providing reference standards in order to validate the methods according to general chapters <1225> and <1226>.

Response: Comment partially incorporated. Due to the challenges of handling asbestos and developing physical reference standards, USP included 5 representative XRD diffractograms and 85 PLM images in the chapter (1901) as references.

Comment Summary #6: Commenters recommended only performing the X-ray Diffraction (XRD) test to be consistent with the *European Pharmacopeia* (EP), as the Talc monograph is a PDG harmonized monograph.

Response: Comment not incorporated. As explained in the *Stimuli* article “[Modernization of Asbestos Testing in USP Talc—Part 2](#)” published in *PF* 46(5), both XRD and PLM are mandatory for asbestos testing in pharmaceutical talc. The asbestos testing is currently a non-harmonized attribute in the Pharmacopeial Discussion Group (PDG) harmonized Talc monograph, however, EP is also planning to align with the XRD and PLM testing procedures proposed in the USP chapters <901> and <1901>. Therefore, both XRD and PLM procedures will be implemented by EP as well. Additionally, contract labs are available for testing if pharmaceutical manufacturers do not have the capability to perform the tests.

Comment Summary #7: The commenter stated the following:

“This method has been well-tested. Many laboratories have participated in establishing quantitative measures of reliability. The detection limit is robust and equivalent to methods based on electron microscopy. The including of a wet sieving method enhances the possibility of detecting asbestos given that its high tensile strength and resistance to grinding leaves long fibers intact. The method can be applied to raw materials or to materials that have been concentrated by heavy liquids. Of particular importance is the inclusion of criteria by which asbestiform amphibole can be discriminated from non-asbestiform habits of the same mineral. This is an excellent method and a significant advance for screening talc for the presence of asbestos.”

Response: Comment noted.

Comment Summary #8: The commenter provided the following comment:

No testing institution which would be able to carry out the proposed tests is found in Japan, in terms of wet sieving pretreatment, appropriate analytical equipment, and experienced analyst. It is difficult for both excipient manufacturers and pharmaceutical manufacturers to conduct the tests in Japan.

Response: Comment not incorporated. In the USA, contract laboratories are available for testing if stakeholders do not have the capability to perform the tests. To protect public health, it is important to test asbestos in pharmaceutical talc.

Comment Summary #9: The commenter recommended the following regarding wet sieving:

- a. The wet sieve preparation should be optional.
- b. Should provide some flexibility in the sieve size used and allow for use of disposable screening materials which would remove or reduce the possibility of transfer of material from sample to sample.

- c. If, after sieving, the mass of material remaining on the sieve is less than 0.01% of the initial sample, the protocol should end. If less than 0.01% remains, the result is certain to be lower than the stated limit of detection and quantification (0.01%).

Response: Comment a: Not incorporated. Based on the round robin study results, the wet sieving procedure is mandatory to achieve the desired detection limit (0.01%). According to [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#), alternative method or procedure can be used. However, they 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.

Comment b: Partially incorporated. Sieves should be cleaned and maintained in accordance with manufacturers recommendations and/or instructions. Step #9 was added to <901> for this procedure. Flexibility of using sieve size should follow [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#).

Comment c: Not incorporated. According to the testing procedure in chapter <901>, sieving should be continued until a minimum of 5 mg of material remaining on the sieved is collected. However, it may stop earlier if asbestos is detected. Validation is needed if an alternative method is used.

Comment Summary #10: The commenter recommended the following regarding PLM:

- a. The mass of sample placed on slides is stated to be 1-2 mg. In practice, 0.5 mg will produce a more optimal loading of particulate.
- b. If amphibole asbestos is determined by PLM, the option for energy dispersive x-ray spectroscopy (EDS) analysis should be mandatory to confirm the PLM finding.
- c. The Reporting Results section could be edited for clarity, particularly at numbers 3 & 4.

Response: Comment a: Partially incorporated. According to [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#), alternative method or procedure (such as use of 0.5 mg sample) can be used. However, they 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.

Comment b: Not incorporated. Energy dispersive x-ray spectroscopy (EDS) is not within the scope for PLM. A lab may employ it as an optional procedure.

Comment c: Incorporated. The #3 and #4 in *Reporting Results* are edited to be more explicit. See general chapter <901> which will be available on the *USP-NF* platform on June 1, 2023, and become official on December 1, 2023.

Comment Summary #11: The commenter stated the following:

- a. “In chapter <901>, Procedure 2: Polarized Light Microscopy” subsection “Sample Analysis”, in addition to the examples of morphology identified (“straight, curved, bundle, wavy, splayed ends, etc.”) the term “polyfilamentous” should also be listed.
- b. They are supportive of USP referring to the glossary section of EPA 600/R-93/116 in defining the term asbestiform.

Response: Comment a incorporated. Comment b noted.

Comment Summary #12: The commenter stated the following:

- a. The commenter is supportive of the proposed method <901> and supporting information in chapter <1901>. Most notably, they commend the incorporation of the EPA 600/R-93/116 definition for asbestiform into the USP protocol for measurement of asbestos in

talc. They are pleased to see that the panel has addressed FDA's request for modernizing the test method.

- b. The proposed USP method for measuring asbestos in talc for pharmaceutical applications should be considered by the FDA for the measurement of asbestos in talc for cosmetic applications and other related uses of talc. They believe it would be prudent for the USP to recommend that the FDA instruct the Interagency Working Group on Asbestos in Consumer Products (IWGACP) to incorporate this proposed USP Detection of Asbestos in Pharmaceutical Talc method, when determination of asbestos is required in all talc applications including cosmetics. There is no rational scientific reason for having different test protocols for each application of talc.

Response: Comment a: noted and incorporated. Comment b: noted and related information was shared with FDA.

Comment Summary #13: The commenter provided several comments on the XRD instrument conditions and parameters under *Procedure 1: X-ray Diffraction* in the general chapter <901>.

Response: Comments incorporated. See General Chapter <901> which will be available on the USP/NF platform from June 1, 2023, and is anticipated to become official on December 1, 2023.

Comment Summary #14: The commenter made the following comments on Chapter <901>:

- a. For clarity, the commenter suggested including a statement in the Chapter <901> that there is no level of asbestos that is recognized as safe and that the limits are based on limits of detection, not toxicological limits.
- b. Recommended a reference to *(1901) Theory and Practice of Asbestos Detection in Pharmaceutical Talc* be added to the Limit of Detection and Quantification subsections under Procedure 1: X-Ray Diffraction and Procedure 2: Polarized Light Microscopy. This would provide the reader with additional context and clarity.

Response: Comment a: Partially incorporated. The Expert Committee agreed to add a note at the end of "Reporting Results" for both XRD and PLM as following:

- "[Note: The limits are based on limits of detection.]

Comment b: Incorporated. The Expert Committee agreed to add a reference to <1901> in the *Limit of Detection and Quantification* subsections of both XRD and PLM sections in Chapter <901>.

Comment Summary #15: The commenter suggested including a table to summarize the scope, features and advantages/disadvantages of each technique in chapter <1901>. The table would help highlight and clarify why and how the different techniques are complementary to each other.

Response: Comments incorporated. See *Table 1* in Chapter <1901>.

Comment Summary #16: The commenter recommended using categorized subsections and subtitles (e.g., "Purpose", "Scope", "Table of characteristic peaks", "Table of samples", and "Instrument calibration/qualification") in <1901>. This would enhance clarity and readability.

Response: Comments not incorporated. There are already subsections in the XRD and PLM sections of chapter <1901>.

Comment Summary #17: The commenter recommended spelling out "National Institute of Standards and Technology (NIST) or NIST-traceable Standards should be used for all types of asbestos..." in the Standards and Calibration section of chapter <1901>.

Response: Comments incorporated.

Comment Summary #18: The commenter recommended adding references and original sources in the Appendix of chapter <1901>. Original sources of data would be helpful if any update is published, or data verification is needed.

Response: Comments incorporated. International Centre for Diffraction Data (ICDD) was spelled out and included as reference #18. The hyperlink to the ICDD website was also included.

General Chapter/Section(s): <1724> Semisolid Drug Products – Performance Tests/
Multiple Sections
Expert Committee: General Chapters – Dosage Forms
No. of Commenters: 9

Comment Summary #1: Several commenters suggested the inclusion of other types of equipment and accessories such as semisolid adaptor, bubble free cell, and others, and the use of automated systems.

Response: Comments partially incorporated. The text was modified to allow the use of any other equipment, automated system or accessory as far as it has been properly qualified.

Comment summary #2: The commenter suggested to remove the requalification of the equipment on a regular basis. After performing initial qualification, the requalification should be done as needed.

Response: Comment incorporated.

Comment summary #3: The commenter suggested to replace “steady-state” with “pseudo-zero order” throughout the text.

Response: Comment partially incorporated. The text was modified to state “linear (steady state) drug release rate”.

Comment summary #4: Under *Experimentally Length and Sampling*, the commenter suggested to remove the text “whereas shortened (e.g., 2 h) sampling durations may not be representative of the steady-state release kinetics.”

Response: Comment not incorporated. The text allows flexibility to cover other conditions.

Comment Summary #5: Under *Biological Membranes*, the commenter suggested to remove all the not to use recommendations.

Response: Comment partially incorporated. The text was modified to clarify when the use of other biological membranes is not recommended.

Comment summary #6: Under *Receptor Solution*, the commenter suggested that the text: “The solubility of the drug in the receptor solution should exceed the highest sample concentration in the IVPT study, ideally by an order of magnitude, if possible.” should be removed. In addition, the commenter suggested stressing the use of PBS and to generalize the surfactants to be used.

Response: Comment not incorporated. The text specifies the minimum requirements allowing other approaches to be used. The text allows the use of physiological buffer based aqueous solutions. The specific surfactant mentioned in the text is the only one that does not affect skin barriers.

Comment summary #7: The commenter suggested to add the precise acceptance criteria for receptor media temperature for initiation of study.

Response: Comment not incorporated. It is already covered in the text.

Comment summary #8: The commenter stated that under the *Sample Withdrawal and Replenishment* procedure, in the case of manual sampling the sample needs to be withdrawn after stopping of stirrer and replacement needs to be done before initiation of stirring.

Response: Comment not incorporated. The text provides the necessary information.

Comment summary #9: The commenter suggested to include more specific information under method validation and method transfer.

Response: Comment not incorporated. It may be addressed in a future revision of the chapter.

Comment summary #10: Under *Receptor solution*, “*Sample solution* to be withdrawn within a tolerance of +/- 15 min or 2%”, the commenter stated that this may be a wide window for IVRT where time points are close to each other (on hourly basis).

Response: Comment not incorporated. The text specifies to select the narrowest interval.

Comment summary #11: The commenter suggested that the number of replicates needs to be better defined.

Response: Comment not incorporated. The text under Data Reporting provides information on the number of replicates to be evaluated.

Comment summary #12: The commenter suggested to revise the text “The total receptor compartment volume of VDC typically ranges from 5–15 mL, while the total vessel volume for the immersion cell typically varies between 50 and 200 mL; *values outside of those typical ranges may be available depending on the manufacturer of the equipment.*” to volumes outside of those ranges may be available commercially and may be useful depending on the situation

Response: Comment not incorporated. The text in the chapter states that other volumes outside the stated ranges are available.

Comment summary #13: In the text “The inclusion of a non-dosed control (no formulation) is recommended and may help ensure the skin source(s) and receptor solution are absent of contaminants that may influence the results”, the commenter is suggesting with replacing “recommended” with “may be helpful”.

Response: Comment not incorporated. The text provides enough flexibility.

Comment summary #14: In the text “Removal of the entire volume of the receptor solution, or sampling of relatively large volume aliquots of the receptor solution for VDCs; FDCs offer a different sampling methodology due to the continuous flow of receptor solution into the collection vials” the commenter is proposing replacing “sampling” with “sampling aliquots”.

Response: Comment not incorporated. It is already covered in the text.

Comment summary #15: The commenter made some suggestions to modify the text related to the mixing in the cells.

Response: Comments not incorporated.

Comment summary #16: In the *Introduction*, the expressions “influence of specific process(es)” or “influence of certain processes” are used. The commenter suggested that if there is no difference between these processes use a single term.

Response: Comment incorporated.

Comment summary #17: Under the *Qualification of Stirring/Agitation/Flow Rate* subsection, the second paragraph begins with the following statement: “*Stirring rates are relevant for FDC, but not necessarily for VDC or immersion cells.*”, the commenter stated that this affirmation may not be corrected.

Response: Comment incorporated. Stirring rates are relevant for VDC and not FDC.

Comment summary #18: Under the General IVPT VDC Equipment Set Up subsection, “*Ideally, the skin should be gently stretched to ensure that it is flat (with no folds or wrinkles) when mounted upon the diffusion cell.*” the commenter suggested expanding this statement as follows: “*Ideally, the skin should be gently stretched to ensure that it is flat (with no folds or wrinkles) when mounted upon the diffusion cell, with the stratum corneum of the skin facing toward the air and the dermatome part of the skin in contact with the receptor solution.*”

Response: Comment incorporated.

Comment summary #19: The commenter pointed out that in “*a smaller version of USP Apparatus 2 (see<711>) with vessel volumes that vary from 50-00mL; however, 150- or 200-mL vessels are typically used.*” there is a typo.

Response: Comment incorporated. The correct text is “that vary from 50 – 200 mL”.

Comment summary #20: In the sentence “*Donor compartments range from holding 300 mg to 4 g; some models are adjustable.*” The commenter suggested revising this statement as follows:

“Donor compartments range from holding 300 mg to 4 g of **formulation**; some models are adjustable.”

Response: Comment incorporated.

Comment summary #21: Under the General IVPT FDC Equipment Set Up subsection, “Ideally, the skin should be gently stretched to ensure that it is flat (with no folds or wrinkles) when mounted upon the diffusion cell.” the commenter suggested expanding this statement to: “Ideally, the skin should be gently stretched to ensure that it is flat (with no folds or wrinkles) when mounted upon the diffusion cell, **with the stratum corneum of the skin facing toward the air and the dermatome part of the skin in contact with the receptor solution.**”

Response: Comment incorporated.

General Chapter/Section(s): <1912> Measurement of Yield Stress of Semisolids
Expert Committee: General Chapters—Chemical Analysis
No. of Commenters: 1

Background

Comment Summary #1: The commenter recommended incorporating text stating that both shear and temperature may influence viscoelastic behavior of the drug product and provided two references.

Response: Comment partially incorporated. ~~The two first recommended sentences were not incorporated to focus on temperature only as shear concept has yet to be properly introduced.~~ The following text was added: “For temperature-sensitive materials, viscoelastic properties at both ambient conditions (i.e., storage conditions) and physiological conditions [i.e., skin surface temperature (32°) or body temperature (37°)] are useful. For example, an anesthetic topical cream may require characterization at 32°, whereas a vaginal cream may require characterization at 37° (1–2).” The two new suggested references were added.

EC-initiated Change #1: The following text was added “[Note—Additional models for viscosity versus shear rate are also discussed in Rheometry (1911), see Figure 3).]” for clarity.

EXPERIMENTAL METHODS

Yield Stress via the Viscosity Maximum

Comment Summary #2: The commenter suggested including some additional text to further emphasize the relationship between shear rate, shear strain, and time. It should be clearly stated that shear strain increases linearly over time and is equivalent to the shear rate multiplied by time.

Response: Comment not incorporated to keep consistency with the terminology and concepts described in <1911> *Rheometry* for Newtonian Viscosity.

EC-initiated Change #2: Additional lines were added to *Figure 1A* and *1B* to identify the shear stress value, for clarity.

Comment Summary #3: The commenter recommended revising the statement on parameters that can influence the measurement to also include “air bubbles in the sample” and provided one reference.

Response: Comment partially incorporated. Presence of air bubbles relies on the measurement system. The following text was revised: “Because air pockets may be of concern, ideally, the sample should be loaded gently, without significant shearing and without introducing any air...” The new suggested referenced was added to the section “Additional Sources of Information”.

Yield Stress via Shear Rate Ramps or Shear Stress Ramps (flow curves)

Comment Summary #4: The commenter suggested including some text to state that stress vs shear strain can be fitted to many models.

Response: Comment not incorporated. There are existing descriptions of the models for Newtonian and Non-Newtonian fluids in <1911> *Rheometry*. A future revision to <1911> could elaborate more on these models.

Yield Stress by Amplitude Sweep

Comment Summary #5: The commenter suggested including additional definitions of yield stress.

Response: Comment partially incorporated. In the sentence stating that this test may be used to evaluate the viscosity behavior and the stiffness (rigidity) of a gel in the linear viscoelastic range (LVR), the following text was deleted: "...and may also be used to evaluate the yield stress." The following text was added: "The yield stress value is correlated with the storage modulus drop that occurs beyond the limit of the LVR. The limit of the LVR may be considered the onset of yielding or, alternatively, the onset point for yielding may be located as the intersection of an initial tangent line (from the LVR) with a final tangent line (where the G' curve or complex viscosity drops rapidly). Additionally, the G' and G'' crossover point may be considered a transition from elastic to viscous behavior. A yield point or yield stress may be identified from these plots in multiple ways." The following sentence was deleted: "Therefore, it is recommended that amplitude sweeps are performed at various (angular) frequencies."

Comment Summary #5: The commenter suggested adding text to discuss abating wall slippage.

Response: Comment partially incorporated. The following text was added: "One benefit of dynamic oscillation stress or strain sweep tests is that it provides a lower probability of wall slippage."

Penetrometry Measurements

Comment Summary #5: The commenter requested using a subscript to revise the variable for the density of the semisolid as follows: " ρ_r " for clarity.

Response: Comment incorporated.

Comment Summary #6: The commenter suggested including some text to clearly state that mechanical measurements (i.e., penetrometry) should be calibrated/validated before conducting studies, and that studies should be conducted in replicates accompanied with appropriate statistical analysis.

Response: Comment not incorporated. The current procedure with a gravity-driven penetrometer is consistent with <915> *Measurement of Structural Strength of Semisolids by Penetrometry* (and the *European Pharmacopoeia*, 2.9.9. *Measurement of Consistency by Penetrometry*).

EC-initiated Change #3: The penetration depth in the caption of *Figure 6* was changed from "16,000-20,000 Pa range" to "200-16,000 Pa range" because the maximum of the plot is 16,000 Pa.

Monographs

Monograph/Section(s): Acetazolamide Extended-Release Capsules/ Multiple Sections
Expert Committee: Small Molecules 3

No. of Commenters: 2

Comment Summary #1: The commenter recommended revising the acceptance criterion for the Assay for consistency with what has been approved.

Response: Comment incorporated. The acceptance criterion for the Assay is revised from “90.0%- 105.0%” to “90.0%- 110.0%”. In addition, the upper limit in the *Definition* is revised from “NMT 105.0%” to “NMT 110.0%”.

Comment Summary #2: The commenter recommended adding the missing degradation products with the approved limits.

Response: Comment incorporated. The RRF of 0.46 with limit of NMT 0.2% for Acetamidothiadiazole, and the RRF of 0.49 with limit of NMT 0.2% for Acetazolamide related compound E (free acid) are added to *Table 3* of the *Organic Impurities* section.

Comment Summary #3: The commenter recommended revising the acceptance criterion for “Total degradation products” for consistency with what has been approved.

Response: Comment incorporated. The acceptance criterion for the “Total degradation products” is revised from “NMT 0.5%” to “NMT 1.5%” in *Table 3* of the *Organic Impurities* section.

Comment Summary #4: The commenter recommended removing the “reporting threshold” as it will vary based on product-specific factors.

Response: Comment not incorporated. USP is considering the issue of the removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #5: The commenter requested their approved dissolution method and/or tolerances be added to the monograph.

Response: Comment not incorporated. As appropriate, a second dissolution test can be added upon receipt of the supporting data.

EC-initiated Change #1: The EC decided to make the following changes to the *Organic Impurities* section: in the *System suitability* section, revise the text in the *Note* to align with the current practice; in the *Analysis* section, change the “each unspecified degradation product” to “acetazolamide related compound E (free acid), acetamidothiadiazole and any unspecified degradation product,” as applicable, based on updated information; delete the statement “Users need to determine if an impurity is process related or a degradation product” from the *Acceptance criteria*, as the statement is not necessary under the current format.

EC-initiated Change #2: Change the molecular weight of USP Acetazolamide Related Compound D RS from “180.21” to “180.20,” based on updated chemical information.

Monograph/Section(s): Betamethasone Acetate/ Organic Impurities

Expert Committee: Small Molecules 5

No. of Commenters: 4

Comment Summary #1: The commenter requested replacing the proposed procedure in the test for *Organic impurities* with their in-house procedure.

Response: Comment not incorporated. The Expert Committee determined that the proposed method is consistent with validation data and suitable for its intended use.

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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Commentary for USP–NF 2023, Issue 3*

Determined Reporting Thresholds, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #3: The commenter requested aligning the impurity limits in the test for *Organic Impurities* with EP/BP monograph.

Response: Comment not incorporated. The Expert Committee determined that that the proposed limits are consistent with sponsor data for an FDA approved product.

Monograph/Section(s): Bivalirudin/ Multiple Sections
Expert Committee: Biologics Monographs 1– Peptides and Oligonucleotides
No. of Commenters: 2

Comment Summary #1: The commenter requested to widen the *Acceptance criteria* of the *Identification C* test to be consistent with the FDA-approved specification.

Response: Comment incorporated. The *Acceptance criteria* of the *Identification C* test were changed to:

Name	Acceptance Criteria
Glycine	Between 4.5 to 5.9
Aspartic acid	Between 1.6 to 2.4
Glutamic acid	Between 3.6 to 4.4
Proline	Between 2.6 to 3.4
Leucine, isoleucine, arginine, and tyrosine	Between 0.7 to 1.3
Phenylalanine	Between 1.6 to 2.4

Comment Summary #2: The commenter requested to move the *Identification D* test to the *Specific Tests* section.

Response: Comment incorporated. The *Identification D* test was moved to the *Specific Tests* section because the Expert Committee determined that the method is beneficial during development, instead of as a routine test.

Comment Summary #3: The commenter requested more clarification about [Asp9]-bivalirudin in the Product-Related Substances and Impurities, Procedure 1.

Response: Comment incorporated. For clarity, the chemical name of [β -Asp9]-bivalirudin was added to footnote d in *Table 3*.

Monograph/Section(s): Bromelain/ Assay
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1

Comment Summary # 1. Under the *Assay*, the commenter suggested to include the use of Hammarsten grade casein *or equivalent* in the footnote for this reagent.

Response: Comment incorporated. The wording "equivalent" was added to allow users the flexibility of using a potential new supplier of the reagent, if needed.

Monograph/Section(s): Calcium Pantothenate/ Assay, Impurities
Expert Committee: Non-botanical Dietary Supplements
No. of Commenters: 1

Comment Summary #1: The commenter recommended to rename "Any other unidentified impurity" with "Any unspecified impurity" to be consistent with ICH Q3A terminology.

Response: Comment incorporated for consistency with ICH Q3A terminology.

Comment Summary #2: The commenter requested removing “reporting threshold” for impurities.

Response: Comment not incorporated. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Monograph/Section(s): Carbamazepine/ Multiple sections
Expert Committee: Small Molecules 4
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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: The commenter indicated that some of the specified impurity limits are higher for their in-house material than what was proposed in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee determined that the proposed limits are consistent with sponsor data and will consider future revisions to this monograph upon receipt of supporting information.

EC-initiated Change #1: The Expert Committee updated the chemical information for USP Carbamazepine Related Compound A RS in the *USP Reference Standards <11>* section from “10,11-Dihydrocarbamazepine” to “10,11-Dihydro-5H-dibenz[b,f]azepine-5-carboxamide,” to be consistent with USP reference standard certificate.

Monograph/Section(s): Cefoperazone Sodium/ Multiple Sections
Expert Committee: Small Molecules 1
No. of Commenters: 1

Comment summary #1: The commenter recommended adding two tests, an Identification test based on infrared spectroscopy and an optical rotation test under *Specific Tests* in the monograph.

Response: Comment not incorporated. The comment is out of the scope of the proposal. If necessary, the Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

EC-initiated Change #1: The Expert Committee decided to remove the chemical information for USP Cefoperazone Dihydrate RS in the *USP Reference Standards <11>* section as this information is not needed for an Article with a *USP-NF* monograph.

Monograph/Section(s): Cetostearyl Alcohol/ Impurities
Expert Committee: Complex Excipients
No. of Commenters: 1

Comment Summary #1: Commenter requested rationale for adding the Linoleyl Alcohol reference standard in the *Impurities* section since there are many reference standards for this test to compare. The commenter also expressed concern about the cost of testing.

Response: Comment not incorporated. The Expert Committee decided to move ahead with USP-RS instead of Analytical grade reagent based on scientific, and material perspectives. The expert committee determined that in order to identify unsaturated alcohols, the USP-RS is required. Furthermore, Linoleyl Alcohol is prone to degradation and the USP-RS packaging and labelling instructions are reasonable.

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

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

Response: Comment not incorporated. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) User-Determined Reporting Thresholds, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: The commenter recommended revising the acceptance criterion for “Transplatin” for consistency with what has been approved.

Response: Comment incorporated. The acceptance criterion for “Transplatin” is revised from “NMT 1.5%” to “NMT 2.0%” in *Table 1* of the *Organic Impurities* section.

Comment Summary #3: The commenter recommended revising the acceptance criterion for “Aminotrichloroplatinum” for consistency with what has been approved.

Response: Comment not incorporated. The Expert Committee determined that the acceptance criterion for “Aminotrichloroplatinum” may be revised in the future upon receipt of the supporting data.

Comment Summary #4: The commenter recommended deleting the acceptance criterion for “Total unspecified degradation products”.

Response: Comment incorporated. The “Total unspecified degradation products: NMT 1.5%” was deleted from *Table 1* of the *Organic Impurities* section due to limited data on appropriate limits.

Comment Summary #5: The commenter recommended revising the limit of pH for consistency with what has been approved.

Response: Comment incorporated. The limit of pH is widened from “3.5- 5.0” to “3.2- 6.0” in the *Specific Tests* section.

EC-initiated Change #1: Revise “any individual unspecified degradation product” to “any unspecified degradation product” in the *Organic Impurities* section to align with the ICH terminology.

EC-initiated Change #2: Add “Disregard any peak due to cisplatin aquo complex” to the *Acceptance criteria* in the *Organic Impurities* section.

Monograph/Section(s): Clobazam/ Organic impurities
Expert Committee: Small Molecules 4
No. of Commenters: 1

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

Commentary for USP–NF 2023, Issue 3

Response: Comment not incorporated. USP is considering the issue of the removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: The commenter recommended revising the limits for 'Deschloroclobazam,' '3-Methylclobazam,' '3,3-Dimethylclobazam,' 'Clobazam related compound E,' and 'Malonate analog' to be consistent with ICH Q3A Qualification Threshold.

Response: Comment not incorporated. The Expert Committee determined that the proposed limits are consistent with the approved limits for the sponsor product.

Comment Summary #3: The commenter indicated that the limit for Clobazam related compound G is different from what has been proposed.

Response: Comment incorporated. The limit for Clobazam related compound G has been widened from "NMT 0.10%" to "NMT 0.15%" to be consistent with the FDA-approved specification.

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

Identification B

Comment Summary # 1. Under *Identification B, HPLC Profile of Flavonoids (Profile at 365 nm)*, the following statement in the acceptance criteria: "No other peak between myricetin-3-O-galactoside and quercetin ***is more intense*** than the peaks corresponding to myricetin-pentoside derivatives", deserves attention because:

1. On a typical chromatogram, the intensity of each peak of myricetin-pentoside derivatives is not equivalent. The area and height of myricetin-pentoside derivative-1 peak is more or less 50% less intense than the two other ones.
2. The intensity of some other peaks between myricetin-3-O-galactoside and quercetin are equivalent or more intense than this reference peak.
3. Some peaks between myricetin and quercetin peaks are greater than any myricetin-pentoside derivative.

To be suitable, the acceptance criteria need to be modified to end on myricetin peak, to define more precisely the term "intense" and to indicate a single reference, for example: "No other peak between myricetin-3-O-galactoside and **myricetin** is more intense (**area**) than the peaks corresponding to **myricetin-pentoside derivative 3**".

Response: Comment incorporated. The statement in the acceptance criteria has been modified as follows for clarity: "From the identified peaks eluting between myricetin-3-O-galactoside and quercetin peaks, the less intense peak corresponds to myricetin-pentoside derivative-1".

Comment Summary # 2. Under *Identification B, HPLC Profile of Flavonoids (Profile at 520 nm)*, for the following statement in the acceptance criteria: "The peak area ratio of peonidins (sum of peonidin-3-O-galactoside and peonidin-3-O-arabinoside) and cyanidins (sum of cyanidin-3-O-galactoside and cyanidin-3-O-arabinoside) ranges between 0.5 and 1.9;," it would be valuable to clarify if this ratio needs to include area of glucoside peaks in the calculation.

Response: In response to the commenter, this ratio does not include the peak area of peonidin glucoside and cyanidin glucoside because these are very minor peaks.

Adulterants

Comment Summary # 3. Under *Adulterants, HPLC Profile of Phenolic Compounds (Profile at 278 nm)*, the following statement in the acceptance criteria: “*The Sample solution exhibits characteristic peaks corresponding to the retention times of the same constituents in the Standard solution. Peaks that are observed are due to p-coumaroyl glucose isomer-1, cyanidin-3-O-galactoside, chlorogenic acid, p-coumaroyl glucose isomer-2, myricetin-3-O-galactoside, p-coumaric acid, quercetin-3-O-galactoside (hyperoside), myricetin, and quercetin,*” deserves attention. Based on our analysis, this peak sequence is not correct. In *Table 2* the relative retention time (RRT), calculated based on hyperoside retention time, for 2nd, 3rd and 4th peaks in the chromatogram are: Cyanidin-3-O-galactoside, 0.36; chlorogenic acid, 0.38, and p-coumaroyl glucose isomer-2, 0.39.

Response: Comment not incorporated. Currently, we do not have additional data to support the change.

Comment Summary # 4. Under *Adulterants, HPLC Profile of Phenolic Compounds (Profile at 278 nm)*, the following statement in the acceptance criteria: “*The p-coumaroyl glucose isomer-1 peak is not more intense than the chlorogenic acid peak,*” deserves attention because the sequence of peak between RRT 0.35 and 0.40 could be wrong (see Commenter Summary 3).

Response: Comment not incorporated. Currently, we do not have additional data to support the change.

Comment Summary # 5. Under *Adulterants, HPLC Profile of Phenolic Compounds (Profile at 278 nm)*, the following statement in the acceptance criteria: “*No additional significant peaks, beside the one observed in the standard solution, should elute between p-coumaroyl glucose isomer-2 and myricetin-3-O-galactoside; in particular at the approximate relative retention times of 0.49 and 0.55,*” deserves attention because the sequence of peak between RRT 0.35 and 0.40 could be wrong (see Commenter Summary 3).

Response: Comment not incorporated. Currently, we do not have additional data to support the change.

Comment Summary # 6. Under *Adulterants, HPLC Profile of Phenolic Compounds (Profile at 278 nm)*, considering the following statement in the acceptance criteria: “*No additional peaks, besides the one observed in the standard solution, should elute immediately before myricetin-3-O-galactoside, between p-coumaric acid and quercetin-3-O-galactoside, or immediately before or after quercetin-3-O-galactoside,*” the USP Cranberry Fruit Juice Dry Extract RS is not yet available and due the complexity of the chromatographic profile between myricetin-3-O-galactoside peak and the peak at RRT 0.77, it is not possible to provide complete feedback.

Response: Comment not incorporated. The USP Cranberry Fruit Juice Dry Extract RS is now available on catalog, and we encourage further testing.

Monograph/Section(s): Cranberry Fruit Juice Dry Extract Capsules/ Identification B
Expert Committee: Botanical Dietary Supplements and Herbal Medicines
No. of Commenters: 0

EC- initiated Change: Under *Identification B, HPLC Profile of Flavonoids (Profile at 365 nm)*, the following statement in the acceptance criteria : “*No other peak between myricetin-3-O-galactoside and quercetin is more intense than the peaks corresponding to myricetin-pentoside derivatives*”, has been replaced by: “*From the identified peaks eluting between myricetin-3-O-galactoside and quercetin peaks, the less intense peak corresponds to myricetin-pentoside derivative-1*”.

Monograph/Section(s): Cromolyn Sodium/ Organic Impurities
Expert Committee: Small Molecules 5
No. of Commenters: 2

Commentary for USP–NF 2023, Issue 3

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. USP is considering the issue of the removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: The commenter requested updating the chemical information for Cromolyn tricarboxylic acid analog impurity in *Table 2* in the test for *Organic impurities*.

Response: Comment incorporated. The chemical information in the *Table 2* footnote is updated from “5-{3-[(2-Carboxy-4-oxo-4H-chromen-5-yl)oxy]-2-hydroxypropoxy}-6-{3-[(2-carboxy-4-oxo-4H-chromen-5-yl)oxy]-2-hydroxypropyl}-4-oxo-4H-chromene-2-carboxylic acid” to “5-{3-[(2-Carboxy-4-oxo-4H-chromen-5-yl)oxy]-2-hydroxypropoxy}-8-{3-[(2-carboxy-4-oxo-4H-chromen-5-yl)oxy]-2-hydroxypropyl}-4-oxo-4H-chromene-2-carboxylic acid”.

Monograph/Section(s): Cyanocobalamin/ Impurities
Expert Committee: Non-botanical Dietary Supplements
No. of Commenters: 1

Comment Summary #1: The commenter noted that the proposed clarification regarding the hydration form of the reagent used for *Solution A* could affect the chromatographic impurities profile when the anhydrous form of the reagent was used.

Response: Comment not incorporated. The commenter did not follow the procedures recommended in the monograph, so the supporting data provided was not acceptable for consideration.

Monograph/Section(s): Dapagliflozin Propanediol/ Multiple Sections
Expert Committee: Small Molecules 3
No. of Commenters: 3

Comment summary #1: The commenter recommended removing the reporting threshold in the tests for *Organic Impurities, Procedures 1 and 2*, as it will vary based on product-specific factors.

Response: Comment not incorporated. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: The commenter stated the *Organic Impurities* method proposed in the monograph is not suitable for their drug substance analysis as some impurities identified for their product are not well resolved.

Response: Comment not incorporated. The Expert Committee will consider future revision to this monograph upon receipt of supporting information.

Comment Summary #3: The commenter indicated that the proposed *Organic Impurities* procedure lacks sensitivity and suggested their method for the Expert Committee’s consideration.

Response: Comment not incorporated. The Expert Committee determined that the method is consistent with the validation data and suitable for its intended use.

Comment Summary #4: The commenter requested to widen the limit of total impurities from “NMT 0.30%” to “NMT 0.60%” in the test for *Organic Impurities*.

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

Comment Summary #5: The commenter stated that the acceptance criteria for *Water Determination* is not suitable for the anhydrous form of the drug substance. The commenter recommended setting appropriate acceptance criteria to accommodate the anhydrous form of the drug substance.

Response: Comment partially incorporated. To avoid confusion, the anhydrous form is removed from the *Chemical Information* section. The Expert Committee will consider future revision to this monograph upon receipt of supporting information.

Comment Summary #6: The commenter requested widening the limit for *Water Determination* from “3.2%-4.0%” to “3.0%-5.0%”.

Response: Comment not incorporated. The Expert Committee will consider future revision to this monograph upon receipt of supporting information.

Comment Summary #7: The commenter observed an unknown peak in the solvent elutes closely to the Internal Standard in the test for *Content of Propanediol* that may affect the result.

Response: Comment not incorporated. The Expert Committee determined that the method is consistent with the validation data. USP lab evaluation of the method did not show interference from the unknown peak.

Comment Summary #8: The commenter requested to widen the *Acceptance criteria* in the test for *Content of Propanediol* from “14.0%-16.5%” to “13.6-16.6%”.

Response: Comment not incorporated. The Expert Committee will consider future revision to this monograph upon receipt of supporting information.

Monograph/Section(s): Dimethyl Fumarate/ Multiple sections

Expert Committee: Small Molecules 4

No. of Commenters: 3

Comment Summary #1: The commenter suggested removing the autosampler temperature requirement in the *Assay* as it is not a critical chromatographic parameter for this material.

Response: Comment not incorporated. The Expert Committee determined that the method is consistent with validation data and suitable for its intended use.

Comment Summary #2: The commenter indicated that the *Sample solution* concentration of 0.3 mg/mL in the *Assay* and test for *Organic Impurities* is high and observed peak response above 1.0 AU while performing linearity analysis.

Response: Comment not incorporated. The Expert Committee determined that the method is consistent with validation data and suitable for its intended use.

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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #4: The commenter requested replacing the *Signal-to-noise ratio* requirement of NLT 10 for the Sensitivity solution with a recovery requirement of 70.0 -130.0% in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee determined that the *Signal-to-noise ratio* requirement is widely used and is suitable as a public standard.

Monograph/Section(s): Dimethyl Fumarate Delayed-Release Capsules/ Multiple sections
Expert Committee: Small Molecules 4
No. of Commenters: 4

Comment Summary #1: The commenter requested replacing the Assay procedure for *Identification* tests with their in-house procedure.

Response: Comment not incorporated. The Expert Committee determined that the proposed test is consistent with the validation data and suitable as a public standard.

Comment Summary #2: The commenter requested widening the *Relative standard deviation* requirement in the Assay from “NMT 1.0%” to “NMT 1.5%” to be consistent with approval for their product.

Response: Comment not incorporated. The Expert Committee determined that the proposed requirement is sufficient.

Comment Summary #3: The commenter requested the addition of their *Dissolution* test as the *Dissolution* parameters and limits are different from what has been proposed.

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

Comment Summary #4: The commenter requested revising the solution preparations in the *Dissolution* test to not reference label claims.

Response: Comment not incorporated. The Expert Committee determined that the proposed test is suitable as a public standard.

Comment Summary #5: 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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, <477> *User-Determined Reporting Thresholds*, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #6: The commenter indicated that the limit for fumaric acid in the test for *Organic Impurities* is tighter for their product than what was proposed.

Response: Comment not incorporated. The Expert Committee determined that the proposed specification is consistent with sponsor data for an FDA approved product.

Comment Summary #7: The commenter indicated that their in-house test for *Organic Impurities* includes an additional specified impurity with a limit of NMT 0.2%.

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

Comment Summary #8: The commenter recommended revising the acceptance criteria for any unspecified degradation product to be consistent with ICH Q3B and/or FDA approval, in the test for *Organic Impurities*.

Response: Comment incorporated. The limit for any unspecified degradation product has been widened from “NMT 0.1%” to “NMT 0.2%.”

Comment Summary #9: The commenter commented that the acceptance criteria for total degradation product is different from what has been approved by the agency, in the test for *Organic Impurities*.

Response: Comment incorporated. The limit for total degradation product has been widened from “NMT 1.7%” to “NMT 2.0%.”

Comment Summary #10: The commenter recommended including instructions to ‘protect from light’ in the *Packaging and Storage* section to be consistent with FDA approved product labeling.

Response: Comment incorporated to include “protect from light” in the *Packaging and Storage* section.

Monograph/Section(s): Flurbiprofen/ 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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, <477> *User-Determined Reporting Thresholds*, was published in *PF* 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: Commenter recommended including “(±)” for the second chemical name for flurbiprofen in the Chemical Information section.

Response: Comment partially incorporated. The “(±)-” is being phased out and replaced with “(RS)-” as a stereochemical qualifier for this compound.

Monograph/Section(s): Gabapentin Compounded Cream
Expert Committee: Compounding Expert Committee
No. of Commenters: 1

Comment Summary #1: The commenter notes the formulation lists “Gabapentin” as the active pharmaceutical ingredient (API) but omits the source of the API (i.e., powder).

Response: Comment not incorporated. This is consistent with USP Style Guide for Compounded Preparation Monographs.

Comment Summary #2: The commenter notes the formulation in the monograph for *Gabapentin Compounded Cream* uses the proprietary ingredient Lipoderm as an excipient. They have concerns with using proprietary excipients where there is no information about the identity of the excipient. They recommend that the ingredients in the proprietary excipient be provided so that the identity of the excipient is understood by the public. It is important that the public has the information that will help them understand the risks and benefits associated with the use of the drug product, including any excipients in the drug product.

Response: Comment not incorporated. This is the information that has been obtained from the manufacturer.

Comment Summary #3: The commenter notes the following footnote: “This formulation meets the requirements in Antimicrobial Effectiveness Testing <51>”. As currently written, it is unclear what the footnote is trying to convey. For clarity, we recommend revising the footnote as follow: “Preparation has passed Antimicrobial Effectiveness Testing <51>”.

Response: Comment incorporated for clarity.

Comment Summary #4: The commenter recommends that the *Packaging and Storage* section state what material (e.g., metal or plastic) and type of container closure system the BUD testing was performed.

Response: Comment incorporated to maintain consistency with other monographs and <797>.

Comment Summary #5: The commenter recommends the following be added to the *Labeling*: “Discard if lack of homogeneity, phase separation, or change in color is noted upon visual inspection.” This statement should be considered for inclusion to include in monographs for creams and ointments to inform patients to not use the product if it is a different color or if it appears to have a different consistency from what the label states it should be.

Response: Comment not incorporated. Statement is out of scope of the labeling section of compounded preparation monographs.

Monograph/Section(s): Glucagon/ Product-related Substances and Impurities
Expert Committee: Biologics Monographs 1– Peptides and Oligonucleotides
No. of Commenters: 1

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

Response: Comment not incorporated. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Monograph/Section(s): Inositol Niacinate/ Labeling
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 1

EC-initiated change #1: The Expert Committee added the following requirement to the *Labeling* section: “Consult your healthcare provider before use if you have had a cerebrovascular or cardiovascular condition, including angina, stroke, heart attack, or heart failure.” due to potential health risks associated with this ingredient.

Monograph/Section(s): Isopropyl Alcohol/ Multiple Sections
Expert Committee: Simple Excipients
No. of Commenters: 3

Comment Summary #1: The commenter recommended that step-by-step preparation of the *System suitability solution* be added to the *Assay*.

Response: Comment incorporated.

Comment Summary #2: The commenter suggested adding a description of the sample in the *Ultraviolet Absorption* test.

Response: Comment incorporated.

Monograph/Section(s): Lactobacillus Reuteri/ Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0

EC-initiated Change #1: Under *Enumeration*, include a note indicating that cysteine hydrochloride solution needs to be added to the Lactobacilli MRS agar medium in the Enumeration test referenced in General Chapter <64> *Probiotic tests*, as follows:

(See *Probiotic Tests* (64), *Enumeration*, *Enumeration for Non-Spore-Forming Bacteria Strains*.)

Agar medium: Prepare *Lactobacilli* MRS agar as directed in the chapter with addition of 1 mL of sterile 5% (w/v) cysteine hydrochloride solution to each 100 mL for a final cysteine hydrochloride concentration of 0.05% immediately before use.

EC-initiated Change #2: Under *Additional requirements, Packaging and Storage*, replace the statement “*Preserve in high barrier foil laminate bags and store at or below 4°.*” by “*Protect from moisture using high barrier foil laminate bags and store at or below 4°.*”.

Monograph/Section(s): Lactobacillus Rhamnosus/ Additional Requirements,
Packaging and Storage
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0

EC-initiated Change #1: Under *Additional requirements, Packaging and Storage*, replace the statement “*Preserve in high barrier foil laminate bags and store at or below 4°.*” by “*Protect from moisture using high barrier foil laminate bags and store at or below 4°.*”.

Monograph/Section(s): Morphine Sulfate/ Specific Tests
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter questioned the purpose of the *Ammonium Salts* test under the *Specific Tests* section.

Response: Comment not incorporated. The removal of this test was due to a safety concern raised pertaining to inhaling ammonia gas for the test.

Monograph/Section(s): Nadolol/ 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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF* 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: The commenter recommended including a requirement “protect from light” under the *Packaging and Storage* section.

Response: Comment not incorporated. This request is currently outside the current revision's scope. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

Monograph/Section(s): Oxycodone Hydrochloride Tablets/ Organic Impurities
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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-*

Determined Reporting Thresholds, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Monograph/Section(s): Pantoprazole Sodium/ Multiple Sections
Expert Committee: Small Molecules 3
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the reporting threshold in the tests for *Organic Impurities, Procedures 1 and 2*, as it will vary based on product-specific factors.

Response: Comment not incorporated. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

EC-initiated Change #1: The *Labeling* statement is revised to remove the phrase "to ensure acceptable levels of bacterial endotoxins, it is so labeled," **as the statement is not relevant and is confusing.**

Monograph/Section(s): Sucralose/ Multiple Sections
Expert Committee: Simple Excipients
No. of Commenters: 1

Comment Summary #1: The commenter recommended indicating that the *Optical Rotation* test should be carried out on the dried basis.

Response: Comment incorporated. This information was erroneously omitted from the monograph during the redesign, the conversion of the monograph from classic style to current USP monograph style.

Comment Summary #2: The commenter suggested that either description and solubility information be included, or a link be given to the *Description and Solubility* table in each individual monograph.

Response: Comment not incorporated. This recommendation should be sent to the USP—NF/PF Online support team.

Monograph/Section(s): Sulbactam Sodium/ Multiple Sections
Expert Committee: Small Molecules 1
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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in PF 48(5) for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment summary #2: The commenter commented that the CAS number for Sulbactam (free acid) in the *Chemical Information* section immediately after the monograph title is incorrect.

Response: Comment incorporated. The CAS number for Sulbactam (free acid) is corrected from [69373-14-8] to [68373-14-8] based on the supporting information.

Comment summary #3: The commenter indicated that an additional impurity (impurity G, (2S)-2-[[[(2E)-2-carboxyethenyl]amino]-3-methyl-3-sulfinobutanoic acid), which is mentioned in the corresponding *European Pharmacopeia* monograph and is extremely labile in solution, is not listed in the test for *Organic Impurities*.

Response: Comment not incorporated. The impurity profile and limits, which were not revised in the proposal, are consistent with sponsor provided data.

EC-initiated Change #1: The Expert Committee removed the statement “to ensure acceptable levels of bacterial endotoxins” in the *Labeling* section as the statement is not relevant and confusing.

Monograph/Section(s):	Talc/ Multiple sections
Expert Committee:	Simple Excipients
No. of Commenters:	14

Comment Summary #1: Commenters recommended additional time for implementation (i.e., ~3 years), as X-ray diffraction (XRD) and Polarized Light Microscopy (PLM) are not commonly used for routine release testing.

Response: Comment partially incorporated. The Expert Committee approved an official date of December 1, 2023, for the two general chapters <901> and <1901>, while the Expert Committee also approved an extended official date of December 1, 2025, for the *USP* Talc monograph, with changes to be published in *USP–NF 2023 Issue 3*. The additional two years are intended to provide the time needed by manufacturers and users to implement the test methods and make necessary changes.

Though chapter <901> will become official before the *USP* Talc monograph becomes official, the chapter will only become applicable when revisions to the *USP* Talc monograph (which references chapter <901>) becomes official. Additionally, the chapter <1901> is for informational purpose only. The earlier official date for both chapters will help stakeholders in the adoption of the of the *USP* Talc monograph revisions that will become official later.

Please see [Compendial Notice](#) published on the USP web site on May 26, 2023.

Comment Summary #2: Commenters recommended retaining "suppliers" to perform the asbestos testing, as indicated in the original note of the Talc monograph.

Response: Comment not incorporated. Based on the discussions of the Expert Committee and the FDA's input, both suppliers and end users need to certify to the FDA that their products comply with the compendial standard and cGMP requirements. They may have third parties (such as contract laboratories) test for asbestos if they do not have the capability to perform the asbestos tests.

Comment Summary #3: Commenters recommended the following:

- changing the format of microbial limits according to the current USP style, such as changing from “NMT 100 cfu/g” to “NMT 10² cfu/g”, etc.
- changing the limit for Talc intended for topical administration from “Total combined molds and yeasts count: NMT 50 cfu/g” to “Total combined molds and yeasts count: NMT 10¹ cfu/g”

Response: Comment a incorporated, but Comment b not incorporated. The updated texts are shown as below:

- Intended for topical administration
 - Total aerobic microbial count: NMT 10² cfu/g
 - Total combined molds and yeasts count: NMT 5 x 10¹ cfu/g

- Intended for oral administration
- Total aerobic microbial count: NMT 10³ cfu/g
- Total combined molds and yeasts count: NMT 10² cfu/g

According to general chapter <1111> *MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS AND SUBSTANCES FOR PHARMACEUTICAL USE*, for pharmaceutical substance, the total combined molds and yeasts count is NMT 10² cfu/g. Additionally, the commenter did not provide data to support the limit change to “NMT 10¹ cfu/g”. Therefore, this comment b is not incorporated.

Comment Summary #4: The commenter is willing to implement the proposed changes/update in the *Definition, Limit of Calcium, and Labeling* sections.

Response: Comment noted.

Comment Summary #5: Commenters recommended providing reference standards in order to validate the methods according to general chapters <1225> and <1226>.

Response: Comment partially incorporated. Due to the challenges of handling asbestos and developing physical reference standards, USP included 5 representative XRD diffractograms and 85 PLM images in the chapter <1901> as references.

Comment Summary #6: Commenters recommended only performing the X-ray Diffraction (XRD) test to be consistent with the *European Pharmacopeia* (EP), as the Talc monograph is a PDG harmonized monograph.

Response: Comment not incorporated. As explained in the *Stimuli* article [“Modernization of Asbestos Testing in USP Talc—Part 2”](#) published in *PF* 46(5), both XRD and PLM are mandatory for asbestos testing in pharmaceutical talc. The asbestos testing is currently a non-harmonized attribute in the Pharmacopeial Discussion Group (PDG) harmonized Talc monograph, however, the EP is also planning to align with the XRD and PLM testing procedures proposed in the chapters <901> and <1901>. Therefore, both XRD and PLM procedures will be implemented by EP as well. Additionally, contract labs are available for testing if pharmaceutical manufacturers do not have the capability to perform the tests.

Comment Summary #7: The commenter stated the following:

“This method has been well-tested. Many laboratories have participated in establishing quantitative measures of reliability. The detection limit is robust and equivalent to methods based on electron microscopy. The including of a wet sieving method enhances the possibility of detecting asbestos given that its high tensile strength and resistance to grinding leaves long fibers intact. The method can be applied to raw materials or to materials that have been concentrated by heavy liquids. Of particular importance is the inclusion of criteria by which asbestiform amphibole can be discriminated from non-asbestiform habits of the same mineral. This is an excellent method and a significant advance for screening talc for the presence of asbestos.”

Response: Comment noted

Comment Summary #8: The commenter provided the following comment:

No testing institution which would be able to carry out the proposed tests is found in Japan, in terms of wet sieving pretreatment, appropriate analytical equipment, and experienced analyst. It is difficult for both excipient manufacturers and pharmaceutical manufacturers to conduct the tests in Japan.

Response: Comment not incorporated. In the USA, contract laboratories are available for testing if stakeholders do not have the capability to perform the tests. To protect public health, it is important to test asbestos in pharmaceutical talc.

Comment Summary #9: The commenter recommended the following regarding wet sieving:

- a. The wet sieve preparation should be optional.

- b. Should provide some flexibility in the sieve size used and allow for use of disposable screening materials which would remove or reduce the possibility of transfer of material from sample to sample.
- c. If, after sieving, the mass of material remaining on the sieve is less than 0.01% of the initial sample, the protocol should end. If less than 0.01% remains, the result is certain to be lower than the stated limit of detection and quantification (0.01%).

Response: Comment a: Not incorporated. Based on the round robin study results, the wet sieving procedure is mandatory to achieve the desired detection limit (0.01%). According to [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#), alternative method or procedure can be used. However, they 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.

Comment b: Partially incorporated. Sieves should be cleaned and maintained in accordance with manufacturers recommendations and/or instructions. Step #9 was added to <901> for this procedure. Flexibility of using sieve size should follow [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#).

Comment c: Not incorporated. According to the testing procedure in chapter <901>, sieving should be continued until a minimum of 5 mg of material remaining on the sieved is collected. However, it may stop earlier if asbestos is detected. Validation is needed if an alternative method is used.

Comment Summary #10: The commenter recommended the following regarding PLM:

- a. The mass of sample placed on slides is stated to be 1-2 mg. In practice, 0.5 mg will produce a more optimal loading of particulate.
- b. If amphibole asbestos is determined by PLM, the option for energy dispersive x-ray spectroscopy (EDS) analysis should be mandatory to confirm the PLM finding.
- c. The Reporting Results section could be edited for clarity, particularly at numbers 3 & 4.

Response: Comment a: Partially incorporated. According to [General Notices 6.30. Alternative and Harmonized Methods and Procedures](#), alternative method or procedure (such as use of 0.5 mg sample) can be used. However, they 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.

Comment b: Not incorporated. Energy dispersive x-ray spectroscopy (EDS) is not within the scope for PLM. A lab may employ it as an optional procedure.

Comment #c: Incorporated. The #3 and #4 in Reporting Results are edited to be more explicit. See general chapter <901> which will be available on the *USP-NF* platform on June 1, 2023, and become official on December 1, 2023.

Comment Summary #11: The commenter stated the following:

- a. "In chapter <901>, Procedure 2: Polarized Light Microscopy" subsection "Sample Analysis", in addition to the examples of morphology identified ("straight, curved, bundle, wavy, splayed ends, etc.") the term "polyfilamentous" should also be listed.
- b. They are supportive of USP referring to the glossary section of EPA 600/R-93/116 in defining the term asbestiform.

Response: Comment a: incorporated by adding "polyfilamentous" to the text.

Comment Summary #12: The commenter stated the following:

- a. The commenter is supportive of the proposed method <901> and supporting information in chapter <1901>. Most notably, they commend the incorporation of the EPA 600/R-93/116 definition for asbestiform into the USP protocol for measurement of asbestos in

talc. They are pleased to see that the panel has addressed FDA's request for modernizing the test method.

- b. The proposed USP method for measuring asbestos in talc for pharmaceutical applications should be considered by the FDA for the measurement of asbestos in talc for cosmetic applications and other related uses of talc. They believe it would be prudent for the USP to recommend that the FDA instruct the Interagency Working Group on Asbestos in Consumer Products (IWGACP) to incorporate this proposed USP Detection of Asbestos in Pharmaceutical Talc method, when determination of asbestos is required in all talc applications including cosmetics. There is no rational scientific reason for having different test protocols for each application of talc.

Response: Comment a: noted and incorporated. Comment b: noted and USP relayed this comment to the FDA.

Comment Summary #13: The commenter provided several comments on the XRD instrument conditions and parameters under *Procedure 1: X-ray Diffraction* in the general chapter <901>.

Response: Comments incorporated because those additional conditions and parameters also apply to XRD analysis. See general chapter <901> which will be available on the *USP-NF* platform on June 1, 2023, and become official on December 1, 2023.

Comment Summary #14: The commenter made the following comments on Chapter <901>:

- a. For clarity, the commenter suggested including a statement in the Chapter <901> that there is no level of asbestos that is recognized as safe and that the limits are based on limits of detection, not toxicological limits.
- b. Recommended a reference to *(1901) Theory and Practice of Asbestos Detection in Pharmaceutical Talc* be added to the *Limit of Detection* and *Quantification* subsections under *Procedure 1: X-Ray Diffraction* and *Procedure 2: Polarized Light Microscopy*. This would provide the reader with additional context and clarity.

Response: Comment a: Partially incorporated. The Expert Committee agreed to add a note at the end of "Reporting Results" for both XRD and PLM as following:

- "[Note: The limits are based on limits of detection.]

Comment bb: Incorporated. For additional context and clarity, the Expert Committee agreed to add a reference to <1901> in the *Limit of Detection* and *Quantification* subsections of both XRD and PLM sections in Chapter <901>.

Comment Summary #15: The commenter suggested including a table to summarize the scope, features, and advantages/disadvantages of each technique in chapter <1901>. The table would help highlight and clarify why and how the different techniques are complementary to each other.

Response: Comments incorporated for additional clarity. See *Table 1* in the Chapter <1901>.

Comment Summary #16: The commenter recommended using categorized subsections and subtitles (e.g., "Purpose", "Scope", "Table of characteristic peaks", "Table of samples", and "Instrument calibration/qualification") in <1901>. This would enhance clarity and readability.

Response: Comments not incorporated. There are already subsections in the XRD and PLM sections of chapter <1901>.

Comment Summary #17: The commenter recommended spelling out "National Institute of Standards and Technology (NIST) or NIST-traceable Standards should be used for all types of asbestos..." in the Standards and Calibration section of chapter <1901>.

Response: Comments incorporated for additional clarity.

Comment Summary #18: The commenter recommended adding references and original sources in the Appendix of chapter <1901>. Original sources of data would be helpful if any update is published, or data verification is needed.

Response: Comments incorporated for additional context. International Centre for Diffraction Data (ICDD) was spelled out and included as reference #18. The hyperlink to the ICDD website was also included.

Monograph/Section(s): Terbutaline Sulfate/ Organic Impurities
Expert Committee: Small Molecules 5
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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Monograph/Section(s): Terbutaline Sulfate Injection/ Organic Impurities
Expert Committee: Small Molecules 5
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. USP is considering the issue of removing reporting thresholds from certain monographs. A proposal for a new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *PF 48(5)* for public comment. The responsible Expert Committee will review the comments and determine the next steps for the chapter.

Comment Summary #2: The commenter commented that the acceptance criteria for *Total Degradation Product* in the test for *Organic Impurities* is different from what has been approved by the agency.

Response: Comment incorporated. The acceptance criteria for total degradation product has been widened from “NMT 0.6%” to “NMT 1.0%.”