



## **Commentary**

### **USP–NF 2024 Issue 1**

**November 1, 2023 (updated December 26, 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.

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

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

**Reference Tables**

[USP and NF Excipients, Listed by Functional Category](#)

**General Chapters**

[<4> Mucosal Drug Products- Product Quality Tests](#)

[<232> Elemental Impurities](#)

[<477> User-Determined Reporting Thresholds](#)

[<601> Inhalation and Nasal Drug Products- Aerosols, Sprays, and Powders- Performance Quality Tests](#)

[<789> Subvisible Particulate Matter in Intraocular Solutions](#)

[<1059> Excipient Performance](#)

[<1117.1> Microbiological Chapters – Glossary](#) (added December 26, 2023)

[<1153> Drug Products Containing Nanomaterials](#)

[<1705> Quality Attributes of Tablets Labeled as Having a Functional Score](#)

**Monographs**

[Acetazolamide](#)

[Aloe Vera Dry Juice](#)

[Aloe Vera Leaf Juice](#)

[Aloe Vera Leaf Juice Concentrate](#)

[Aspartame Acesulfame](#)

[Bitter Orange Young Fruit](#)

[Bitter Orange Young Fruit Powder](#)

[Bumetanide](#)

[Bumetanide Injection](#)

[Bumetanide Tablets](#)

[Carrageenan](#)

[Cefipime Hydrochloride](#)

[Cinnamomum Cassia Bark](#)

[Cinnamomum Cassia Bark Powder](#)

[Cocoyl Caprylocaprate](#)

[Diluted Isosorbide Mononitrate](#)

[Etodolac Tablets](#)

[Fludeoxyglycose F18 Injection](#)

[Formic Acid](#)

[Hydrocortisone Compounded Oral Suspension](#)

[Isosorbide Mononitrate Tablets](#)

[Liothyronine Sodium Injection](#)

[Methyltestosterone](#)

[Nadolol](#)

[Nortriptyline Hydrochloride Capsules](#)

[Pirfenidone](#)

[Perfenidone Capsules](#)

[Perfenidone Tablets](#)

[Pyrimethamine](#)

[Sodium Bicarbonate Compounded Injection](#)

[Valganciclovir for Oral Solution](#)

**No comments were received for the following proposals:**

**General Chapters**

<705> Quality Attributes of Tablets Labeled as Having a Functional Score

**Monographs**

Alumina and Magnesium Trisilicate Tablets  
Aspirin Suppositories  
Astaxanthin Esters  
Astaxanthin Esters Capsules  
Boric Acid  
Chondroitin Sodium, Shark  
Cranberry Fruit Juice  
Cranberry Fruit Juice Concentrate  
Cranberry Fruit Powder  
Digitalis  
Digitalis Capsules  
Digitalis Tablets  
Ethyl Butyrate  
Fentanyl Citrate and Ropivacaine Hydrochloride Compounded Injection  
Guaifenesin and Pseudoephedrine Hydrochloride Capsules  
Ioxilan  
Ioxilan Injection  
Levofloxacin Oral Solution  
Menoquinone-7 Preparation  
Oil-Soluble Vitamins Preparation  
Ondansetron Injection  
Oxytetracycline Hydrochloride and Polymixin B Sulfate Vaginal Inserts  
Paraldehyde  
Paromomycin Oral Solution  
Picrorhiza Species Root and Rhizome  
Picrorhiza Species Root and Rhizome Dry Extract  
Picrorhiza Species Root and Rhizome Powder  
Powdered Digitalis  
Quinidine Sulfate Extended-Release Tablets  
Tolnaftate Cream  
Tolnaftate Topical Aerosol  
Tolnaftate Topical Powder  
Tolnaftate Topical Solution  
Tyrothricin  
Vitamin E  
Vitamin E Capsules  
Vitamin E Preparation

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**Reference Tables**

**Reference Table(s):** USP and NF Excipients, Listed by Functional Category  
**Expert Committee(s):** USP Headquarters/ Excipient Test Methods  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter asked to add Carbomer Homopolymer, Carbomer Copolymer, and Carbomer Interpolymer to the following functional categories: *Dry Binder*, *Mucoadhesive*, *Colloid Stabilizing Agent*, and *Buffering Agent*.

**Response:** Comment partially incorporated. Carbomer Homopolymer, Carbomer Copolymer, and Carbomer Interpolymer were added to the *Mucoadhesive* functional category. Carbomers are not the first excipients in the *Dry Binder* and *Buffering Agent* functional categories; formulators will choose as a Dry Binder and Buffering Agent. These are more secondary functions than primary. Supporting information is needed to add Carbomer Homopolymer, Carbomer Copolymer, and Carbomer Interpolymer to the *Colloid Stabilizing Agent* functional category.

**Comment Summary #2:** The commenter asked to add Carbomer Homopolymer, Carbomer Copolymer, and Carbomer Interpolymer to the *Taste Masking* and *Neutralizing Agent* functional categories.

**Response:** Comment not incorporated. These functional categories do not exist in the revised reference table *USP and NF Excipients, Listed by Functional Category*. The commenter is encouraged to submit a revision request to add these functional categories to the table in a future version.

### **General Chapters**

**Monograph/Section(s):** <4> Mucosal Drug Products- Product Quality Tests/ Multiple Sections

**Expert Committee(s):** General Chapters-Dosage Form Expert Committee

**No. of Commenters:** 3

**Comment Summary #1:** The commenter stated that the microbial quality test expectations are not clear in the chapter and suggested to add General Chapter <1111> *Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substance for Pharmaceutical Use* as a reference.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter stated that <5> *Inhalation and Nasal Drug Product—General Information and Product Quality Tests* does not cover nasal gel and nasal ointment dosage forms.

**Response:** Comment incorporated. Gel and ointment dosage forms are now added for nasal route.

**Comment Summary #3:** The commenter suggested adding more details with the chapter to clarify the requirements of dissolution test for some dosage forms.

**Response:** Comment not incorporated. This chapter is focused on drug quality testing not performance testing. <4> is consistent with several other chapters in the same category. <1004> *Mucosal Drug Products – Performance Tests* has guidance for performance testing of mucosal drug products. <1004> will be revised and updated to include more detailed guidance in the future.

**Comment Summary #4:** The commenter recommended adding pulmonary administration route to <1004> *Mucosal Drug Products – Performance Tests* for consistency.

**Response:** The comment will be incorporated for the next proposed revision to <1004> *Mucosal Drug Products – Performance Tests*. In addition, <5> *Inhalation and Nasal Drug*

*product—General Information and Product Quality Tests* is referenced in <4> for pulmonary products.

**Comment Summary #5:** The commenter suggested adding *Softening time of lipophilic suppositories* test as a product-specific test for suppositories.

**Response:** Comment incorporated.

**General Chapter/Sections:** <232> Elemental Impurities

**Expert Committee:** General Chapters—Chemical Analysis

**No. of Commenters:** 2

**Comment #1:** The commenter recommended revising “Route of Exposure” to “Route of Administration” to be consistent with ICH Q3D-R2 guidelines.

**Response:** Comment incorporated.

**Comment #2:** The commenter suggested the following revision for clarity: “*The extent of exposure has been determined for each of the elemental impurities of interest for ~~three~~ four routes of administration: oral, parenteral, and inhalational inhalation, and cutaneous/transcutaneous.*”

**Response:** Comment incorporated. Sentence revised as follows:

The extent of exposure has been determined for each of the elemental impurities of interest for the following routes of administration: oral, parenteral, inhalational, and cutaneous and transcutaneous.

**Comment #3:** The commenter suggested including an additional equation in the *Options for Demonstrating Compliance* subsection (consistent with ICH Q3D-R2 guidelines) to calculate cutaneous PDEs.

**Response:** Comment not incorporated. The Expert Committee believes that the existing equations in the chapter cover the compliance verification when considered with footnote in *Table 1* which covers the special case, CTCL for Ni and Co.

**Comment #4:** The commenter suggested making a correction in the text under “*Permitted Daily Exposures*” since it states that “this table does not apply to products intended for mucosal products...” This should be corrected because mucosal administration includes oral products.

**Response:** Comment not incorporated. The Expert Committee stated that the chapter <232> is aligned the terminology and descriptions used in ICH Q3D.

**Comment #5:** The commenter requested clarifying whether CoAs and statements may be used to satisfy risk assessment requirements, as some of these statements in which the manufacturer claims to meet ICH Q3D and chapter <232> guidelines does not include any mention whether any metal is intentionally added nor provides analytical results.

**Response:** Comment not incorporated. This information is provided in FDA’s guidance on Elemental Impurities and in ICH Q3D training materials. The requested level of detail is not within the scope of this chapter.

**Comment #6:** The commenter requested clarifying the “*Analytical Testing*” section as it is not clear how manufacturers can demonstrate compliance because the way that it is described suggests that if results below the permissible limits are obtained in the risk assessment, it is not necessary to establish a routine analysis. How should one address cases where the results obtained are close to the maximum permissible limit? Is the control threshold of 30 % of the PDE applied only to the PDE or can it be applied on the values of concentrations that were obtained through the conversion of the PDE using the maximum daily dose of the drug product?

**Response:** Comment not incorporated. As stated in the response to the previous question, the Expert Committee recommends the following resources for implementation guidance:

1. the ICH Q3D training materials which have more extensive examples that can answer these general topics and

2. the FDA Guidance to Industry (*Elemental Impurities in Drug Products- Guidance for Industry*) is also a good source for implementation guidance.

**Monograph/Section(s):** <477> User-Determined Reporting Thresholds / Multiple Sections  
**Expert Committee(s):** General Chapters-Chemical Analysis Expert Committee  
**No. of Commenters:** 2

### **General**

**Comment Summary #1:** The commenter suggested adding information of chemically derived materials used as excipients in related text in the chapter.

**Response:** Comment not incorporated. Excipients are not in the scope of ICH Q3A and Q3B, and therefore, this new chapter is focused on drug substances and drug products.

### **Introduction**

**Comment Summary #2:** The commenter recommended revising the last sentence in second paragraph for clarity as follows: “For other users of the monograph, the information provided in this chapter can support the determination of an appropriate numeric value **for the reporting threshold.**”

**Response:** Comment incorporated.

### **Relevant Product Factors**

**Comment Summary #3:** The commenter suggested revising the second sentence for clarity as follows: “For many drug products, the maximum daily dose (MM) is the essential factor in determining an appropriate numeric value **for the reporting threshold.**”

**Response:** Comment incorporated.

### **Maximum Daily Dose Based Reporting Thresholds**

**Comment Summary #4:** The commenter recommended adding a footnote for the title of *Table 1*, third column: “Reporting threshold is expressed as a percentage of the drug substance.”

**Response:** Comment incorporated.

**General Chapter/Section:** <601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests.

**Expert Committee(s):** Dosage Forms

**No. of Commenters:** 3

Editorial changes suggested by commenters have been reviewed by the Expert Committee. Some of these changes as approved by the Expert Committee have been incorporated in the chapter. Where they have not been incorporated, the Expert Committee’s response is indicated below.

### **Introduction**

**Comment Summary #1:** The commenter noticed the use of both “delivered dose uniformity” and the acronym (DDU) and suggested revising the text to use one or the other throughout the chapter.

**Response:** Comment incorporated.

#### **A.1.1.1 Sampling the delivered dose from inhalation aerosols and inhalation sprays Paragraph below Figure 1a**

**Comment Summary #1:** The commenter suggested to delete the following sentence or state that this is not applicable to all inhalation aerosols and inhalation sprays because setting a limit on the total volume of air sampled during delivered dose testing makes sense based on the way

that DPI aerosols are generated since the energy to aerosolize the powder is provided by the patient inhalation airflow. However, such a testing requirement does not make sense for all inhalation aerosols and inhalation sprays, such as a press & breathe MDI. This requirement adds unnecessary testing variability since there would be a short duration (~4 seconds for a 2 L limit) where airflow is present through the test apparatus.

*“The volume of air sampled per actuation should not exceed 2.0 L”*

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #2:** The commenter recommended keeping the original caption for **Figures 1a and 2** (and in the text in section A. 2.1.2) and adding at the end of the caption: “For nasal spray drug products, an appropriate apparatus can be used in place of the sample collection tube (I) outlined above for sampling of the delivered dose using a validated assay.” Because traditionally DUSA tubes like what is outlined in *Figure 1a* and *Figure 2* are not used for delivered dose uniformity with nasal sprays. This proposed addition is to minimize confusion on this topic and matches language seen in various FDA product specific guidance documents for different nasal sprays.

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #3:** The commenter requested modifying *Figure 1a* and its description as follows:

“The sample collection tube is connected to a system comprising a vacuum pump and flow-control valve **and optional timer-operated solenoid valve**”

**Response:** Comment not incorporated. This chapter describes a standard approach only.

#### **Table 1—**

**Comment Summary #1:** The commenter requested adding a footnote or asterisk with the following text under description for *DDU sampling apparatus A* and next to Item “Filter” to state: “not required for testing of delivered dose for nasal sprays” because traditionally, nasal sprays are not actuated under flow conditions but rather into a closed container for delivered dose testing. Therefore, a filter is not required to perform this test.

*“25-mm glass fiber, stainless steel fiber, or microfiber polypropylene filter”*

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #2:** The commenter requested correcting description of Code A under *DDU sampling apparatus B* as follows:

“A Short length of suitable vacuum tubing, e.g., silicone tubing with 10.0-mm ID, 16.0-mm OD, and a connector to pressure tap P2 ~~and P3~~”.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter indicated that in cases where Code E (optional) is not used, this tubing is 10.00 mm ID and 16.0 mm OD tubing. Including this information would allow for either option.

**Response:** Comment not incorporated. Code E is not optional. Correction made in *Table 1* to remove “(optional)” reference.

**Comment Summary #4:** The commenter indicated that the tubing between vacuum pump and solenoid valve, and separately between solenoid valve and flow control valve, are commonly described with Code D. Ideally, they would have different codes as the description here implies that Code D tubing can be with or without a tap to P3. This is not optional; only that the P3 tap only exists between the solenoid valve and the flow control valve, not between the vacuum pump and solenoid valve. Hopefully *Figure 1b* provides sufficient clarity if this is to remain unchanged.

**Response:** Comment not incorporated as information for code D is already in the table and provides sufficient clarity.

**Comment Summary #5:** The commenter suggested adding the same description of code E under *DDU sampling apparatus A* as currently specified under *DDU sampling apparatus B*.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested adding the same description of code G under *DDU sampling apparatus A* as currently specified under *DDU sampling apparatus B*.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter requested aligning codes in *Figure 7c* with codes in *Table 1* as deletion of Code B in this table has shifted all the codes up the alphabet by one.

**Response:** Comment incorporated. *Table 1* and *Figure 7c* were revised for alignment.

**Comment Summary #8:** The commenter requested replacing 47-mm glass fiber filter, stainless steel fiber filter, or Microfiber polypropylene filter specified under description for *DDU sampling apparatus A* and next to Item “Filter” with 75 mm filters because in some cases, when trying to use the standard DUSA tubes described in <601>, sufficient powder deposits on the filter such that air flow is restricted. This can result in significantly less than the target 2L actuation volume. In cases of this filter blinding/air flow restriction, an apparatus with a larger filter/area for air flow should be used.

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #9:** The commenter requested keeping the original language and adding a footnote or asterisk with the following text under description for *DDU sampling apparatus A* and next to Item “Vacuum” because traditionally nasal sprays are not actuated under flow conditions but rather into a closed container. Therefore, a vacuum tubing is not required to perform this test.

“not required for testing of delivered dose for nasal sprays.”

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #10:** The commenter requested removing “nasal spray products” from following in *Table 1*, under description for *DDU sampling apparatus A* and next to Item “Flow meter or test product” because traditionally, nasal sprays are not actuated under flow conditions but rather into a closed container. Therefore, a flow meter is not required to perform this test. “*Inhalation or nasal aerosol or spray products to be evaluated.*”

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #11:** The commenter requested keeping the original language and adding a footnote or asterisk with the following text under description for *DDU sampling apparatus A*



and next to Item “Vacuum Pump” because traditionally nasal sprays are not actuated under flow conditions but rather into a closed container. Therefore, a vacuum tubing is not required to perform this test.

“not required for testing of delivered dose for nasal sprays.”

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #12:** The commenter requested keeping the original language and adding a footnote or asterisk with the following text under description for *DDU sampling apparatus A* and next to Item “Sample Collection Tube” because traditionally DUSA tubes like what is outlined in *Table 1* are not used for delivered dose uniformity with nasal sprays. This proposed addition is to minimize confusion on this topic and matches language seen in various product specific guidance documents for different nasal sprays.

“For nasal spray drug products, an appropriate apparatus can be used in place of the sample collection tube (I) outlined above for sampling of the delivered dose using a validated assay”

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #13:** The commenter requested replacing 34.85-mm ID × 12-cm IL specified under description for *DDU sampling apparatus A* and next to Item “Sample Collection Tube” with “Housing of sufficient diameter to accommodate the filter specified above” because in some cases, when trying to use the standard DUSA tubes described in <601>, sufficient powder deposits on the filter such that air flow is restricted. This can result in significantly less than the target 2L actuation volume. In cases of this filter blinding/air flow restriction, an apparatus with a larger filter/area for air flow should be used. The use of 75 mm filters should alleviate this problem.

**Response:** Comment not incorporated. This chapter incorporates the USP standard approach to minimize unnecessary testing variability. This test is to ensure consistent quality of the drug product only. USP *General Notices* section 6.30 allows for alternative methods that have been appropriately justified.

**Comment Summary #14:** The commenter noticed use of different units for length and diameter (mm vs cm) Under Code I, the descriptions for both DDU Sampling Apparatus A and B (26.70-mm ID x 9.4-cm IL and 34.85-mm ID x 12-cm IL, respectively) and suggested using **mm** for both measurements for consistency.

**Response:** Comment not incorporated. Degree of precision is correct for components designated in cm. Changed 12-cm to 12.0 cm.

### **Section 3.1**

**Comment Summary #1:** The commenter recommended revising the sentence as follows since burden of controlling temperature and humidity will be too great for many products and unnecessary if demonstrated compliance of testing within a range.

“Perform this test under conditions of **controlled** monitored temperature and humidity”

**Response:** Comment not incorporated. The sentence was revised for clarity and to specify the standard approach for this chapter.

**Comment Summary #2:** The commenter recommended revising the first paragraph under the *DDU sampling apparatus B procedure* subsection (Section A.3.1.1) as follows for clarity to include the range,

*“The volume of the air sampled should not exceed 2.0 L ±5%.”*

**Response:** Comment incorporated.

### **Section C.1**

**Comment Summary #1:** The commenter indicated that the term “ballistic fraction” used in the following sentence is not a commonly used term:

“The aerodynamic size distribution defines the manner in which aerosol droplets/particles deposit during inhalation. In use, many inhalers ▲ test products ▲ discharge drug in the form of large droplets or particles (**the "ballistic fraction"**) that leave the inhaler at high velocity and impact on and are captured by the moist surfaces in the mouth, throat, or nose. The remainder of the discharge from the inhaler is the "nonballistic fraction" that is inhaled into the remainder of the respiratory tract.

**Response:** Comment not incorporated. The term “ballistic fraction” was identified as an accurate description.

**Comment Summary #2:** The commenter requested defining the surface roughness of inlet as Ra (arithmetic mean roughness).

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter requested adding a reference to section on stage mensuration (C.1.1) with the following sentence:

“These dimensions are carefully defined and are held constant for all apparatuses.”

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter requested clarification of following sentence in subsection C.1.3 Re-entrainment:

“If temperature or humidity limits for use of the product are stated on the label, it may be necessary to control the temperature and humidity of the air surrounding and passing through the device to conform to those limits. Ambient conditions are presumed unless otherwise specified in individual monographs.”

**Response:** Comment incorporated. Sentence modified/re-arranged as follows for clarity.

“Ambient conditions are presumed unless otherwise specified in individual monographs. However, it may be necessary to control the temperature and humidity of the air surrounding and passing through the device.”

**Comment Summary #5:** The commenter requested removing the example of 5 units for minimum number of drug product units since there are many factors that would result in an assessment of minimum drug product units and therefore quoting 5 as an example is not required.

“An appropriate minimum number of drug product units (e.g., 5) should be tested individually, and the determination for each unit should be performed with the minimum number of actuations justified by the sensitivity of the analytical procedure used to quantitate the deposited drug.”

**Response:** Comment incorporated. Example of 5 units replaced with, “A justified minimum number----”.

**Comment Summary #6:** The commenter requested allowing use of other types of induction ports as appropriate.

**Response:** Comment not incorporated. This chapter covers use of one standard induction port, but any other induction port can be used as long as it is approved by the regulatory agency in question.

### **Table 5:**

**Comment Summary #1:** The commenter requested aligning codes in *Figure 7c* with codes in *Table 1* as deletion of Code B in this table has shifted all the codes up the alphabet by one.

**Response:** Comment incorporated. *Table 1* and *Figure 7c* revised for alignment.

**Comment Summary #2:** The commenter indicated that the tubing between vacuum pump and solenoid valve, and separately between solenoid valve and flow control valve, are commonly described with Code D (or C incorrectly here). Ideally, they would have different codes as the description here implies that Code D tubing can be with or without a tap to P3. This is not optional; only that the P3 tap only exists between the solenoid valve and the flow control valve, not between the vacuum pump and solenoid valve. Hopefully *Figure 7c* provides sufficient clarity if this is to remain unchanged.

**Response:** Comment not incorporated. *Figure 7c* provides sufficient clarity.

## **Figures**

**Comment Summary #1:** The commenter recommended aligning *Table 5* with labeling in *Figure 7c*.

**Response:** Comment incorporated. *Table 5* and *Figure 7c* revised to address mislabeling.

**General Chapter/Sections:** <789> Particulate Matter in Ophthalmic Solutions

**Expert Committee(s):** General Chapters—Dosage Forms

**No. of Commenters:** 2

## **General**

**Comment Summary #1:** The commenter recommends using the term “ocular solution in the chapter rather than ophthalmic solution or injection.

**Response:** Comment incorporated.

## **Introduction**

**Comment Summary #1:** The commenter recommends adding text clarifying what is meant by “certain injection products”.

**Response:** Comment not incorporated. This is already defined in <789> and <771>

**Comment Summary #2:** The commenter suggests clarifying that the test for various ophthalmic products is in <771>

**Response:** Comment incorporated.

## **Microscopic Particles Count Test**

**Comment Summary #1:** The commenter suggests stating that for viscosity solutions the filtration membrane material and porosity should be carefully considered.

**Response:** Comment incorporated.

**General Chapter/Section:** <1059> Excipient Performance

**Expert Committee:** Excipient Test Methods

**No. of Commenters:** 2

**Comment Summary #1:** The commenter wanted to know the reason for renaming functional categories *Chelating and/or Complexing Agents* to *Chelating Agent* and *Wetting and/or Solubilizing Agent* to *Solubilizing Agent*.

**Response:** Comment not incorporated. *Chelating Agent* was considered a more accurate term than *Complexing Agent* based on the description of its *Functional Mechanism*. The term *Wetting Agent* was deleted because it can apply to excipients that are not specifically described in the *Solubilizing Agent* functional category. For example, anything that alters surface tension could be considered a *Wetting Agent* such as alcohols and those excipients are likely better described

in other functional categories. The reason *Wetting* was eliminated from the functional category title was because the description is focused on surfactants specifically and not the variety of molecules that alter surface properties and wetting.

**Comment Summary #2:** In *Physical Properties* of the *Solubilizing Agent* functional category when listing what dictates the solubilization capacity and the melt characteristics of the surfactant, the commenter suggested to consider the addition of polarity.

**Response:** Comment incorporated. The sentence “The solubilization capacity and the melt characteristics of the surfactant are dictated by the type and size of the molecular moieties” was changed to “The solubilization capacity and the melt characteristics of the surfactant are dictated by the type, size and polarity (see HLB) of the molecule.”

**Comment Summary #3:** The commenter noted that each functional category includes sections that describe physical and chemical properties of excipients that fit in that functional category, however, biological, or microbiological properties are not being discussed even though they are mentioned in the *Introduction* as part of performance-related properties and critical material attributes. The commenter recommended including a statement in the *Introduction* to explain that biological and microbiological properties are outside the scope of the chapter.

**Response:** Comment not incorporated. Because excipients in functional categories such as *Antimicrobial Preservatives*, *Tonicity Agent*, and *Permeation Enhancer* inherently possess biological or microbiological properties the following sentence was added to the *Introduction* instead: “Relevant biological and microbiological properties are discussed under Antimicrobial Preservatives, Tonicity Agent, and Permeation Enhancer functional categories.”

**Comment Summary #4:** The commenter suggested adding a table of contents (TOC) at the beginning of the chapter to help readers quickly find where to look for information of interest. This will make it easier for readers to find appropriate functional categories given the length of the chapter.

**Response:** Comment not incorporated. Document Contents can be viewed under Document Info in *USP-NF* online. Document Contents provide the functionality of the TOC requested by the commenter.

**Comment Summary #5:** To be consistent with terminology, the commenter recommended replacing the term “reducing agents” with the term “antioxidant” in the *Functional Mechanism* section of the *Antioxidant* functional category.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested to remove the word “particles” from the sentence “PLGA particles and implants are generally amorphous” appearing in the *Physical Properties* section of the *Biodegradable Polymer* functional category because “amorphous” applies to PLGA as a material, but not specifically the PLGA particles and implants.

**Response:** Comment not incorporated. The sentence “PLGA particles and implants are generally amorphous” was deleted instead because the next sentence in the paragraph described that morphology of the polymer can be amorphous or crystalline.

**Expert Committee-initiated Change #1:** To be consistent with the terminology proposed for lactide (or lactic acid) and/or glycolide (or glycolic acid) polymer in the *Stimuli* article [A Practical Approach to Compendial Nomenclature and Testing For Lactide and Glycolide Polymers and Related Polymeric Excipients](#), which appeared in *PF* 48(2) [Mar.–Apr. 2022], the abbreviations PLGA and PLA for lactide (or lactic acid) and/or glycolide (or glycolic acid) polymer were replaced with LG.

**General Chapter/Sections:** <1079.4> Temperature Mapping for the Qualification of Storage Areas

**Expert Committee(s):** General Chapters—Packaging and Distribution

**No. of Commenters:** 8

## **General**

**Comment Summary #1:** The commenter recommends including the number of repetitions for close/open door study for controlled room and refrigerator/freezer during the thermal mapping study.

**Response:** Comment not incorporated. The number of repetitions and time opened should be determined by the operational use as closely as possible.

**Comment Summary #2:** The commenter recommends discussing the extreme temperature areas where probes should be relocated.

**Response:** Comment not incorporated. Mapping identifies problem areas.

**Comment Summary #3:** The commenter suggests specifying the frequency of requalification.

**Response:** Comment not incorporated. This is a part of risk management and should be a part of change control.

**Comment Summary #4:** The commenter recommends stating that the results of thermal mapping should lead to continuous monitoring devices placement.

**Response:** Comment incorporated

**Comment Summary #5:** The commenter recommends including  $\pm$  for the set point

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggests that mean may not be appropriate for set point.

**Response:** Comment incorporated. Mean may be an appropriate set point, if determined from the results of the mapping.

**Comment Summary #7:** The commenter suggests reviewing all figures to ensure accuracy and consistency.

**Response:** Comment incorporated.

## **1.0 Introduction**

**Comment Summary #1:** The commenter suggests defining the terms “handling” and “transport” throughout the chapter.

**Response:** Comment incorporated.

## **2.0 Scope**

**Comment Summary #1:** The commenter recommends revising to include some additional text and examples to clarify storage during transportation.

**Response:** Comment incorporated

**Comment Summary #2:** The commenter recommends including medical devices within the scope of the chapter.

**Response:** Comment not incorporated. USP is currently exploring the utility of this standard in the medical device and combination product space and will revisit this topic at a later date.

## **3.0 Evaluate Storage Areas**

**Comment Summary #1:** The commenter recommends editing the first bullet to note the dimension of the “wall opening” in the storage areas.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommends editing the eight bullet to note that the loading volume should be one of the factors for temperature mapping.

**Response:** Comment incorporated.

## **3.1 Temperature Monitoring Device Probe Placement**

**Comment Summary #1:** The commenter recommends analyzing data vertically and in scored set-up to cover potential air flow issues.

**Response:** Comment not incorporated. Already included in the proposal

**Comment Summary #2:** The commenter suggests that consistency is needed as to where product will be stored, even for a short time.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggests that product storage height is a relevant parameter.

**Response:** Comment incorporated. The chapter states that the highest product storage must be measured.

**Comment Summary #4:** The commenter suggests that there is no need to have a probed unit next to the thermostat as it should be properly calibrated.

**Response:** Comment incorporated. This is to verify that the thermostat is within acceptable ranges.

#### **4.0 Obtain Monitoring Device**

**Comment Summary #1:** The commenter recommends revising the first bullet to suggest that user obtain extra probes acceptable for use within the intended temperature range.

**Response:** Comment incorporated

**Comment Summary #2:** The commenter recommends clarifying if user must ensure appropriate documentation attesting to device calibration.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggests clarification as to what is expected regarding calibrations (e.g. pre/post calibration, 3 point certificates)

**Response:** Comment not incorporated. It is best to include such topic into <1079.3> and chapter will be reviewed for potential inclusion.

**Comment Summary #4:** The commenter suggests clarification monitoring device sensor accuracy.

**Response:** Comment not incorporated. It is best to include such topic into <1079.3> and chapter will be reviewed for potential inclusion.

#### **5.0 Develop Probe Placement Map Based on Evaluation**

**Comment Summary #1:** The commenter suggests clarifying the meaning and intent of early detection thermostat controller.

**Response:** Comment incorporated.

#### **Figure 9**

**Comment Summary #1:** The commenter recommends including some additional information to help the reader better understand incorrect probe placement outline in *Figure 9*.

**Response:** Comment incorporated

#### **6.0 Schedule and Execute Mapping**

**Comment Summary #1:** The commenter recommends revising the third bullet to include additional guidance on representative load size.

**Response:** Comment incorporated

**Comment Summary #2:** The commenter recommends adding text on the need to test temperature alarm functionality.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter suggests that the door opening length (time) and interval should be determined according to the workflow described in an SOP or a rationale.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggests adding text discussing the need for both internal and external temperature sensors.

**Response:** Comment not incorporated. An edit is not necessary; weather data can be used to determine external temperature.

**Comment Summary #5:** The commenter suggests that the goal of opening door and power failure testing should be defined.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter recommends adding a reference to section 9. *Frequency of Temperature Mapping* that discusses seasonal consideration for mapping.

**Response:** Comment incorporated

**Comment Summary #7:** The commenter suggests including a discussion on the potential impact of large thermal mass differences on recovery time.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggests discussing risky spots, such as dock doors, sky lights, windows, etc., in the mapping.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter recommends referencing <1079>.

**Response:** Comment incorporated

[The following chapter commentary was added on December 26, 2023)

**General Chapter/Section(s):** <1117.1> Microbiological Chapters – Glossary/Multiple Sections

**Expert Committee(s):** General Chapters – Microbiology

**No. of Commenters:** 6

### General

**Comment Summary #1:** The commenter stated that FDA guidances contain glossaries that apply to microbiology-related topics, and the compendium should not define terms that significantly differ from the FDA definitions.

**Response:** Comment partially incorporated. Definitions were carefully considered based on the use and context within the pharmacopeial chapters and alignment with established definitions. Regulations and guidances are key sources of established definitions; the definitions identified do not differ in principle or concept and are in alignment with these sources.

**Comment Summary #2:** The commenter suggested to include definitions that apply to sterilization, including Vacuum cycle, Liquid cycle, Hard goods cycle, and Bowie-Dick test.

**Response:** Comment not incorporated. These terms are not used in the *USP-NF*.

**Comment Summary #3:** The commenter suggested to include definitions for  $F_0$  Value and  $1F_0$  as the number of minutes to kill a specified number of microorganisms with a z-value of  $10^\circ$  at a temperature of  $121.1^\circ$  and the equivalent of 1 minute at  $121.1^\circ$ , respectively.

**Response:** Comment not incorporated. These terms are specific examples of the term “F value,” which is already included in the glossary.

**Comment Summary #4:** The commenter suggested adding definitions for Overkill sterilization, Lag time/Equilibration time during sterilization, and expiry/use before date.

**Response:** Comment partially incorporated. Lag time/Equilibration time and expiry/use before date are not present or are not implicit to the microbiology chapters.

**Comment Summary #5:** The commenter suggested adding a definition for Overkill approach as a sterilization approach based on assuming worst-case conditions (a bioburden of  $10^{-6}$  of highly heat-resistant bacteria).

**Response:** Comment partially incorporated. The term “Overkill sterilization” was added.

**Comment Summary #6:** The commenter suggested adding a definition for Microbiological media.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested including aerobic and anaerobic microorganisms.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested adding a definition for Microbial culture as a microbiological culture, or microbial culture, is a method of multiplying microbial organisms by letting them reproduce in a predetermined culture medium under controlled laboratory conditions.

**Response:** Comment not incorporated. These terms do not appear in the *USP-NF*.

**Comment Summary #9:** The commenter suggested a definition for Test Microorganism be added as cultures used in compendial tests, with traceability back to a strain type listed in a culture collection.

**Response:** Comment not incorporated. "Test Microorganism" is a term that may not necessarily apply to strain types from a culture collection.

**Comment Summary #10:** The commenter requested to add a definition for Comparable, as this word is being used in several general chapters and the growth promotion test.

**Response:** Comment not incorporated. "Comparable" is a term that may be used in different contexts throughout the *USP-NF* and may have varied meanings.

**Comment Summary #11:** The commenter requested to add definitions to distinguish Microbiological Validation and Microbiological Verification, whereas, for microbiological methods, verification includes the demonstration of the method to recover challenge microorganisms added to the test system.

**Response:** Comment not incorporated. Validation is not specific to microbiology chapters, and context on microbiological application is given in <1223>. Verification is not the term used in microbiology test chapters; this is method suitability, which is defined.

## ***Introduction***

**Expert Committee-initiated change #1:** Changes were made to this section by the Expert Committee for the term "biological" to include biological assays.

## ***Glossary***

### ***Aseptic process simulation***

**Comment Summary #12:** The commenter suggested adding worst-case conditions and examples (e.g., duration, interventions) to provide additional context to the aseptic process simulation.

**Response:** Comment not incorporated. The concept of 'worst-case' can be applied in many other contexts. The EC notes that there may be opportunities to describe these conditions in more extensive detail within the relevant chapters. This should be evaluated and addressed during the revision of those specific chapters.

### ***Aseptic processing***

**Comment Summary #1:** The commenter suggested inserting "appropriately validated" in order to emphasize that the process should be validated.

**Response:** Comment not incorporated. "Appropriately validated" is a context-specific term and elaborated on in the relevant chapter.

## ***Autochthonous***



**Comment Summary #1:** The commenter requested the removal of this term because it is no longer used and is only referenced in a chapter published in the *Pharmacopeial Forum*, which is not official.

**Response:** Comment incorporated.

### ***Bioburden***

**Comment Summary #1:** A commenter provided a literature reference for bioburden and suggested using language found in recent publications.

**Response:** Comment incorporated

### ***Cleanroom***

**Comment Summary #1:** The commenter requested consideration to align this definition with published guidance.

**Response:** Comment incorporated.

### ***Contamination control***

**Comment Summary #1:** The commenter suggested rewriting this definition for clarity.

**Response:** Comment incorporated.

### ***Decontamination***

**Comment Summary #1:** The commenter requested to ensure that the USP definition does not contradict other industry and regulatory publications.

**Response:** Comment incorporated.

### ***Endotoxin and Endotoxin calibration analytes***

**Comment Summary #1:** The commenter suggested using the most common definition of endotoxin from PDA TR 82.

**Response:** Comment not incorporated. This definition is not in agreement with the scientific literature, which is aligned on using LPS and endotoxin interchangeably.

### ***Environmental isolate***

**Comment Summary #1:** The commenter recommended inserting “including water systems” to the proposed definition.

**Response:** Comment incorporated.

### ***Isolate***

**Expert Committee-initiated change #1:** This definition was revised to state that an isolate is a pure culture of a microorganism obtained from a microbiological test.

### ***Isolator***

**Comment Summary #1:** The commenter stated that this definition is inconsistent with Aseptic Processing Guidance and could create confusion.

**Response:** Comment incorporated.

### ***Objectionable microorganism***

**Comment Summary #1:** The commenter suggested expanding the scope to align with <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.

**Response:** Comment not incorporated. The term “unique to a product” is applicable to the dosage form and route of administration.

### ***Parametric release***

**Comment Summary #1:** The commenter stated that this definition is not in alignment with the regulatory definition and policy, which could create confusion for users.

**Response:** Comment incorporated.

### ***Physicochemical integrator***

**Comment Summary #1:** The commenter stated that this definition needs to be clarified and recommended to use an already established definition in the regulatory guidance.

**Response:** Comment incorporated.

### ***Spore***

**Comment Summary #1:** The commenter requested to include additional information on the resistance characteristics of spores.

**Response:** Comment not incorporated. The resistance of spores can vary significantly and is provided in more detail in the relevant *USP* chapters.

### ***Sterility assurance level (SAL)***

**Comment Summary #1:** The commenter stated this definition is ambiguous and inconsistent with published definitions.

**Response:** Comment incorporated. Based on this feedback and further discussion, this definition was removed.

### ***Sterilization***

**Comment Summary #1:** The commenter stated that this definition is informal and incomplete, and the definition should be replaced with a more formal definition that is well defined in regulatory references and international standards.

**Response:** Comment incorporated.

### ***Unidirectional airflow***

**Comment Summary #1:** The commenter recommended aligning with already published guidances to avoid unnecessary confusion.

**Response:** Comment incorporated.

**General Chapter/Section:** < 1153> Drug Products Containing Nanomaterials

**Expert Committee(s):** General Chapters-Dosage Forms

**No. of Commenters:** 3

Editorial changes suggested by commenters have been reviewed by the Expert Committee. Some of these changes as approved by the Expert Committee have been incorporated in the chapter. Where they have not been incorporated, the Expert Committee's response is indicated below.

**Comment Summary #1:** The commenter suggested referencing the 2022 *FDA Guidance for Industry – Drug Products, Including Biological Products, that Contain Nanomaterials* in this Chapter.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended adding the following text under the *Excipients* section to aid the reader.

*“Changes in the grade and source of nanomaterial excipients during development should be addressed regarding how these changes may impact the safety or efficacy of the product. When an excipient is deliberately modified into a nanomaterial, an adequate safety evaluation should be provided when the nanomaterial’s safety is not fully demonstrated by existing safety data with respect to level of exposure, duration of exposure, and route of administration.”*

**Response:** Comment incorporated

**Comment Summary #3:** The commenter suggested adding the following to address orthogonal separation techniques under the *Composition and Structure* subheading as these have been shown to provide useful complementary analysis for all the analytes listed in *Table 1*.

*“Photon correlation spectroscopy (dynamic light scattering) also may be used for molecular weight determination. Additionally, complementary multidetector separation techniques like Asymmetrical Flow Field-Flow Fractionation (AF4) can be used for analysis of molecular weight and size distribution of both organic polymeric systems and inorganic systems. At a fundamental level, surfactants and polymer-based systems can be...”*

**Response:** Comment incorporated. Additional article references were also added to the chapter.

**Comment Summary #4:** The commenter recommended revising the following statement under the *Particle Size and Particle Size Distribution* subsection as follows since laser diffraction is able to measure sizes in the micron and submicron range (down to tens of nanometers) and should be mentioned here:

*“Low-angle laser light scattering (laser diffraction) can also be used to measure the particle size and distribution of nanoparticles, although this technique may be somewhat limited depending on the size of the nanomaterials to be measured. Further information on this technique, including methodology, measurement, and analysis is provided in <429> Light Diffraction Measurement of Particle Size.”*

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended revising the text as follows for clarity:

*“Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) can be valuable tools to measure the particle size of individual nanoparticles. Atomic force microscopy (AFM) also may be used to visualize individual particles and may aid in measuring their size, shape, and surface texture. **Due to their complexity, these methods may not be appropriate for routine testing. Other methods such as DLS (see below) can be used to determine particle size as well as distribution.**”*

**Response:** Comment not incorporated. DLS is already included in this section.

**Comment Summary #6:** The commenter suggested including some specific examples of the stability issues one could encounter during development of drug products containing nanomaterials. And proposed the following list of stability issues which may impact nanomaterial properties:

- Changes to nanomaterial size and size distribution
- Changes to nanomaterial morphology
- Self-association (agglomeration/aggregation)
- Changes in surface charge (e.g., zeta potential)
- Changes in dissolution/release rate of drug substance
- Drug leakage from a nanomaterial carrier
- Degradation of nanomaterial (e.g., removal/exchange of surface ligands)
- Interaction with formulation or container closure (e.g., compatibility, denaturing of proteins)
- Changes to the reconstitution properties of the product
- Changes in the solid state (e.g., crystal structure)

**Response:** Comment not incorporated. The suggestion is already covered/implied by the current text.

**Comment Summary #7:** The commenter recommended including “pH” in the list of tests under “*Description of Product Quality Tests*” section as pH is a quality test for many drug products containing nanomaterials (e.g., internal pH for liposome preparations).

**Response:** Comment incorporated. An additional sentence was added: “In addition, depending on the route of administration further tests may be considered.”

**Chapter/Section(s):** <1705> Quality Attributes of Tablets Labeled as Having a Functional Score / Multiple sections

**Expert Committee(s):** General Chapters-Dosage Form Expert Committee

**No. of Commenters:** 6

**Comment Summary #1:** The commenter stated that the splitting tablet test should be performed only using the recommended method by the manufacturer. It might not be suitable to use a tablet splitter when the tablet had a snap-tab design.

**Response:** Comment not incorporated. This chapter is consistent with the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. Any deviation from the chapter can be justified with the relevant regulatory body.

**Comment Summary #2:** Two commenters suggested removing the splitting tablet test using a tablet splitter since the hand splitting of tablet is the least accurate and represents the worst-case scenario.

**Response:** Comment not incorporated. This chapter is consistent with the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. Any deviation from the chapter can be justified with the relevant regulatory body.

**Comment Summary #3:** The commenter stated that elderly patients may not have the hand strength to break the tablet. Thus, splitting by hand would not apply. The commenter suggested adding text for this case.

**Response:** Comment not incorporated. This chapter is consistent with the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. Any deviation from the chapter can be justified with the relevant regulatory body.

**Comment Summary #4:** The commenter suggested adding more details on the suitability of the tablet splitter.

**Response:** Comment not incorporated. This chapter is a guidance chapter and is for information only. USP will leave it to the drug manufacturer to justify that the splitter functions appropriately. The drug manufacturer is encouraged to discuss this topic with the regulatory body for more guidance.

**Comment Summary #5:** The commenter recommended to add the requirement of *Splitting Tablets with Functional Scoring* test acceptance criteria (NLT 75% and NMT 125%) in the current <705>. The commenter considered this requirement a key factor for the success of dissolution testing.

**Response:** Comment partially incorporated. For clarity, the sample preparation for both preparation methods are changed to add a step 5 as the following:

5. Once the criteria in step 4 have been met, then proceed to *Tablet Friability and Dissolution*.

**Comment Summary #6:** The commenter recommends that USP harmonize the *Splitting Tablets* test with *Uniformity of Mass of Subdivided Tablets* in the *European Pharmacopoeia*.

**Response:** Comment not incorporated. USP will consider the recommendation and will direct it to the proper harmonization group.

**Comment Summary #7:** The commenter stated that tests have to be conducted on tablets compressed at the targeted hardness.

**Response:** Comment not incorporated. FDA guidance refers to the hardness range for these tests.

**Comment Summary #8:** The commenter recommends removing the test of friability on split portions, as splitting of the tablets only occurs after transportation, at the administration step.

**Response:** Comment not incorporated. The split portions need to meet the specification of the whole tablet either in process or as finished product. This chapter is consistent with the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. Any deviation from the chapter can be justified with the relevant regulatory body.

**Comment Summary #9:** The commenter requested to use the same criteria that described in the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*: dissolution data on split tablet portions should meet finished-product release requirement. The commenter asked the following to be added: 1. Allowing S1, S2 and S3 stage testing as appropriate; 2. In the case of 2 time points included in the finished-product release specification, only the latter one should be considered.

**Response:** Comment not incorporated. Stage S1 cannot be used as it only used 6 dosage units. The use of 12 dosage units corresponds with the FDA guidance. Chapter text was revised for clarity.

**Comment Summary #10:** The commenter request to allow use statistic models other than the one in the chapter (f2).

**Response:** Comment not incorporated. This chapter is consistent with the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. Any deviation can be justified with the relevant regulatory body.

**Comment Summary #11:** The commenter recommends removing the *Dissolution* acceptance criteria (e.g., The average of the 12 results is NLT quantity (Q), and no result is less than Q–15%.) as this is an informational chapter.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter recommends adding text to clarify that f2 similarity assessment apply only for the extended-release dosage forms if that is the intention of the chapter.

**Response:** Comment partially incorporated. Some clarity texts were added under Immediate-Release Tablet. This chapter is consistent with the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. Any deviation can be justified with the relevant regulatory body.

**Comment Summary #13:** The commenter stated that the chapter text is much too prescriptive.

**Response:** Comment not incorporated. The Subcommittee has gone through the whole chapter text and added more clarity on some sections. This chapter is consistent with the FDA *Guidance for Industry Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation*. Any deviation could be justified with the relevant regulatory body.

**Comment Summary #14:** One commenter requested clarification that if these tests are needed for routine product release test and stability study. The other commenter has a similar request regarding the stability study.

**Response:** Comment incorporated. The SC had clarified these under the *Purpose* section with revised text.

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## Monographs

<b>Monograph/Sections:</b>	Acetazolamide / Organic Impurities
<b>Expert Committee:</b>	Small Molecules 3
<b>No. of Commenters:</b>	1

**Comment Summary #1:** The commenter recommended removing the reporting threshold in the test 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 new general chapter, (477) *User-Determined Reporting Thresholds*, was published in *USP-NF 2024, Issue 1* to address considerations of reporting thresholds.

**Monograph/Section(s):** Aloe Vera Dry Juice / Multiple sections

**Expert Committee(s):** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 6

**Comment Summary #1:** The commenter proposed to include the word “purified” in the *Title*.

**Response:** Comment not incorporated. Current titles for this family of monographs were approved by Nomenclature and Labeling Expert Committee consistent with USP’s [Guideline for Assigning Titles to USP Dietary Supplement Monographs](#).

**Comment Summary #2:** The commenter proposed to include aloe-emodin (aloin and aloin) in the *Definition*.

**Response:** Comment not incorporated. Only determination of aloin is included in the monograph for limit test at this time, so a definition of aloe-emodin is not needed at this time.

**Comment Summary #3:** The commenter proposed to provide a range for identification of  $\alpha$ -glucose,  $\beta$ -glucose, malic acid, and isocitric acid NMR peak locations with the same  $\pm 0.01$  ppm range in the *Identification*.

**Response:** Comment incorporated as follows consistent with the variability in the rest of the identification section based on the NMR method: add  $\pm 0.01$  ppm for these components as in below.

$\alpha$ -glucose ( $5.20 \pm 0.01$  ppm)

$\beta$ -glucose ( $4.60 \pm 0.01$  ppm)

malic acid ( $4.30 \pm 0.01$  ppm)

isocitric acid ( $4.25 \pm 0.01$  ppm).

**Comment Summary #4:** The commenter pointed out that “Temperature: 25” is missing “C” in the *Composition*.

**Response:** Comment not incorporated. As stated in *General Notices* 8.180, all temperatures in the *USP-NF* are expressed in centigrade (Celsius), unless otherwise indicated.

**Comment Summary #5:** In *Absence of Specified Microorganisms <2022>*, the commenter recommended adding the test for absence of *Staphylococcus aureus*. The comment noted that this is a common food pathogen that is tested for quality control. In FDA’s *Bad Bug Book* it is described that “*S. aureus* is a versatile human pathogen capable of causing staphylococcal food poisoning, toxic shock syndrome, pneumonia, postoperative wound infection, and nosocomial bacteremia.”

**Response:** Comment not incorporated. This may be considered for a future revision upon the receipt of supporting data.

**Comment Summary #6:** Under *Table 1*, the commenter pointed out that “50° water bath” is missing “C” in *Specific Tests, Limit of Anthrone Glycosides*

**Response:** Comment not incorporated. As stated in *General Notices* 8.180, all temperatures in the *USP-NF* are expressed in centigrade (Celsius), unless otherwise indicated.

**Monograph/Section(s):** Aloe Vera Leaf Juice / Multiple sections

**Expert Committee(s):** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 6

**Comment Summary #1:** The commenter proposed to include the word “purified” in the *Title*.

**Response:** Comment not incorporated. Current titles for this family of monographs were approved by Nomenclature and Labeling Expert Committee consistent with USP's [Guideline for Assigning Titles to USP Dietary Supplement Monographs](#).

**Comment Summary #2:** The commenter proposed to include aloe-emodin (aloins and aloe-emodin) in the *Definition*.

**Response:** Comment not incorporated. Only determination of aloins is included in the monograph for limit test at this time, so a definition of aloe-emodin is not needed at this time.

**Comment Summary #3:** The commenter proposed to provide a range for identification of  $\alpha$ -glucose,  $\beta$ -glucose, malic acid, and isocitric acid NMR peak locations with the same  $\pm 0.01$  ppm range in the Identification.

**Response:** Comment incorporated as follows consistent with the variability in the rest of the identification section based on the NMR method: add  $\pm 0.01$  ppm for these components as in below.

$\alpha$ -glucose ( $5.20 \pm 0.01$  ppm)

$\beta$ -glucose ( $4.60 \pm 0.01$  ppm)

malic acid ( $4.30 \pm 0.01$  ppm)

isocitric acid ( $4.25 \pm 0.01$  ppm).

**Comment Summary #4:** The commenter pointed out that "Temperature: 25°" is missing "C" in the Composition.

**Response:** Comment not incorporated. As stated in *General Notices* 8.180, all temperatures in the *USP-NF* are expressed in centigrade (Celsius), unless otherwise indicated.

**Comment Summary #5:** In *Absence of Specified Microorganisms <2022>*, the commenter recommended adding the test for absence of *Staphylococcus aureus*. The comment noted that this is a common food pathogen that is tested for quality control. In FDA's Bad Bug Book it is described that "S. aureus is a versatile human pathogen capable of causing staphylococcal food poisoning, toxic shock syndrome, pneumonia, postoperative wound infection, and nosocomial bacteremia."

**Response:** Comment not incorporated. This may be considered for a future revision upon the receipt of supporting data.

**Comment Summary #6:** Under *Table 1*, the commenter pointed out that "50° water bath" is missing "C" in *Specific Tests, Limit of Anthrone Glycosides*

**Response:** Comment not incorporated. As stated in *General Notices* 8.180, all temperatures in the *USP-NF* are expressed in centigrade (Celsius), unless otherwise indicated.

**Monograph/Sections:** Aloe Vera Leaf Juice Concentrate/Multiple

**Expert Committee(s):** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 6

**Comment Summary #1:** The commenter proposed to include the word "purified" in the *Title*.

**Response:** Comment not incorporated. Current titles for this family of monographs were approved by Nomenclature and Labeling Expert Committee consistent with USP's [Guideline for Assigning Titles to USP Dietary Supplement Monographs](#).

**Comment Summary #2:** The commenter proposed to include aloe-emodin (aloins and aloe-emodin) in the *Definition*.

**Response:** Comment not incorporated. Only determination of aloins is included in the monograph for limit test at this time, so a definition of aloe-emodin is not needed at this time.

**Comment Summary #3:** The commenter proposed to provide a range for identification of  $\alpha$ -glucose,  $\beta$ -glucose, malic acid, and isocitric acid NMR peak locations with the same  $\pm 0.01$  ppm range in the Identification.

**Response:** Comment incorporated as follows consistent with the variability in the rest of the identification section based on the NMR method: add  $\pm 0.01$  ppm for these components as in below.

A-glucose ( $5.20 \pm 0.01$  ppm)  
 $\beta$ -glucose ( $4.60 \pm 0.01$  ppm)  
malic acid ( $4.30 \pm 0.01$  ppm)  
isocitric acid ( $4.25 \pm 0.01$  ppm).

**Comment Summary #4:** The commenter pointed out that “Temperature: 25°” is missing “C” in the Composition.

**Response:** Comment not incorporated. As stated in *General Notices* 8.180, all temperatures in the *USP-NF* are expressed in centigrade (Celsius), unless otherwise indicated.

**Comment Summary #5:** In *Absence of Specified Microorganisms <2022>*, the commenter recommended adding the test for absence of *Staphylococcus aureus*. This is a common food pathogen that is tested for quality control. In FDA’s Bad Bug Book it is described that “*S. aureus* is a versatile human pathogen capable of causing staphylococcal food poisoning, toxic shock syndrome, pneumonia, postoperative wound infection, and nosocomial bacteremia.”

**Response:** Comment not incorporated. This may be considered for a future revision upon the receipt of supporting data.

**Comment Summary #6:** Under *Table 1*, the commenter pointed out that “50° water bath” is missing “C” in *Specific Tests, Limit of Anthrone Glycosides*

**Response:** Comment not incorporated. As stated in *General Notices* 8.180, all temperatures in the *USP-NF* are expressed in centigrade (Celsius), unless otherwise indicated.

**Monograph/Section(s):** Aspartame Acesulfame

**Expert Committee(s):** Simple Excipients

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested that USP clarify the process for determining whether a monograph can be removed without impact to stakeholders. The commenter wanted to know how USP determined that Aspartame Acesulfame is no longer produced in the United States; not used in any human or veterinary drug products currently marketed in the United States; and whether USP has considered the potential impact of removing the monograph on international excipient and drug product manufacturers, since regions of the world without local pharmacopeias rely on the *USP-NF*.

**Response:** Comment not incorporated. USP has an internal process for omitting monographs for which triggers, necessary data, and step by step instructions are well-defined. In the case of Aspartame Acesulfame, USP worked closely with the sponsor of the monograph and reference standard. The sponsor has confirmed that they no longer manufacture and/or sell Aspartame Acesulfame in the United States. In addition, the sponsor was not aware of other manufacturers of Aspartame Acesulfame in the United States market. USP can share the details of the omission process upon request.

**Monograph/Section(s):** Bitter Orange Young Fruit / Multiple sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 4

### **Definition**

**Comment Summary #1:** The commenter suggested revising the second sentence of the *Definition* for the proposed Bitter Orange Young Fruit monograph with the following: "The fallen young fruit at an early stage of development from bitter orange trees is collected whole or sliced in half, and either dried in the sun or at a low temperature."



**Response:** Comment incorporated.

#### **Identification**

**Comment Summary #2:** The commenter questioned if the synephrine positional isomers are the same in the samples as the standards (ortho, para, meta).

**Response:** Comment not incorporated. *p*-Synephrine often exists in plants in the *Citrus* family. The USP Synephrine RS is a racemic *p*-synephrine and matches the synephrine in Bitter Orange Young Fruit.

**Comment Summary #3:** The commenter questioned if the flavonoids were visible after treating the HPTLC plate with *Derivatization reagent B*.

**Response:** Comment not incorporated. The USP HPTLC test spotted 5 flavonoids as reference standards: the flavonoids neohesperidin, naringin, narirutin, and hesperidin were not visible after treating the plate with *Derivatization reagent B*. Nobiletin showed up as a light-yellow band in the upper-third section, while synephrine showed up as a brown band in the lower-half section after treating the plate with *Derivatization reagent B*.

**Comment Summary #4:** The commenter is concerned that coeluting flavonoids and biogenic amines are possibly creating confounding interferences.

**Response:** Comment not incorporated. In the lower-half section, the flavonoids are observed after treating the plate with *Derivatization reagent A*, while synephrine is not visible; after treating the plate with *Derivatization reagent B*, synephrine is observed but the flavonoids are not visible.

**Monograph/Section(s):** Bitter Orange Young Fruit Powder / Multiple sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 4

#### **Definition**

**Comment Summary #1:** The commenter suggested revising the first sentence of the *Definition* for the proposed Bitter Orange Young Fruit Powder monograph with the following: "...consists of the dried fallen young fruit at an early stage of development from bitter orange trees, *Citrus x aurantium*..."

**Response:** Comment incorporated.

#### **Identification**

**Comment Summary #2:** The commenter questioned if the synephrine positional isomers are the same in the samples as the standards (ortho, para, meta).

**Response:** Comment not incorporated. *p*-Synephrine often exists in the plants in the *Citrus* family. The USP Synephrine RS is a racemic *p*-synephrine and matches the synephrine in Bitter Orange Young Fruit Powder.

**Comment Summary #3:** The commenter questioned if the flavonoids were visible after treating the HPTLC plate with *Derivatization reagent B*.

**Response:** Comment not incorporated. The USP HPTLC test spotted 5 flavonoids as reference standards: the flavonoids neohesperidin, naringin, narirutin, and hesperidin were not visible after treating the plate with *Derivatization reagent B*. Nobiletin showed up as a light-yellow band in the upper-third section, while synephrine showed up as a brown band in the lower-half section after treating the plate with *Derivatization reagent B*.

**Comment Summary #4:** The commenter is concerned that coeluting flavonoids and biogenic amines are possibly creating confounding interferences.

**Response:** Comment not incorporated. In the lower-half section, the flavonoids are observed after treating the plate with *Derivatization reagent A*, while synephrine is not visible; after treating the plate with *Derivatization reagent B*, synephrine is observed but the flavonoids are not visible.

**Monograph/Section(s):** Bumetanide / Organic Impurities  
**Expert Committee:** Small Molecules 2  
**No. of Commenters:** 4

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

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee may consider incorporating this new approach in future revisions, as applicable.

**Comment Summary #2:** The commenter expressed difficulty in dissolving the USP Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate RS in the *Standard stock solution* preparation.

**Response:** Comment incorporated. The concentration of USP Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate RS was changed from 0.05 mg/mL to 0.005 mg/mL to aid better solubility.

**Comment Summary #3:** The commenter indicated the *Resolution* requirement between bumetanide related compound A and bumetanide related compound B could not be achieved.

**Response:** Comment incorporated. The *Resolution* requirement was revised from NLT 25 to NLT 20 based on supporting data.

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

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

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will be published in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Comment Summary #2:** The commenter stated that disintegration of Tablets for the preparation of stock solutions was not achieved in the *Assay* and *Organic Impurities* tests and may not be possible only with methanol as *Diluent*.

**Response:** Comment not incorporated. The Expert Committee determined that the method is consistent with the validation data. The Expert Committee will consider future revisions to this monograph upon receipt of supporting data.

**EC-initiated Change#1:** The Expert Committee decided to update the resolution requirement in the test for *Organic Impurities* from NLT 25 to NLT 20 to align with Bumetanide API monograph.

**Monograph/Section(s):** Bumetanide Injection / Organic impurities  
**Expert Committee:** Small Molecules 2  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended that USP work with the approved manufacturers to ensure the proposed requirements can be met by all manufacturers to avoid drug shortage.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed acceptance criteria are consistent with the currently official monograph and should not pose any risk to the drug product manufacturers.

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

**Response:** Comment not incorporated. A new USP general chapter, <477> *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**EC-initiated Change#1:** The Expert Committee decided to update the resolution requirement in the test for *Organic Impurities* from NLT 25 to NLT 20 to align with the *Bumetanide* API monograph.

**Monograph/Section(s):** Carrageenan / Identification B and Identification D

**Expert Committee(s):** Complex Excipients

**No. of Commenters:** 1

**Comment Summary #1:** The commenter suggested to include a reference to specific drying process in the *Total Ash* section.

**Response:** Comment not incorporated. The Carrageenan monograph is an umbrella monograph which supports multiple grades of commercially available Carrageenan. The Expert Committee cannot include a specific condition which might be applicable to only certain grades of Carrageenan material. Moreover, the Expert Committee determined that the comment cannot be incorporated due to lack of supporting data.

**Monograph/Section(s):** Cefepime Hydrochloride / Organic impurities

**Expert Committee:** Small Molecules 1

**No. of Commenters:** 1

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

**Response:** Comment not incorporated. A new USP general chapter, <477> *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Comment Summary #2:** The commenter commented that the reporting threshold of NMT 0.2% is not suitable for the thiazolyloxime acetaldehyde impurity.

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

**Monograph/Section(s):** *Cinnamomum cassia* Bark / Multiple sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 3

### **Specific Tests**

**Comment Summary #1:** The commenter suggested changing volatile oil content setting from NLT 1.5% to NLT 1.2% to be harmonized with other pharmacopeias.

**Response:** Comment incorporated and is consistent with supporting data.

**Comment Summary #2:** The commenter commented that other pharmacopeial standards report the width and thickness differently and suggested changing the width and thickness of *Cinnamomum cassia* Bark to be consistent with or cover those in the monographs of other pharmacopoeias.

**Response:** Comment incorporated and is consistent with supporting data. The *Cinnamomum cassia* Bark monograph under *Macroscopic* is changed the width from 3-10 cm to 1.5 -10 cm which is same as that from PhYN and to cover those from ISO (2 cm), JP (1.5-5 cm) and KP (1.5-5 cm); and the thickness is changed from 0.2-0.8 cm to 0.1-0.8 cm which is same as that from PhYN; and to cover those from HKCCMS (0.1-0.6 cm), ISO (0.3-0.6 cm), JP (0.1-0.5 cm) and KP (0.1-0.5 cm).

**Comment Summary #3:** The commenter suggested under *Macroscopic* adding “In comparison, the bark of *C. verum* is only 0.2-0.8 mm thick and occurs in closely packed compound quills made up of single or double quills.”

**Response:** Comment incorporated. The commenter’s suggested content is added.

**Monograph/Section(s):** *Cinnamomum cassia* Bark Powder / Multiple sections

**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**No. of Commenters:** 2

### **Specific Tests**

**Comment Summary #1:** The commenter expressed that setting the same content requirement of volatile oil for the bark pieces and the bark powder may be problematic. Other pharmacopeial standards have set the volatile oil content requirement different for the bark and bark powder with lower content requirement for the bark powder as typical.

**Response:** Comment incorporated. The *Cinnamomum cassia* Bark Powder monograph set the volatile oil content to NLT 1.0%, lower than NLT 1.2% required in other *Cinnamomum cassia* Bark monographs because essential oil is more easily lost from the powder than from the raw plant material.

**Comment Summary #2:** The commenter suggested under *Microscopic* adding “This powder is very similar to *C. verum* bark powder but may be distinguished by the larger size of the starch granules (often > 10 um in diameter vs rarely > 10 um), and the abundance of cork fragments.”

**Response:** Comment incorporated for clarity.

**Monograph/Section(s):** Cocoyl Caprylocaprate / Specific Tests

**Expert Committee(s):** Complex Excipients

**EC-initiated Change #1:** In the *Specific Tests* section, the *Water Determination*, flexible approach has been updated to <921> *Water Determination, Method I, Method Ic*: NMT 0.1%.

**Monograph/Sections:** Diluted Isosorbide Mononitrate / Multiple sections

**Expert Committee:** Small Molecules 2

**No. of Commenters:** 1

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

**Response:** Comment not incorporated. A new USP general chapter, <477> *User-Determined Reporting Thresholds*, which was published in PF 48(5) and will become official in *USP-NF*

2024 Issue 1, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**EC-Initiated Change #1:** The chemical name for the USP Diluted Isosorbide Mononitrate Related Compound A RS in the *Reference Standards* section was changed to include “in lactose” to align with the USP Reference Standard label information for USP Diluted Mononitrate Related Compound A RS. 1,4:3,6-Dianhydro-D-glucitol 2-nitrate in lactose

**Monograph/Sections:** Etodolac 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 as it will vary based on product-specific factors.

**Response:** Comment not incorporated. A new USP general chapter, (477) User-Determined Reporting Thresholds, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Monograph/Section(s):** Fludeoxyglucose F 18 Injection / Radiochemical Purity  
**Expert Committee:** Small Molecules 4  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended including a range of 0.2 mm - 0.25 mm for the absorbent to provide flexibility for users instead of replacing 0.25 mm with 0.2 mm in the test for *Radiochemical purity*.

**Response:** Comment incorporated.

**Monograph/Section(s):** Formic Acid / Assay  
**Expert Committee(s):** Simple Excipients

**EC-initiated Change #1:** In the *Assay*, the statement describing that each mL of sodium hydroxide is equivalent to 46.03 mg of formic acid has been updated into a titrimetric equation for consistency to align with *USP* style.

**Monograph/Section:** Hydrocortisone Compounded Oral Solution  
**Expert Committee:** Compounding  
**Number of Commenters:** 1

**Comment Summary #1:** A commenter indicates the monograph includes proprietary ingredients as an excipient, and 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 to 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 information was obtained from the manufacturer. Nothing in the *USP-NF* should be construed as a representation as to such intellectual property rights. Furthermore, the inclusion in the *USP-NF* of a monograph, general chapter, or other reference addressing any substance, product, method, test, assay, or equipment with respect to which intellectual property rights may exist shall not be deemed, and is not intended as, a grant of, or authority to exercise, any right or privilege protected by such patent, trademark, copyright,

and/or trade secret. All such rights and privileges are vested in their respective owners. See also the Intellectual Property Policy Section in USP's Commitment to Confidentiality: <https://www.usp.org/sites/default/files/usp/document/about/usp-commitment-to-confidentiality.pdf>

**Comment Summary #2:** A commenter notes the following footnote: "This formulation meets the requirements in *Antimicrobial Effectiveness Testing* (51)". As currently written, the commenter states that it is unclear what the footnote is trying to convey. The commenter recommends revising the footnote as follows: "Preparation has passed *Antimicrobial Effectiveness Testing* (51)".

**Response:** Comment incorporated for clarity.

**Comment Summary #3:** A commenter notes the following criteria for *Appearance*: "Cloudy, white suspension with visible particulates". The commenter states that they find the inclusion of "with visible particulates" in the criteria unnecessary and potentially confusing and recommends revising the criteria as follows: "Cloudy, white suspension."

**Response:** Comment incorporated for clarity.

**Comment Summary #4:** A 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 in.

**Response:** Comment incorporated.

**Monograph/Sections:** Isosorbide Mononitrate Tablets / Multiple Sections

**Expert Committee:** Small Molecules 2

**No. of Commenters:** 1

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

**Response:** Comment not incorporated. USP is considering the issue of the removing reporting thresholds from certain monographs. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**EC-Initiated Change #1:** The chemical name for the USP Diluted Isosorbide Mononitrate Related Compound A RS in the *Reference Standards* section was changed to include "in lactose" to align with the USP Reference Standard label information for USP Diluted Mononitrate Related Compound A RS. 1,4:3,6-Dianhydro-D-glucitol 2-nitrate in lactose

**Monograph/Sections:** Liothyronine Sodium Injection / Organic Impurities

**Expert Committee:** Small Molecules 3

**No. of Commenters:** 2

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

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Comment Summary #2:** The commenter noted that not all impurities listed in *Table 2* and *Table 3* have chemical names in the footnote and recommended adding them.

**Response:** Comment incorporated. Additional footnotes with chemical information added.

**Comment Summary #3:** Commenter suggested a lower concentration for the *Sensitivity solution* in the test method.

**Response:** Comment not incorporated. The current concentration of the *Sensitivity solution* better aligns with the reporting threshold in the test method.

**Monograph/Section(s):** Methyltestosterone / Organic impurities

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended widening the acceptance criteria for androstenedione impurity to be consistent with ICH Q3A Qualification Threshold, in the test for *Organic Impurities*.

**Response:** Comment incorporated. The limit for androstenedione impurity has been widened from NMT 0.10% to NMT 0.15% in accordance with ICH Q3A.

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

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Monograph/Sections:** Nadolol Tablets / Organic Impurities

**Expert Committee:** Small Molecules 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested a note be added in *Table 3* for Nadolol related compound A impurity indicating “if present” or “this is a formulation specific impurity.”

**Response:** Comment not incorporated. The acceptance criteria in *Table 3* are consistent with what has been approved by the FDA.

**Monograph/Section(s):** Nortriptyline Hydrochloride Capsules / Organic impurities

**Expert Committee:** Small Molecules 4

**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended including key degradation products with limits consistent with what has been approved by the FDA.

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

**Comment Summary #2:** The commenter recommended including chemical information for all impurities listed in the impurity table.

**Response:** Comment not incorporated. The chemical information for all the specified impurities is listed in the proposal and is consistent with *USP* style.

**Comment Summary #3:** The commenter recommended removing the “Amitriptyline related compound B” and “Cyclobenzaprine related compound B” from *Table 1*.

**Response:** Comment incorporated. The relative retention times for cyclobenzaprine related compound B and Nortriptyline are included as a ‘Note’ within the *System suitability* section. The amitriptyline related compound B impurity is not used in the monograph and has been removed.

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

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Comment Summary #5:** The commenter requested to widen the limit for total degradation products to be consistent with what has been approved by the FDA.

**Response:** Comment incorporated. The acceptance criteria for total degradation products has been widened from NMT 0.4% to NMT 1.5%.

**Monograph/Section(s):** Pirfenidone / Multiple sections

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 3

**Comment Summary #1:** The commenter recommended updating the acceptance criteria for Assay to be consistent with what has been approved by the FDA.

**Response:** Comment incorporated. The *Acceptance criteria* has been changed from “98.5% to 101.5%” to “98.0% to 102.0%”. The *Definition* section is updated to reflect the changes.

**Comment Summary #2:** The commenter recommending widening the *Relative standard deviation* requirement in the Assay to be consistent with <621>.

**Response:** Comment incorporated. The *Relative standard deviation* requirement has been widened from NMT 0.55% to NMT 0.73% for consistency with <621>.

**Comment Summary #3:** The commenter indicated that the impurity profile for their in-house material is different and requested replacing the proposed procedure with their in-house procedure in the test for *Organic Impurities*.

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

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Monograph/Section(s):** Pirfenidone Capsules / Organic impurities

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 3

**Comment Summary #1:** The commenter recommended revising the acceptance criteria for Pirfenidone related compound A, Pirfenidone related compound B, Phenol, and Bromobenzene to be consistent with what has been approved by the FDA.

**Response:** Comment partially incorporated. The Expert Committee determined that the listed specified impurities are process related and therefore determined that they should not be included in the impurity table.

**Comment Summary #1:** The commenter recommended removing the specified impurities listed in *Table 3* as they are process related, in the test for *Organic Impurities*.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter indicated that the information for *Solution B* is not included in the test for *Organic Impurities*.

**Response:** Comment incorporated. The typo/error has been fixed to include *Solution B* as acetonitrile.



**Comment Summary #3:** The commenter recommended widening the acceptance criteria for total degradation products from NMT 0.30% to NMT 0.50%, 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 #4:** The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in PF 48(5) and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Monograph/Section(s):** Pirfenidone Tablets / Organic impurities

**Expert Committee:** Small Molecules 5

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended widening the acceptance criteria for total degradation products from NMT 0.30% to NMT 0.50%, 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.

**Monograph/Section(s):** Pyrimethamine / Organic impurities

**Expert Committee:** Small Molecules 1

**No. of Commenters:** 1

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

**Response:** Comment not incorporated. A new USP general chapter, (477) *User-Determined Reporting Thresholds*, which was published in PF 48(5) and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Monograph/Section:** Sodium Bicarbonate Compounded Injection / Multiple sections

**Expert Committee:** Compounding

**Number of Commenters:** 1

**Comment Summary #1:** Commenter suggests including information on what the final yield of each preparation should be. This would help ensure consistent reproducibility of the compounded preparations.

**Response:** Comment not incorporated. *General Notices* 5.20.20.1 in *Compounded Preparations* states that, "Deviation from the specified processes or methods of compounding, although not from the ingredients or proportions thereof, may occur provided that the finished preparation conforms to the relevant standards and to preparations produced by following the specified process."

**Comment Summary #2:** Commenter recommends that the *Packaging and Storage* section state what material (e.g., glass or plastic), size, and type of container closure system the BUD testing was performed in, as that information would help guide appropriate container closure selection.

**Response:** Comment incorporated.

**Comment Summary #3:** Commenter notes that this monograph may produce a drug product that is essentially a copy of an FDA-approved product, as described in the final guidance document entitled “Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act.” They recommend using only FDA-approved drug products unless the patient has a specific medical need (e.g., an allergy) that cannot be met by the approved drug products. Because they do not go through the drug approval process, compounded drugs should only be used when an FDA-approved product is not available to meet the medical needs of an individual patient.

**Response:** Comment not incorporated. USP compounded preparation monographs may be used by compounders to prepare specific formulations for patients for whom there are no suitable commercially available products.

**Comment Summary #4:** Commenter suggests including additional information regarding how the sodium bicarbonate is to be dissolved (e.g., heating or stirring).

**Response:** Comment not incorporated. Additional information about how the sodium bicarbonate was dissolved was not included in the methods.

**Comment Summary #5:** Commenter recommends including Appearance and Filter Integrity testing in the *Specific Tests* section as described in <1229.4>. Additionally, the commenter recommended that a visual inspection of the product be conducted along with a statement on whether the product can be reheated to dissolve the particles. Specific details on heating instructions, number of times the product can be heated and reheated to dissolve, and what to do if the product still has visible particles.

**Response:** Comment partially incorporated. The changes to the *Appearance* section are incorporated. The Filter integrity testing is already specified in <797>.

**Monograph/Section(s):** Valganciclovir for Oral Solution / Multiple sections

**Expert Committee:** Small Molecules 1

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended that USP work with the approved manufacturers to ensure that the proposed requirements can be met by all manufacturers to avoid a drug shortage.

**Response:** Comment not incorporated. The Expert Committee determined that the proposed changes are consistent with supporting data and that the product has been removed from the FDA drug shortage list.

**Comment Summary #2:** The commenter indicated that the *Acceptance criteria* in the *Definition* and *Assay* are different from what has been approved by the agency.

**Response:** Comment incorporated. The *Acceptance criteria* has been widened from NLT 91.0% and NMT 107.0% to NLT 90.0% and NMT 110.0%.

**Comment Summary #3:** The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

**Response:** Comment not incorporated. A new USP general chapter, <477> *User-Determined Reporting Thresholds*, which was published in *PF 48(5)* and will become official in *USP-NF 2024 Issue 1*, supports a flexible reporting threshold to accommodate product-specific factors. The Expert Committee will consider incorporating this new approach in future revisions, as applicable.

**Comment Summary #4:** The commenter recommended removing Methoxymethylguanine, Isovalganciclovir, peak 1 and Isovalganciclovir, peak 2 from *Table 2*, in the test for *Organic impurities*, as they are process impurities and should not be listed in a public standard for drug products and removing Valganciclovir diester analog from *Table 2* as it is controlled in the drug substance.

**Response:** Comment incorporated. Additionally, the footnote in *Table 2* is updated to reflect the changes by removing the chemical information for the impurities and the statement about process impurities. The relative retention times for Methoxymethylguanine, Valganciclovir diester analog, Isovalganciclovir, peak 1, and Isovalganciclovir, peak 2 are added to the Analysis section.

**EC-initiated Change#1:** The Expert Committee updated the terminology for the text regarding unspecified impurities in the test for *Organic impurities, Table 2*, from “Any individual unspecified degradation product” to “Any unspecified degradation product” to align with ICH terminology.