



## **Commentary**

### **Second Supplement to USP 43–NF 38**

**June 1, 2020**

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

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees' responses to public comments on proposed revisions. If there is a difference between the contents of the *Commentary* and the official text, the official text prevails. In case of a dispute or question of interpretation, the language of the official text, alone and independent of the *Commentary*, shall prevail.

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**Comments were received for the following when they were proposed in PF:**

**General Chapters**

[<5> Inhalation and Nasal Drug Products General Information and Product Quality Tests](#)  
[<121> Insulin Assays](#)  
[<381> Elastomeric Components in Injectable Pharmaceutical Product Packaging/Delivery Systems](#)  
[<382> Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems](#)  
[<607> Pharmaceutical Foams–Product Quality Tests](#)  
[<659> Packaging and Storage Requirements](#)  
[<671> Containers–Performance Testing](#)  
[<698> Deliverable Volume](#)  
[<755> Minimum Fill](#)  
[<785> Osmolality and Osmolarity](#)  
[<1079> Risks and Mitigation Strategies for the Storage and Transportation of Finished Drug Products](#)  
[<1079.2> Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products](#)  
[<1087> Apparent Intrinsic Dissolution - Dissolution Testing Procedures for Rotating Disk and Stationary Disk](#)  
[<1092> The Dissolution Procedure–Development and Validation](#)  
[<1105> Immunological Test Methods-Surface Plasmon Resonance](#)  
[<1108> Assays to Evaluate Fragment Crystallizable \(Fc\)-Mediated Effector Function](#)  
[<1381> Assessment of Elastomeric Component Used in Injectable Pharmaceutical Product Packaging/Delivery Systems](#)  
[<1382> Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems](#)  
[<1430.3> Analytical Methodologies Based on Scattering Phenomena- Dynamic Light Scattering](#)  
[<1430.6> Analytical Methodologies Based on Scattering Phenomena- Particle Counting Via Light Scattering](#)  
[<1430.7> Analytical Methodologies Based on Scattering Phenomena- Nephelometry and Turbidimetry](#)  
[<1603> Good Cascade Impactor Practices](#)  
[<1671> The Application of Moisture Vapor Transmission Rates for Solid Oral Dosage Forms in Plastic Packaging Systems](#)

**Monographs**

[Bitter Orange Fruit Flavonoids Dry Extract](#)  
[Budesonide Nasal Spray](#)  
[Ciprofloxacin Ophthalmic Solution](#)  
[Cod Liver Oil](#)  
[Cod Liver Oil Capsules](#)  
[D-Chiro-Inositol](#)  
[Dicyclomine Hydrochloride](#)  
[Dicyclomine Hydrochloride Injection](#)  
[Dicyclomine Hydrochloride Oral Solution](#)  
[Doxazosin Tablets](#)  
[Fish Oil Omega-3 Acid Ethyl Esters Concentrate](#)  
[Hydroxychloroquine Sulfate](#)

[Indian Barberry Stem](#)  
[Indian Barberry Stem Dry Extract](#)  
[Indian Barberry Stem Powder](#)  
[Magnesia Tablets](#)  
[Magnesium Carbonate](#)  
[Magnesium Hydroxide](#)  
[Magnesium Hydroxide Paste](#)  
[Magnesium Oxide](#)  
[Magnesium Oxide Capsules](#)  
[Magnesium Oxide Tablets](#)  
[Magnesium Trisilicate](#)  
[Milk of Magnesia](#)  
[Piroxicam](#)  
[Potassium Carbonate](#)  
[Pseudoephedrine Hydrochloride Oral Solution](#)  
[Pummelo Peel](#)  
[Pummelo Peel Flavonoids Dry Extract](#)  
[Pummelo Peel Powder](#)  
[Thalidomide](#)  
[Triamcinolone Acetonide Nasal Spray](#)  
[Vincristine Sulfate Injection](#)  
[Vincristine Sulfate for Injection](#)

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

**General Chapters**

<232> Elemental Impurities—Limits  
<691> Cotton

**Monographs**

Absorbable Dusting Powder  
Absorbable Surgical Suture  
Acetaminophen and Diphenhydramine Citrate Tablets  
Amphotericin B Cream  
Amphotericin B Lotion  
Amphotericin B Ointment  
Ampicillin and Probenecid for Oral Suspension  
Aspirin, Caffeine, and Dihydrocodeine Bitartrate Capsules  
Aztec Marigold Zeaxanthin Extract  
Barium Hydroxide Lime  
Bromodiphenhydramine Hydrochloride Oral Solution  
Brompheniramine Maleate Injection  
Calcium Glubionate Syrup  
Carbenicillin for Injection  
Carbenicillin Disodium  
Carbenicillin Indanyl Sodium  
Carbenicillin Indanyl Sodium Tablets  
Cefoperazone Injection  
Cefoperazone for Injection  
Ceforanide  
Ceforanide for Injection

Cefotiam Hydrochloride  
Cefotiam for Injection  
Cefpiramide  
Cefpiramide for Injection  
Cellulose Sodium Phosphate  
Cellulose Sodium Phosphate for Oral Suspension  
Cephalothin Injection  
Cephalothin for Injection  
Chloramphenicol Cream  
Chloramphenicol Ophthalmic Solution  
Chloramphenicol for Ophthalmic Solution  
Chloramphenicol Oral Solution  
Chloramphenicol Otic Solution  
Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension  
Chlorpheniramine Maleate Injection  
Clofibrate  
Clofibrate Capsules  
Codeine Phosphate Injection  
Cromolyn Sodium Inhalation Powder  
Cyclandelate  
Cyromazine  
Dicyclomine Hydrochloride Capsules  
Dicyclomine Hydrochloride Tablets  
Dihydrotachysterol  
Dihydrotachysterol Capsules  
Dihydrotachysterol Oral Solution  
Dihydrotachysterol Tablets  
Dipivefrin Hydrochloride Ophthalmic Solution  
Dirithromycin  
Dirithromycin Delayed-Release Tablets  
Dyphylline Injection  
Dyphylline Oral Solution  
Dyphylline Tablets  
Ergoloid Mesylates Capsules  
Ergoloid Mesylates Oral Solution  
Estropipate Vaginal Cream  
Ethchlorvynol Capsules  
Ethyl Maltol  
Felbamate Oral Suspension  
Ferumoxsil Oral Suspension  
Fluorometholone Cream  
Furazolidone Oral Suspension  
Furazolidone Tablets  
Isopropamide Iodide Tablets  
Isoproterenol Inhalation Solution  
Isoproterenol Hydrochloride Tablets  
Isoproterenol Sulfate  
Isoproterenol Sulfate Inhalation Aerosol  
Isoproterenol Sulfate Inhalation Solution  
Menadiol Sodium Diphosphate  
Monobenzene

Moricizine Hydrochloride  
Nonabsorbable Surgical Suture  
Pindolol Tablets  
Purified Cotton  
Purified Rayon  
Sodium Ferrous Citrate  
Sodium Fluoride F 18 Injection  
Sterile Erythromycin Gluceptate  
Succinylcholine Chloride  
Sulfabenzamide  
Sulfacetamide  
Sulfadiazine Sodium Injection  
Sulfamethizole Oral Suspension  
Sulfamethoxazole Tablets  
Telmisartan And Amlodipine Tablets  
Testolactone  
Testolactone Tablets  
Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets  
Tigecycline for Injection  
Triple Sulfa Vaginal Cream  
Triple Sulfa Vaginal Inserts  
Trypsin  
Vinblastine Sulfate  
Vinblastine Sulfate for Injection  
Vincristine Sulfate

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### **General Chapters**

**General Chapter/Section:** <5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests  
**Expert Committee(s):** General Chapters—Dosage Forms  
**No. of Commenters:** 4

**Comment Summary #1:** The commenter suggested revising the “Note” in the *Introduction* section as follows to avoid confusion:

“[Note—All references to general information chapters are for informational purposes only, for use as a helpful resource. ~~These chapters are not mandatory unless explicitly called out for application.]”~~”

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter requested inclusion of “Residual Solvents” as quality tests for powder characterization.

**Response:** Comment incorporated.

**Comment #3:** The commenter requested addition of “Description” as a quality test for powder characterization.

**Response:** Comment not incorporated. The section already includes a “Description” test with relevant quality aspects/attributes for consideration.

**Comment #4:** The commenter suggested adding a category of nasal powder in the description for the test for Plume Geometry because if the device is pump dependent, a powder plume will be generated.

**Response:** Comment incorporated.

**Comment #5:** The commenter suggested using the term “Shot Weight” in place of “Valve or Pump Delivery” for clarity.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <121> Insulin Assays  
**Expert Committee:** Biologics Monographs 1 – Peptides and Insulins Expert Committee  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended changing “Store in a cold place” to specify the temperature range of the cold place.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended specifying the minimum time frame between the first and second injection in the Analysis section for the Rabbit Blood Sugar Method.

**Response:** Comment not incorporated. The description provided in the Analysis section is common practice for similar assays.

**Comment Summary #3:** The commenter recommended clarifying the “time of injection” in the Blood Samples section of the Rabbit Blood Sugar Method.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended clarifying the instructions for dilution in the Diluted Standard Solutions and Sample Solutions of In Vitro Cell-Based Bioidentity Test for Insulin Glargine and Insulin Lispro.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended revising the suitability requirement for the signal-to-noise ratio for the system to clearly define the ratio for a set requirement under System Suitability section of In Vitro Cell-Based Bioidentity Test for Insulin Glargine and Insulin Lispro.

**Response:** Comment incorporated. Text was revised to omit sample solutions from the signal-to-noise calculation for System Suitability and from calculation of the background signal in the In Vitro Cell-Based Bioidentity Test for Insulin Glargine and Insulin Lispro section. Additional clarification was provided in the In Vitro Cell-Based Bioidentity Test for Insulin Glargine and Insulin Lispro section to separate Sample Acceptance criteria from System Suitability criteria.

**General Chapter/Sections:** <381> Elastomeric Closures for Injections/Multiple  
**Expert Committee(s):** General Chapters—Packaging and Distribution  
**No. of Commenters:** 4

### General

**Comment Summary #1:** The commenter suggested inserting “elastomeric” before “component” throughout the chapter.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended including language in this chapter to clearly state which parties are responsible for testing.

**Response:** Comment not incorporated. Meeting the requirement of the standard is the responsibility of the end-user.

**Comment Summary #3:** The commenter recommended including a section or table that outlines the difference between Type I and Type II elastomeric components.

**Response:** Comment not incorporated. Section 4.2 contains a paragraph that describes Type I and Type II elastomeric components.

**Comment Summary #4:** The commenter recommended revising Type 'X' to "Type 'X' elastomeric component" throughout the chapter.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended a 5-year delayed implementation period to provide industry an adequate time to implement the requirements.

**Response:** Comment not incorporated. There are no new testing requirements in the chapter.

### ***Introduction***

**Comment Summary #6:** The commenter recommended including a statement that allows the use of a risk-based approach to establish chemical suitability of elastomeric closures.

**Response:** Comment not incorporated. General Chapter <381> is a baseline standard and end-user should determine if other testing is necessary to qualify a component.

### ***Scope***

**Comment Summary #7:** The commenter recommended stating that component functional suitability tests described in this chapter are within scope until <382> is fully implemented.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter recommended stating that medical devices are out of scope.

**Response:** Comment incorporated.

### ***Test Samples***

**Comment Summary #9:** The commenter requested clarification on testing requirements for sterilized components.

**Response:** Comment incorporated.

### ***Biological Reactivity***

**Comment Summary #10:** The commenter recommended adding a statement that in some situations, additional testing beyond <87> and <88> will be necessary.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter recommended revising this section to clearly state that both Type I and Type II elastomeric components are expected to pass the biological reactivity tests.

**Response:** Comment incorporated.

### ***Physicochemical Test***

**Comment Summary #12:** The commenter recommended using the term "suitable" glass instead of "Type I" glass.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter recommended revising "Type I" and "Type 2" to read "Type I elastomeric component" and "Type II elastomeric component," respectively, throughout the section.

**Response:** Comment incorporated.

### ***Appearance (Turbidity/Opaescence)***

**Comment Summary #14:** The commenter recommended referencing <630> for Procedure A.

**Response:** Comment incorporated.

### ***Color***

**Comment Summary #15:** The commenter recommended referencing <631> instead of <630> for Matching Fluid O.

**Response:** Comment incorporated.

**General Chapter/Sections:** <382> Elastomeric Component Functional Suitability in Parenteral Products Packaging/Delivery Systems/Multiple  
**Expert Committee(s):** General Chapters—Packaging and Distribution  
**No. of Commenters:** 6

### ***General***

**Comment Summary #1:** The commenter recommended replacing “Glide Force” with “Extrusion Force” throughout the chapter.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested adding a clarified sampling rate as low frequency sampling rates will not reproducibly capture sharp peak forces.

**Response:** Comment incorporated.

### ***Scope***

**Comment Summary #3:** The commenter recommended specifying that all elastomeric components that are in contact, either direct or indirect, with the pharmaceutical product are within scope.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended excluding products and their packaging that are regulated as medical devices.

**Response:** Comment incorporated.

### ***Packaging/Delivery Systems—Vial and Bottle Systems***

**Comment Summary #5:** The commenter recommended changing the term for seal component from “cap” to “ferrule.”

**Response:** Comment incorporated.

### ***Packaging/Delivery Systems—BFS Systems***

**Comment Summary #6:** The commenter recommended changing the term “single-use only” to “single penetration.”

**Response:** Comment incorporated.

### ***General Test Requirements***

**Comment Summary #7:** The commenter suggested ensuring that everything needed to meet the requirements in the chapter are contained within the chapter instead of <1382>.

**Response:** Comment incorporated.

### ***General Test Requirements—Test Samples***

**Comment Summary #8:** The commenter suggested including details of all interfacing components as they also have direct influence on performance.

**Response:** Comment incorporated.

### ***General Test Requirements—Acceptance Criteria***

**Comment Summary #9:** The commenter suggested including language around variable and attribute tests because depending on the result type, the acceptance criterion can have upper and lower limits or pass/fail.

**Response:** Comment incorporated.



### ***Packaging/Delivery System Integrity Tests***

**Comment Summary #10:** The commenter suggested edits to clarify the purpose of keeping the product contents in as it relates to safety and effectiveness.

**Response:** Comment not incorporated. Proposed edits do not provide additional clarity to what is already written.

**Comment Summary #11:** The commenter suggested adding justification for the method of choice.

**Response:** Comment incorporated.

### ***Needle and Spike Access Functional Suitability Tests***

**Comment Summary #12:** The commenter suggested adding some language to Table 1 to clarify why fragmentation testing would not be applicable.

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter suggested using “product-access piercing devices” instead of “hypodermic needles” because degreasing is not required for other piercing devices (e.g., plastic spikes).

**Response:** Comment incorporated.

### ***Fragmentation–Acceptance criteria***

**Comment Summary #14:** The commenter suggested that the particle size acceptance criterion of 150 µm should be reduced to 50 µm.

**Response:** Comment not incorporated. Particles 50 µm in size fall into the subvisible and not the visible size range.

### ***Fragmentation–Vial and Bottle Systems***

**Comment Summary #15:** The commenter suggested mentioning the impact of both elastomeric particles and film particles.

**Response:** Comment incorporated.

**Comment Summary #16:** The commenter suggested eliminating the ability to reuse the spike /closed system transfer device (CSTD) as most of these piercing devices are not designed for multiple uses.

**Response:** Comment incorporated.

### ***Penetration Force–Vial and Bottle Systems***

**Comment Summary #17:** The commenter suggested clarifying how many samples should be performed for this test.

**Response:** Comment incorporated.

### ***Needle Self-Sealing Capacity–Vial and Bottle Systems***

**Comment Summary #18:** The commenter recommended including a description of what constitutes a medium bevel angle.

**Response:** Comment incorporated.

### ***Needle Self-Sealing Capacity—Cartridge Systems***

**Comment Summary #19:** The commenter recommended allowing a designated penetration needle instead of specifying a one needle option.

**Response:** Comment not incorporated. A standard needle is appropriate for a standard test.

**Comment Summary #20:** The commenter recommended the use of a 27-gauge needle for dental cartridge systems.

**Response:** Comment incorporated.

### ***Plunger Break–Loose and Glide Force***

**Comment Summary #21:** The commenter recommended changing the elution speed of 1–2 mm/sec to 3–4 mm/sec because it is low for a filled syringe system.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter suggested including text to acknowledge that it may be possible to feel slip behavior with no impact to the performance of the device. It was recommended to state that any degree of stick slip should be investigated, and acceptability justified by the manufacturer.

**Response:** Comment incorporated.

**Comment Summary #23:** The commenter suggested that there can be other reasons such as the variation in size of the plunger, variation and size of the barrel, or inconsistencies in the molding process that can create differences between the maximum and minimum plunger glide force.

**Response:** Comment incorporated.

### ***Plunger Seal Integrity***

**Comment Summary #24:** The commenter recommended changing “Result” to “Force” in the equation.

**Response:** Comment not incorporated. The sentence preceding the equation states that the result is force, in Newtons.

### ***Tip Cap and Needle Shield Functional Suitability Tests***

**Comment Summary #25:** The commenter recommended using a higher testing frequency because it is more optimal to capture sharp force spikes and for consistency throughout all related tests in the section.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <607> Pharmaceutical Foams – Product Quality Tests/Multiple

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

**No. of Commenters:** 2

**Comment Summary #1:** The commenter proposed retaining the test for particle size as described in the *PF 44(4)* proposal and revising it to read “*Particle Size/Globule Size of Cream or Lotions*”.

**Response:** Comment incorporated. The text was added at the end of the chapter under *Particle Size*.

**Comment Summary #2:** In the *Introduction* section of the chapter, chewable foams are mentioned. The commenter recommended removing these dosage forms from the chapter because they are not available on the market, even though there some patents related to this type of pharmaceutical dosage form.

**Response:** Comment incorporated.

**Comment Summary #3:** In the section *Additional Quality Tests Applicable for Topical Foam Products*, under Time to Break, the commenter suggested clarifying “appropriate temperature”.

**Response:** Comment not incorporated. The temperature is product dependent.

**Comment Summary #4:** The commenter recommended including the tests for foam stiffness and foam collapse in 20 seconds.

**Response:** Comment not incorporated. Foam stiffness and foam collapse tests are used to support product development. The scope of this chapter is to cover common product quality tests that comprise the final finished product specifications.

**Comment Summary #5:** In the Propellant (Aerosol Products) test, the commenter requested clarification of whether the requirement is to test the propellant as a raw material before production or to test the propellant in the product

**Response:** Comment not incorporated. The comment may be incorporated in a future revision of the chapter upon receipt of additional information.

**General Chapter/Sections:** <659> Packaging and Storage Requirements/Multiple  
**Expert Committee(s):** General Chapters—Packaging and Distribution  
**No. of Commenters:** 5

### **General**

**Comment Summary #1:** The commenter recommended aligning the chapter definitions with European Good Distribution Practice (GDP) guidance.

**Response:** Comment not incorporated. The definitions used in <659> is aligned with several FDA guidance documents.

**Comment Summary #2:** The commenter recommended adding text mandating that shipping labels clearly state the safe shipping temperature.

**Response:** Comment not incorporated. This is outside the scope of the current revision proposal.

**Comment Summary #3:** The commenter suggested eliminating Mean Kinetic Temperature (MKT) from the chapter because the drug product manufacturer possesses the stability data for the product, therefore, the manufacturer can determine whether MKT is applicable in specific circumstances.

**Response:** Comment not incorporated. MKT is relevant since not every supply chain partner may have access to the drug product manufacturer's stability data.

### **Introduction**

**Comment Summary #4:** The commenter suggested removing medical devices as they are outside the scope of the chapter.

**Response:** Comment incorporated.

### **Packaging**

**Comment Summary #5:** The commenter suggested adding clarity around tight or well-closed containers and editing the wording to clarify that light-resistance does not exclude the selection of a tight or well-closed container.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested adding a disclaimer or guidance for secondary materials that do not come into contact with solid oral drug products.

**Response:** Comment not incorporated. This statement is out of scope for this chapter.

### **Temperature and Storage**

**Comment Summary #7:** The commenter noted several instances where the term "packaging insert" was used. FDA no longer uses the term "packaging insert" and the commenter recommend revising the term to "prescribing information."

**Response:** Comment incorporated.

### **General Definitions**

**Comment Summary #8:** The commenter recommended incorporating text emphasizing the requirement to use tamper-evident packaging for controlled substances.

**Response:** Comment incorporated.

### ***General Definitions—Packaging Definitions***

**Comment Summary #9:** The commenter recommended incorporating information from <1177> into the *Definitions* section.

**Response:** Comment not incorporated. General Chapter <1177> is being omitted from the *USP–NF*.

**Comment Summary #10:** The commenter recommended revising <671> so that the acceptance criteria for light resistant containers is the same as those in <661.2>.

**Response:** Comment incorporated.

### ***General Definitions—Injection Packaging Systems***

**Comment Summary #11:** The commenter recommended adding “single-patient-use container” to the list of defined terms.

**Response:** Comment not incorporated. The EC may consider this in a future revision.

### ***General Definitions—Miscellaneous***

**Comment Summary #12:** The commenter recommended revising the section to remove any mention of medical devices and repackaging.

**Response:** Comment incorporated.

### ***Injection Packaging***

**Comment Summary #13:** The commenter recommended adding the statement “The container is made of material that permits visual inspection of the contents” to the section. This was a statement that once appeared in <1>.

**Response:** Comment not incorporated. This statement was removed from <1> because the EC determined that packaging systems for injectables should not be required to be visually clear. There are injectable packaging systems on the market that are amber or opaque that do not meet this requirement.

### ***Temperature and Storage Definitions—Freezer***

**Comment Summary #14:** The commenter recommended specifying that the starting temperature should be controlled to  $\pm 10^\circ$ .

**Response:** Comment incorporated.

### ***Temperature and Storage Definitions—Controlled Cold Temperature***

**Comment Summary #15:** The commenter recommended clarifying the text and addressing some inconsistencies.

**Response:** Comment incorporated.

**Comment Summary #16:** The commenter suggested that if a product is stored in a cool place or in a refrigerator for any length of time, this timeframe should not be used to calculate MKT.

**Response:** Comment incorporated.

**Comment Summary #17:** The commenter recommended retaining a reference directing the reader to an above <1000> chapter that provides information on calculating MKT.

**Response:** Comment incorporated.

**Comment Summary #18:** The commenter recommended adding definitions for temperature excursion and transient excursion to the chapter.

**Response:** Comment not incorporated. The EC will consider a future revision to <659> and <1079.2> to include a definition for temperature excursion and transient excursion .

<b>General Chapter/Sections:</b>	<671> Containers—Performance Testing/Multiple
<b>Expert Committee(s):</b>	General Chapters—Packaging and Distribution
<b>No. of Commenters:</b>	5

## **General**

**Comment Summary #1:** The commenter suggested adding information on which method is the best to use depending on packaging type, materials, and fill volumes.

**Response:** Comment not incorporated. This is a difficult task considering the various packaging types, materials, and fill volumes.

**Comment Summary #2:** The commenter recommended allowance for “equivalent and suitable” desiccant material in addition to the USP Reference Standards.

**Response:** Comment not incorporated. A standardized method and reagents help users obtain comparable results.

**Comment Summary #3:** The commenter recommended including descriptions for which methods to use for high, ultra-high, and medium-to-low barrier containers.

**Response:** Comment not incorporated. This information is more appropriate in an informational chapter. The EC will consider adding the recommendations in <1671>.

**Comment Summary #4:** The commenter recommended adding instructions for the proper evaluation of in-use conditions.

**Response:** Comment not incorporated. This topic is not within the scope of <671> nor of <1671>.

## ***Desiccant Methods for Packaging Systems: Desiccant***

**Comment Summary #5:** The commenter suggested that the reference standards (small, medium, large) should always be dried prior to use.

**Response:** Comment not incorporated. The current text gives the end-user the option to dry, and the EC determined that this should be kept flexible based on the needs of the end-user.

**Comment Summary #6:** The commenter requested that the desiccant cooling time be added to the section.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter recommended replacing “capacity” with “nominal capacity.”

**Response:** Comment incorporated.

## ***Desiccant Methods for Packaging Systems: Methods 1, 2, and 3***

**Comment Summary #8:** The commenter suggested clarifying the statement “Properly describe the container-closure system tested.”

**Response:** Comment incorporated.

## ***Desiccant Methods for Packaging Systems: Results***

**Comment Summary #9:** The commenter recommended adding acceptance criteria for methods 1, 2, and 3.

**Response:** Comment not incorporated. Acceptance of a packaging system is based on and is specific to the product and its stability data.

## ***Water Method for Packaging Systems: Method 4***

**Comment Summary #10:** The commenter suggested renumbering the test methods so that the new water method is labeled as Method 2A.

**Response:** Comment not incorporated. The numbering of the methods was based on whether it was a desiccant or a water-based method.

**Classification Based on Desiccant Method for Solid Oral Dosage Forms: Header**

**Comment Summary #11:** The commenter recommended allowing the end-user the option of removing the outer closure of an induction sealed bottle because leaving the closure in place can increase variability.

**Response:** Comment incorporated. A clarifying statement was added on how to increase precision by removing the closure.

**Desiccant: Methods 5 and 6**

**Comment Summary #12:** The commenter requested that the desiccant cooling time be added to the section.

**Response:** Comment incorporated.

**Classification Based on Desiccant Method for Solid Oral Dosage Forms: Methods 5, 6, and 8**

**Comment Summary #13:** The commenter suggested clarifying what constitutes an “inert filler” or “spacer.”

**Response:** Comment incorporated.

**Classification Based on Water Method for Liquid Oral Dosage Forms: Header**

**Comment Summary #14:** The commenter suggested that the pre-storage weighing instruction is not necessary and should be omitted.

**Response:** Comment not incorporated. The instructions are intended to standardize how samples are handled.

**Classification Based on Water Method for Liquid Oral Dosage Forms: Method 8**

**Comment Summary #15:** The commenter requested a correction to the equation.

**Response:** Comment incorporated.

**Spectral Transmission**

**Comment Summary #16:** The commenter requested to revise Table 3 so that it is aligned with Table 2 in <661.2>.

**Response:** Comment incorporated.

**Comment Summary #17:** The commenter suggested adding a column for containers greater than 50 mL.

**Response:** Comment incorporated.

**Monograph/Section(s):** <698> Deliverable Volume/ Multiple  
**Expert Committee(s):** General Chapters—Dosage Forms  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended replacing the word “extracted” with the word “discharged” in the third sentence in the *Scope* section to be consistent with the terminology used in multiple locations in *Procedure* section.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter suggested revising the term “single-dose containers” to “single-unit-containers” in item 1 under *Oral Solutions and Oral Suspensions, Procedure*.

**Response:** Comment incorporated.

**Monograph/Section(s):** <755> Minimum Fill/Multiple  
**Expert Committee(s):** General Chapters—Dosage Forms  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter stated that the chapter appears to treat foams and sprays as if these two dosage forms are always aerosol products. The commenter recommended revising the section headings as follows:

1. Change “Procedure for Dosage Forms Other Than Aerosols, Sprays and Foams” to “Procedure for Dosage Forms Other Than Aerosols, Sprays and Aerosol Foams”
2. Change “Procedure for Aerosols, Sprays, and Foams” to “Procedure for Aerosols, Sprays, and Aerosol Foams”.

**Response:** Comment not incorporated. Aerosol, Spray, and Foam are defined in <1151> as three different dosage forms. The term “Aerosol Foams” is not defined in <1151>. Using “Aerosol Foams” may cause confusion when users try to classify their products and follow the specific procedures.

**Comment Summary #2:** The commenter suggested replacing the word “specifications” with “acceptance criteria” in the first sentence in *Scope*.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended adding “less than” before “95% of the labeled amount where the labeled amount is more than 60 g or 60 mL, proceed to Stage 2” in the final sentence in *Acceptance Criteria, Stage 1*.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested changing the word “outsides” to “outside” in the second sentence in *Procedure for Aerosols, Sprays and Foams*.

**Response:** Comment incorporated.

**General Chapter/Section(s):** <785> Osmolality and Osmolarity/Multiple Sections

**Expert Committee(s):** General Chapters–Physical Analysis

**No. of Commenters:** 12

**Comment Summary #1:** Under *Qualification of Osmolality Instruments, Precision/Repeatability*, the commenter suggested using the mid-range osmolality standard solution that was used in the instrument calibration.

**Response:** Comment incorporated.

**Comment Summary #2:** Under *Qualification of Osmolality Instruments, Performance Qualification*, the commenter suggested that the check of the day-of-use calibration over time be performed only where frequent re-calibrations are necessary following failure to meet acceptance criteria of the calibration check.

**Response:** Comment not incorporated. The current text indicates that monitoring the day-of-use calibration check is recommended but does not state it is required. This language provides flexibility for a laboratory to decide whether monitoring of the day-of-use calibration check should be performed if frequent re-calibrations are necessary.

**Comment Summary #3:** Under *Calibration, Procedure for Calibration Check*, the commenter pointed out a conflict between the manufacturer’s recommendation and Table 1 on how to select the concentration of the calibration solution. The commenter suggested changing the text to “unless a different solution is specified as part of the manufacturer’s instructions, select at least one solution from Table 1....”.

**Response:** Comment incorporated.

**Comment Summary #4:** Under *Method 1: Freezing-Point Osmometry, Procedure*, the commenter suggested replacing “NLT 30 min” with “an appropriate amount of time (NLT 30 min unless the instrument contains an internal sensor)”. Equipment used today often has an internal temperature sensor that tells the analyst when it is at the correct temperature. Typically, it can be significantly less than 30 min.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter suggested keeping the preparation of the standard solution the same as in the *European Pharmacopoeia*.

**Response:** Comment not incorporated. The standard solution concentrations were established based on calculations available in the literature and that allow a broader use of the osmolarity/osmolality measurements not only for pharmaceutical dosage forms but for certain processes like cell or tissue culture and biotechnological ones. Thus, there is a need for an expanded range of concentrations.

**Comment Summary #6:** Under *Calibration, Procedure for Calibration Check*, the commenter suggested removing the recalibration of the equipment in case the instrument fails to meet the acceptance criteria for the calibration check. They stated that, in most cases, it is sufficient to defreeze and clean the instrument.

**Response:** Comment not incorporated. After failure of the calibration check, the instrument must be recalibrated. Otherwise, a laboratory could continue testing standard solutions until the values met the calibration check requirements. The EC determined that this is not acceptable.

**Comment summary #7:** The commenter recommended adding that vapor pressure osmometers do not detect volatiles and that other instruments should be considered when volatiles are a component in the formulation.

**Response:** Comment incorporated.

**Comment summary #8:** The commenter suggested revising the text under “Optimization of Adjustable Freezing Parameters” to state that the test parameters may be optimized following the manufacturer’s recommendations.

**Response:** Comment incorporated.

**Comment summary #9:** The commenter suggested replacing the accuracy ranges for purchased solutions with a reference to a manufacturer’s accuracy specifications in Table 1, Footnote b.

**Response:** Comment not incorporated. The Expert Committee determined that the ranges are acceptable for pharmaceutical products.

**Comment Summary #10:** Under Performance Qualification, the commenter suggested removing “e.g. every six months”.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter noted that in the *Calibration, Procedure for Calibration Check Theoretical Background* section, the minus signal was missing in the formula for osmotic pressure as function of water activity.

**Response:** Comment incorporated.

**Comment Summary #12:** Under *Test solutions*, the commenter recommended diluting or resuspending the product using the diluent indicated in the instructions to the patient.

**Response:** Comment incorporated.

**Comment Summary #13:** Under *Types of Osmolality Instruments*, in the sentence “whereas a dew-point depression instrument measures the osmolality of a solution at ambient temperatures,” the commenter suggested replacing “ambient temperatures” with 37°.

**Response:** Comment not incorporated. Most equipment measures the dew-point depression at ambient temperature and do not have means of controlling the temperature of the sample.

**Comment Summary #14:** Under *Types of Osmolality Instruments, Freezing Point Depression Osmometer*, the range for the sample size is 0.02–2 mL. The commenter noted that 2 mL is a large amount of sample that may give false results.

**Response:** Comment not incorporated. Precision and repeatability are typically acceptable for simple solutions.

**Comment Summary #15:** Under *Types of Osmolality Instruments, Freezing Point Depression Osmometer*, the commenter noted that there are no instructions on further steps in case the sample does not freeze.

**Response:** Comment not incorporated. The user should determine the appropriate technique based on the properties/composition of the product during product/method development.



**Comment Summary #16:** Under *Types of Osmolality Instruments, Vapor Pressure Osmometer*, the commenter stated that there is no mention that the osmolality value may need to be selected manually.

**Response:** Comment not incorporated. This level of detail on how to operate the equipment is out of the scope of the chapter. Manufacturer's instructions should be followed.

**Comment Summary #17:** The commenter suggested adding action steps to be followed in case a vapor pressure osmometer equipment is discontinued.

**Response:** Comment not incorporated. It is out of the scope of the chapter.

**Comment Summary #18:** The commenter suggested that osmolality determination should not be included in a USP monograph. Once the formulation is finalized and the osmolality is established, it will not change until the formulation changes.

**Response:** Comment not incorporated. The product manufacturer should establish the product specification.

**Comment Summary #19:** The commenter suggested limiting the variability of vapor pressure osmometer measurements to  $\pm 15\%$ .

**Response:** Comment not incorporated. The EC determined that the variability stated in the chapter is acceptable.

**Comment Summary #20:** The commenter suggested including an explanation of the importance of measuring osmolality in the *Introduction* section.

**Response:** Comment not incorporated. The EC felt that it may be better suited to be mentioned elsewhere in *USP-NF*.

**Comment Summary #21:** The commenter suggested including membrane-based osmometer to the text.

**Response:** Comment not incorporated. The EC will consider future revisions to provide recommendations on this type of osmometer upon receipt of additional supporting information.

**Comment Summary #22:** Under Installation Qualification (IQ), the text states "The installation qualification (IQ) requirements provide evidence that the hardware and software are properly installed in the desired location." The commenter suggested that it should not be mandatory to use software as most of osmometers do not have software interface.

**Response:** Comment not incorporated. The text does not state that the use of software is mandatory.

**Comment Summary #23:** Under Test Solutions, the commenter suggested including how to treat the sample in case of viscous and semisolid products.

**Response:** Comment not incorporated. The EC will consider addressing viscous and semisolid samples in a future revision of the chapter upon receipt of additional supporting information.

**Comment Summary #24:** The commenter recommended having a separate calibration control system suitability acceptance criterion for the vapor pressure depression method because some osmometers on the market cannot deliver the levels of accuracy stated in the chapter.

**Response:** Comment not incorporated. The ranges were kept as proposed. If the equipment does not meet these criteria it may not be appropriate for the evaluation of pharmaceutical products.

**Comment Summary #25:** The commenter recommended including a standard solution with the osmolality of 290 mOsm/kg in *Table 1 – Standard Solution (STD) for Freezing-Point Depression Osmometer Calibration* as many vendors use this concentration for calibration and calibration control.

**Response:** Comment incorporated.

**Comment Summary #26:** The commenter recommended providing an option for using two calibration controls bracketing tests samples that are within 300 mOsm/kg differences to allow batch testing.

**Response:** Comment incorporated.

**Comment Summary #27:** Under *Introduction*, the commenter noted that the text contains two different definitions of the term “tonicity” and recommended deleting the first definition.

**Response:** Comment not incorporated. The text shows that term “tonicity” is not well understood, and it is often used erroneously as a synonym of osmolality.

**Comment Summary #28:** In the *Theoretical Background* section, the commenter suggested explaining in detail how several equations were derived.

**Response:** Comment not incorporated. The text contains enough details to explain the main concepts to the reader.

**Comment Summary 29:** The *Introduction* section defines osmolality and osmolarity as moles of solutes per kilogram of solvent and moles of solutes per liter of solution, respectively. The *Reporting Results* section uses water. The commenter suggested adding some explanatory text to address this discrepancy.

**Response:** Comment not incorporated. The units of the Standard Solutions are expressed per kilograms of water, not diluent.

<b>General Chapter/Sections:</b>	<1079> Risk and Mitigation Strategies for the Storage and Transportation of Finished Drug Products/Multiple General Chapters—Packaging and Distribution
<b>Expert Committee(s):</b>	General Chapters—Packaging and Distribution
<b>No. of Commenters:</b>	3

### **Scope**

**Comment Summary #1:** The commenter requested clarification on what is meant by “infusion/compounding.”

**Response:** Comment incorporated.

### **Table 2**

**Comment Summary #2:** The commenter recommended aligning the entire text of the chapter with terminology from the Drug Supply Chain Security Act (DSCSA).

**Response:** Comment not incorporated. The DSCSA only applies within the US, whereas USP has chosen to pursue a broader scope for this informational chapter, which is utilized globally.

**Comment Summary #3:** The commenter recommended changing packing, sales, and transportation from “no” to “yes” under Hospital and Healthcare Provider.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended changing temporary parking from “no” to “yes” under Pharmacy or Compounding Pharmacy.

**Response:** Comment incorporated.

### **Documentation and Procedures**

**Comment Summary #5:** The commenter recommended deleting the reference to General Notices 10.20 because it does not provide the reader with any useful information.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter suggested using “thermal cycle” instead of “temperature cycling” in Excursion Handling.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter recommended clearly stating that the manufacturer’s instructions are always definitive.

**Response:** Comment incorporated.

### **Resources for Storage, Transportation, and Personnel**

**Comment Summary #8:** The commenter suggested that the product's storage temperature should also be taken into account for appropriate building construction and requested the addition of a bullet point to provide this information.

**Response:** Comment incorporated.

### **Glossary**

**Comment Summary #9:** The commenter suggested clarifying the definition for temperature excursion include all drug products instead of only time- and temperature-sensitive products.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter indicated that the definition for temperature excursion does not differentiate an excursion from a transient spike and requested clarification for these terms.

**Response:** Comment not incorporated. The EC will consider a future revision to <659> and <1079.2> to include definitions for temperature excursion and transient spike.

<b>General Chapter/Sections:</b>	<1079.2> Mean Kinetic Temperature in the Evaluation of Temperature Excursions During Storage and Transportation of Drug Products/Multiple General Chapters—Packaging and Distribution
<b>Expert Committee(s):</b>	
<b>No. of Commenters:</b>	6

### **General**

**Comment Summary #1:** The commenter requested stating that MKT cannot be applied universally to all drugs requiring storage at controlled room temperature (CRT) and controlled cold temperature (CCT) and providing an explanation.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended including Active Pharmaceutical Ingredients (API) in the scope of the chapter.

**Response:** Comment not incorporated. The EC will consider adding APIs in a future revision.

**Comment Summary #3:** The commenter recommended including a statement that manufacturer's supporting stability data, including accelerated and stress (i.e., freeze/thaw) data, can be used to support product stability in products that have undergone temperature excursions.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter suggested that the 30-day time period for calculating MKT should be a general recommendation and that USP should retain the MKT calculation based on the established one-year period to allow flexibility for the manufacturer to perform calculations based on historical information.

**Response:** Comment not incorporated. The 30-day time period is stated as a recommendation in the chapter.

**Comment Summary #5:** The commenter suggested that a definition for temperature excursion and temperature excursion spike be added to the chapter.

**Response:** Comment not incorporated. The EC will consider a future revision to <659> and <1079.2> to include definitions for temperature excursion and temperature excursion spike.

### **Scope**

**Comment Summary #6:** The commenter requested clarification as to what is meant by "infusion/compounding."

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter requested the addition of sterile and nonsterile as a description for compounding pharmacies.

**Response:** Comment incorporated.

### ***Mean Kinetic Temperature***

**Comment Summary #8:** The commenter suggested that the observation period for calculating the MKT should not be fixed to one week.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter suggested that it should be noted that the concept of MKT can follow either zero-order or first-order kinetics.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter recommended including text to address when it may be appropriate to evaluate an excursion without input from the manufacturer.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter suggested including text to state that the chapter's approach should not be applied when the manufacturer-supplied shipping condition information conflicts with the chapter.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter recommended clarifying if the intention is to use weekly mean temperatures for each time point (which may obscure excursions above the maximum).

**Response:** Comment incorporated.

**Comment Summary #13:** The commenter noted that "n<sup>th</sup>" is missing from the definition for T<sub>n</sub>.

**Response:** Comment incorporated.

**Comment Summary #14:** The commenter suggested clearly stating that the "30 days from (and including) the high excursion temperature" must include the entire period of the excursion.

**Response:** Comment incorporated.

### ***Application of MKT***

**Comment Summary #15:** The commenter suggested adding the duration (NMT 24 h) of the excursion to the table.

**Response:** Comment incorporated.

**Comment Summary #16:** The commenter suggested adding guidance for "acceptable excursion range" and "minimum temperature."

**Response:** Comment incorporated.

**Comment Summary #17:** The commenter suggested using integer values to clarify that a temperature of 8.3° is not a deviation from a 2–8° storage condition.

**Response:** Comment not incorporated. General Notices 7.20. *Rounding Rules* provides guidance for rounding.

**Comment Summary #18:** The commenter suggested adding a statement that exposure to higher or lower temperatures beyond what is recommended in chapter should be evaluated using monographs, product labels, or stability data provided by the manufacturer.

**Response:** Comment incorporated.

**Comment Summary #19:** The commenter recommended noting that certain products (e.g., suppositories) may have physical stability issues from exposure to temperatures slightly below the 40° CRT maximum.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter recommended clearly defining the minimum frequency for MKT measurements.

**Response:** Comment not incorporated. This is an informational chapter and it includes a recommendation of 15 minutes.

**Monograph/Section(s):** <1087> Apparent Intrinsic Dissolution – Dissolution Testing Procedures for Rotating Disk and Stationary Disk/Multiple General Chapters—Dosage Forms

**Expert Committee(s):**

**No. of Commenters:**

1

**Comment Summary #1:** The commenter indicated that it is not likely to perform the test at a speed above 300 rpm and requested revising the typical rotation speeds for the rotating disk method from “60 to 500 rpm” to “60 to 300 rpm” in paragraph 3 in the *Rotating Disk* section.

**Response:** Comment not incorporated. For very compactable and poorly water-soluble drug substances, it is possible that a speed >300 rpm is needed. General Chapter <1087> is an informational chapter, USP apparatus is recommended but not required. Also, note that for the Stationary Disk method, a flat bottom surface vessel is recommended which is not a typical USP Apparatus 1 or 2 vessel.

**Comment Summary #2:** The commenter suggested adding detailed dimensions of the intrinsic dissolution apparatus in Figures 1, 2, 3, and 4.

**Response:** Comment not incorporated. General Chapter <1087> is an informational chapter to be used as a guide. Also, intrinsic dissolution studies are characterization studies and are not referenced in individual monographs. Ideally, intrinsic dissolution testing is performed using compendial instruments.

**General Chapter:** <1092> The Dissolution Procedure: Development and Validation/Multiple

**Expert Committee:**

**No. of Commenters:**

General Chapters-Dosage Forms

9

**Comment Summary #1:** The commenter suggested sections 1.1 and 1.3 should be in reverse order.

**Response:** Comment not incorporated. The medium needs to be selected first.

**Comment Summary #2:** The commenter suggested that an approach be delineated to determine filter efficiency to remove particles from dissolution aliquots.

**Response:** Comment partially incorporated. A general statement was added to verify that drug particles have been captured during filtration.

**Comment Summary #3:** The commenter requested the substitution of the term “analyte” for “analytical finish” in discussing interference from filter leachables.

**Response:** Comment not incorporated. The interference would be to the analysis and not the dissolved substance.

**Comment Summary #4:** The commenter requested the inclusion of material to the list of filter characteristics that should be considered.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter suggested that the filter should be requalified after changes in the composition of the drug product, quality of the product ingredients, or dissolution medium.

**Response:** Comment partially incorporated. Less prescriptive text was added to allow flexibility.

**Comment Summary #6:** The commenter suggested that the text should be changed to indicate that stated pore size may not be a conclusive measure of filter effectiveness when comparing different filter types.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter requested mention of the availability of 0.02- $\mu$ m filters.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested that the word “appropriate” be used in place of the word “correct” in the instruction on filter dimension.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter suggested that the section title be changed to *Sample Preparation and Analysis* for clarity.

**Response:** Comment not incorporated. The section title has an established use within the chapter.

**Comment Summary #10:** In the section *Performing Filter Compatibility*, the commenter suggested adding the acceptance range between a filtered and unfiltered solution.

**Response:** Comment partially incorporated. Numeric range was not included.

**Comment Summary #11:** The commenter suggested concluding the section *Performing Filter Compatibility* by stating that the qualified filter, with all its details, should be detailed in the final version of the dissolution method.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter suggested reorganizing the sections *Determining Solubility and Stability of Drug Substance in Various Media* and *Choosing a Medium and Volume* such that stability and solubility are sub-sections of the media selection section.

**Response:** Comment not incorporated. The typical process is to generate data before choosing media and volume.

**Comment Summary #13:** The commenter suggested that in the case where the formulation significantly affects the solubility of the drug substance, e.g., amorphous solid dispersion, the solubility of the intermediate drug product should be evaluated.

**Response:** Comment incorporated. It was added to section *Choosing a Medium and Volume*.

**Comment Summary #14:** The commenter recommended adding a note stating that the critical micellar concentration (CMC) is pH and temperature dependent.

**Response:** Comment incorporated.

**Comment Summary #15:** The commenter suggested adding a short definition of sink condition to the *Solubility* section or a cross-reference to the section *Choosing a Medium and Volume*.

**Response:** Comment incorporated.

**Comment Summary #16:** In the section *Stability*, the commenter suggested carrying out the evaluation of the stability of the drug substance in the dissolution medium at 37°.

**Response:** Comment incorporated.

**Comment Summary #17:** In the section *Stability*, the commenter suggested adding that the stability of the solution should be evaluated over at least the time of the entire dissolution procedure.

**Response:** Comment incorporated.

**Comment Summary #18:** In the section *Stability*, the commenter suggested adding that the acceptable range for the sample solution stability should be adjusted according to the analytical response of the sample solution under test.

**Response:** Comment not incorporated. The range 98–102% is sufficiently broad.

**Comment Summary #19:** The commenter suggested adding information to the section *Stability* concerning the physical stability of the sample solution.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter recommended adding that the sample solution may show precipitation when cooled down to room temperature in the section *Stability*.

**Response:** Comment incorporated.

**Comment Summary #21:** The commenter suggested adding a target range of desirable V/Vsat ratio in the section *Choosing a Medium and Volume*. The language “too large” does not provide sufficient guidance.

**Response:** Comment not incorporated. The current language is used to allow flexibility.

**Comment Summary #22:** In the section *Choosing a Medium and Volume*, the commenter noted that the sentence starting with “There are occasions where such actions are not sufficient” was not clear enough.

**Response:** Comment incorporated. Text was modified accordingly.

**Comment Summary #23:** The commenter suggested adding a statement to the section *Choosing a Medium and Volume* about the changes in the hydrodynamics as function of the medium volume and that this needs to be evaluated as part of method development.

**Response:** Comment not incorporated. The primary driver in volume selection is solubility.

**Comment Summary #24:** The commenter suggested including a specific paragraph discussing the use of peak vessels in the section *Choosing an Apparatus*.

**Response:** Comment not incorporated. Text allows flexibility.

**Comment Summary #25:** In the section *Deaeration*, the commenter suggested adding examples of other deaeration methods.

**Response:** Comment not incorporated. The deaeration procedure in <711> is a benchmark. Other methods are mentioned in the literature.

**Comment Summary #26:** The commenter suggested adding more flexibility regarding deaeration of dissolution media containing surfactants.

**Response:** Comment incorporated.

**Comment Summary #27:** In the section *Deaeration*, the commenter suggested replacing compendial technique with appropriate technique when comparing deaerated and non-deaerated dissolution medium.

**Response:** Comment not incorporated. The compendial technique is a standard one.

**Comment Summary #28:** The commenter suggested elaborating on the procedure to perform the robustness of the deaeration process.

**Response:** Comment incorporated. Reference to the section *Robustness* was included.

**Comment Summary #29:** The commenter suggested adding that sinkers can also be used with tablets.

**Response:** Comment incorporated.

**Comment Summary #30:** The commenter recommended adding a statement that lower rotation speed are preferred during method development for increased discriminative effect.

**Response:** Comment not incorporated. The text allows flexibility.

**Comment Summary #31:** The commenter suggested adding that peak vessels may be appropriate if coning is seen even at 75 rpm.

**Response:** Comment not incorporated. The text currently allows peak vessels to be used with appropriate justification.

**Comment Summary #32:** The commenter suggested adding a reference to the FDA guidance that defines highly soluble drug substances to the section *Time Points*.

**Response:** Comment incorporated.

**Comment Summary #33:** The commenter recommended adding examples of sufficient dissolution time points which are chosen to characterize the performance of most immediate release products.

**Response:** Comment incorporated. A cross-reference to the section *Immediate-Release Dosage Forms*, where this information is discussed, was added.

**Comment Summary #34:** The commenter suggested explicitly stating that in the calculation of the f<sub>2</sub> similarity factor, *n* refers to 12 dosage units.

**Response:** Comment incorporated.

**Comment Summary #35:** The commenter suggested adding the minimum number of timepoints required in the dissolution profiles used in f<sub>2</sub> calculations.

**Response:** Comment incorporated.

**Comment Summary #36:** The commenter noted that the statement “for products containing more than a single active ingredient, determine the drug release for each active ingredient” is applicable for all pharmaceutical dosage forms.

**Response:** Comment incorporated. Text moved to the section *Scope*.

**Comment Summary #37:** The commenter suggested clarifying the term “infinite time point” as it is misleading.

**Response:** Comment incorporated.

**Comment Summary #38:** The commenter recommended adding that more than one sample should be taken during the evaluation of drug release at the infinity point. Sampling at only one time point can be misleading.

**Response:** Comment incorporated.

**Comment Summary #39:** The commenter suggested adding that the information obtained with drug release at the infinity point may be used for the justification of the selection of a medium volume at which sink condition is not obtained.

**Response:** Comment not incorporated. The conditions should be selected on a case-by-case approach.

**Comment Summary #40:** The commenter noted that visual observations should always be recorded, not just during formulation development.

**Response:** Comment incorporated.

**Comment Summary #41:** The commenter suggested adding examples of formulas for the calculation of the amount of drug release in case of multiple time points, with and without medium replacement.

**Response:** Comment not incorporated. Examples of the formulas can be found in the USP monographs for dosage forms.

**Comment Summary #42:** The commenter suggested moving the discussion of in-vitro/in-vivo correlation and bioavailability studies from the section *Data Handling to Interpretation of Dissolution Results*.

**Response:** Comment incorporated.

**Comment Summary #43:** The commenter suggested modifying the last sentence of the section *Dissolution Procedure Assessment* to refer to the discriminatory power of the test.

**Response:** Comment incorporated.

**Comment Summary #44:** The commenter suggested adding that it may be useful to evaluate the filtration steps in the section *Centrifugation*.

**Response:** Comment incorporated.

**Comment Summary #45:** The commenter suggested changing the following text concerning isosbestic point “the analytical wavelength must be at the isosbestic point of the drug substance and degradation product” by replacing “and” with “or”.

**Response:** Comment not incorporated. Two species are measured at the isosbestic point.

**Comment Summary #46:** The commenter pointed out that the last row in the *Figure 6* was not clear.

**Response:** Comment incorporated. *Figure 6* was modified accordingly.

**Comment Summary #47:** The commenter suggested revising the text in the section *Spectrophotometric Analysis* to clarify that a single level standard may be used when it is shown to be suitable.

**Response:** Comment incorporated.

**Comment Summary #48:** The commenter suggested correcting the sentence that describes the typical units of absorptivity.

**Response:** Comment incorporated.

**Comment Summary #49:** The commenter suggested that the sentence on fiber optics was out of place being at the end of the section *Spectrophotometric Analysis*.

**Response:** Comment incorporated. The sentence was moved to the appropriate place.



**Comment Summary #50:** The commenter suggested simplifying the language in the section *Chromatography* to indicate that specificity from media and excipients interferences should be evaluated.

**Response:** Comment incorporated.

**Comment Summary #51:** The commenter suggested modifying the text in the section *Automation* to clarify that different parts of the dissolution process may be automated depending on the design of the instrument.

**Response:** Comment incorporated.

**Comment Summary #52:** The commenter suggested adding more flexibility to the section *Sample Introduction and Timing* because it may be equipment dependent.

**Response:** Comment incorporated.

**Comment Summary #53:** In the section *Validation*, the commenter suggested replacing “drug” with “drug substance” throughout the text.

**Response:** Comment incorporated.

**Comment Summary #54:** The commenter noted that the validation of intermediate precision and reproducibility does not need to be limited to two analysts or two laboratories.

**Response:** Comment incorporated.

**Comment Summary #55:** The commenter suggested that when the physical form of the drug substance differs, the accuracy determination should account for differences in solubility between those forms.

**Response:** Comment not incorporated. The same physical form should be used.

**Comment Summary #56:** The commenter noted that well characterized batches can be used in lieu of spiked placebo for the validation of precision and evaluation of robustness.

**Response:** Comment incorporated. *Table 3* was modified accordingly.

**Comment Summary #57:** The commenter suggested including that the medium blank and other drug substances present in the product should be evaluated for potential interference with the method in the section *Specificity/Placebo Interference*.

**Response:** Comment incorporated.

**Comment Summary #58:** The commenter suggested adding more details regarding the concentration range for the evaluation of linearity and range.

**Response:** Comment not incorporated. The range is defined case-by-case on the dissolution profile.

**Comment Summary #59:** The commenter suggested adding the range for dissolution per ICH guidance Q2(R1).

**Response:** Comment not incorporated. The range is defined on a case-by-case approach as it depends on the product/process.

**Comment Summary #60:** In the section *Linearity and Range*, in the sentence “the y-intercept must not be importantly different from zero”, the commenter suggested replacing the word “importantly” with another word more commonly used with this concept.

**Response:** Comment not incorporated. Other synonyms are not preferable to “importantly”.

**Comment Summary #61:** The commenter suggested adding the maximum allowable difference for the y-intercept.

**Response:** Comment not incorporated. It is defined on a case-by-case approach.

**Comment Summary #62:** The commenter suggested that the validation of accuracy/recovery should be done in the dissolution vessels at 37°.

**Response:** Comment not incorporated. It is at the discretion of the laboratory.

**Comment Summary #63:** The commenter suggested adding the information that organic solvents can be used in the second dilution of the sample solution.

**Response:** Comment incorporated.

**Comment Summary #64:** The commenter suggested that the range for measured recovery should be adjusted according to the concentration levels tested and corresponding analytical response.

**Response:** Comment not incorporated. The EC determined that the range 95%–105% is reasonable.

**Comment Summary #65:** The commenter suggested including the range for the variation in the parameters being evaluated under robustness.

**Response:** Comment not incorporated. General Chapter <711> provides the ranges.

**Comment Summary #66:** The commenter suggested including the option of comparing automated sampling with manual sampling by using developmental data to avoid a formal validation.

**Response:** Comment not incorporated. Each validation parameter needs to be validated in a formal protocol.

**Comment Summary #67:** Under the section *Considerations for Automation*, the commenter suggested clarifying how many units should be used to evaluate the interchangeability of manual and automated sampling procedures.

**Response:** Comment incorporated.

**Comment Summary #68:** The commenter suggested that consideration should be given to the fact that the dissolution specification is being increasingly set using the combination of in-vitro dissolution and physiologically based pharmacokinetic (PKPB) modeling to assess the acceptability of the specification.

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

**Comment Summary #69:** The commenter suggested adding to the section *Immediate-Release* that a Q value of 80% at 30 minutes is generally recommended for immediate-release dosage forms containing a high solubility drug substance.

**Response:** Comment partially incorporated. The text was added with modification.

**Comment Summary #70:** The commenter suggested including that the Q value for immediate-release dosage forms can be established based on a statistical assessment.

**Response:** Comment not incorporated. The EC determined the text to be sufficient as written.

**Comment Summary #71:** In the section 6.3 *Extended-Release Dosage Forms*, the commenter suggested replacing “complete drug release” with “target release”.

**Response:** Comment not incorporated. The EC determined the text to be sufficiently clear.

**Comment Summary #72:** The commenter suggested to add the word “example” in the title of Tables 4, 5, and 6.

**Response:** Comment not incorporated. The text includes the words “example” and “hypothetical.”

<b>General Chapter/Sections:</b>	<1105> Immunological Test Methods—Surface Plasmon Resonance /Multiple Sections
<b>Expert Committee:</b>	General Chapters—Biological Analysis
<b>No. of Commenters:</b>	3

**Comment Summary #1:** The commenter recommended minor editorial changes and clarifying a few sentences in the sections: *Surface Preparation*, *Direct Immobilization*, *Assay Cut-Point Determination*, *Application 3-Kinetic and Affinity Analysis*, *Kinetics and Steady-State Affinity Models*, *Assessing the Fit*, and *Kinetic and Affinity Analysis*.

**Response:** Comments incorporated. Texts were modified according to the commenters’ suggestion.

**Comment Summary #2:** The commenter recommended removing a redundant procedure for surface regeneration in the *Protein Stability Upon Immobilization* section.

**Response:** Comment incorporated.

**Comment Summary #3:** The commenter recommended including instrument and kit variation.  
**Response:** Comment not incorporated. Instrument and kit variation are out of scope of this chapter.

**Comment Summary #4:** The commenter recommended including <1033> as reference.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended including determination for parallelism between reference standard and samples.

**Response:** Comment not incorporated. Discussion on parallelism is outside of the scope of this chapter and is discussed in <1034>, which is already referenced.

**General Chapter/Sections:** <1108> Assays to Evaluate Fragment Crystallizable (Fc)-mediated Effector Function

**Expert Committee:** Biologics Monographs 2– Proteins

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended minor editorial changes and clarifying a few sentences in the sections *Background*, *Binding Assays Format*, and *Critical Reagent*.

**Response:** Comment incorporated. Texts were modified according to the commenter’s suggestion.

**Comment Summary #2:** The commenter recommended correcting typo “K<sub>a</sub>” to “k<sub>a</sub>” in the *Surface Plasmon Resonance* section.

**Response:** Comment incorporated.

**Expert Committee (EC)-Initiated Change #1:** Minor changes were made to *Figure 4* for clarity.

**EC-Initiated Change #2:** Minor editorial changes were made in the *Assay Validation* section.

**General Chapter/Sections:** <1381> Assessment of Elastomeric Components Used in Injectable Pharmaceutical Product Packaging/Delivery Systems

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

**No. of Commenters:** 2

### General

**Comment Summary #1:** The commenter recommended replacing “closure” with “components” throughout the chapter.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended clarifying that rubber and elastomer are interchangeable.

**Response:** Comment incorporated.

### Scope

**Comment Summary #3:** The commenter recommended a revision to emphasize that products regulated as medical devices are out of scope.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended stating that all elastomeric components in contact, either direct or indirect, with the pharmaceutical product are within scope.

**Response:** Comment incorporated

### *Elastomeric Components Materials of Construction— Polymer Types and Attributes*

**Comment Summary #5:** The commenter recommended acknowledging that polymer blends are used by revising the statement that introduces *Table 2*.

**Response:** Comment incorporated.

**Comment Summary #6:** The commenter recommended updating the incomplete CFR reference.

**Response:** Comment incorporated.

***Elastomeric Components Materials of Construction—Surface Coating and Treatments***

**Comment Summary #7:** The commenter suggested adding information for process aids that might be present at the surface of the elastomeric item.

**Response:** Comment not incorporated. Residual processing aids are not intended as surface coatings or treatments.

**Comment Summary #8:** The commenter noted that Parylene is a trade name and recommended replacing “Parylene” with a general term for the process (e.g., chemical vapor disposition).

**Response:** Comment incorporated.

***Elastomeric Components Materials of Construction—Compounds of Concern***

**Comment Summary #9:** The commenter suggested wording to state that some ingredients are carcinogens and that use should be avoided whenever possible.

**Response:** Comment incorporated.

***Elastomeric Component Manufacturing Technology and Sterilization Procedures***

**Comment Summary #10:** The commenter suggested adding a section about the impact of packaging on elastomeric component items.

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

***Elastomeric Component Manufacturing Technology and Sterilization Procedure—Sterilization Procedures***

**Comment Summary #11:** The commenter suggested stating that different standards and requirements may apply for products regulated as medical devices (e.g., unfilled syringes or infusion administration sets).

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter recommended including system design as a factor in the selection of the sterilization method.

**Response:** Comment incorporated.

***Summary of <381> Physicochemical Test—Physicochemical Tests***

**Comment Summary #13:** The commenter recommended consistency with ICH and use the term “acceptance criteria” in the chapter.

**Response:** Comment incorporated.

***Summary of <381> Physicochemical Test—Biocompatibility Tests***

**Comment Summary #14:** The commenter stated that <88> testing is not only performed on materials that fail <87> and should be reflected in the chapter.

**Response:** Comment incorporated. The section *Biocompatibility Tests* has been omitted from the chapter.

<b>General Chapter/Sections:</b>	<1382> Assessment of Elastomeric Component Functional Suitability in Parenteral Product Packaging/Delivery Systems
<b>Expert Committee(s):</b>	General Chapters—Packaging and Distribution

**No. of Commenters:** 4

### **General**

**Comment Summary #1:** The commenter recommended a 5-year delayed implementation of the chapter.

**Response:** Comment not incorporated. This is an informational chapter and thus does not require a delay in implementation.

### **Introduction**

**Comment Summary #2:** The commenter recommended excluding products that have packaging that is regulated as a medical device.

**Response:** Comment incorporated.

### **Early Packaging/Delivery System Selection and Development: Functional Suitability Assessment Considerations—Table 1**

**Comment Summary #3:** The commenter recommended adding a bullet, including “moisture barrier” to the functional suitability tests column, subheading “freeze-drying closures for injections vials.” Moisture deposits on the stopper’s inner surface following lyophilization can lead to drug product instability during shelf storage.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter recommended including a footnote to *Table 1* that provides a definition of “single-use.”

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter recommended using the word “plunger” instead of “piston.”

**Response:** Comment incorporated.

### **Final Product Packaging/Delivery System Fitness-For-Intended-Use Suitability Assessment**

**Comment Summary #6:** The commenter recommended clarifying that adequate test selection is a precursor to design verification of the final finished combination product.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter suggested clarifying that the standard test’s acceptance criterion may not reflect the particular intended use (or indication) of the final delivery system.

**Response:** Comment incorporated.

**Comment Summary #8:** The commenter suggested adding a bullet point to emphasize that reliability requirements may not be captured sufficiently. A higher sample size will be needed to establish reliability requirements in verification and validation testing, depending on the indication.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter stated that it is important to not only focus on normal use conditions but also consider misuse conditions.

**Response:** Comment not incorporated. The focus of the chapter is on in-use condition.

### **General Chapter <382> Background and Guidance—Test Samples**

**Comment Summary #10:** The commenter suggested stating that the feasibility assessment for manual placement can be utilized.

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter recommended including mating interfaces as a factor that can affect a component’s assessment outcome.

**Response:** Comment incorporated.

**Comment Summary #12:** The commenter recommended clarifying that the interfaces and mating components should be analyzed carefully when addressing design.

**Response:** Comment incorporated.

***General Chapter <382> Background and Guidance—Test Sample Population Size***

**Comment Summary #13:** The commenter recommended adding considerations regarding variables versus attributes.

**Response:** Comment incorporated.

***General Chapter <382> Background and Guidance—Packaging/Delivery System Integrity Tests***

**Comment Summary #14:** The commenter suggested adding considerations regarding safety and effectiveness.

**Response:** Comment not incorporated. The EC determined that language related to safety and effectiveness is out of the scope of the chapter.

***General Chapter <382> Background and Guidance— Needle and Spike Access Functionality Tests***

**Comment Summary #15:** The commenter suggested that the particle size acceptance criterion of 150 µm should be reduced to 50 µm because <790> does not contain text related to recent data for visible particle size.

**Response:** Comment not incorporated. The visible range for detecting particles is 150 µm.

**Comment Summary #16:** The commenter suggested adding a general reference regarding the acquisition rate as this can have a direct influence on the ability to capture fast-response spikes in force data.

**Response:** Comment incorporated.

***General Chapter <382> Background and Guidance—Plunger Functional Suitability Tests***

**Comment Summary #17:** The commenter suggested including the rate of delivery as an impact on the functional forces.

**Response:** Comment incorporated.

**Comment Summary #18:** The commenter recommended adding considerations regarding fluid surface tension and related material surface energy of the contacting substrate.

**Response:** Comment incorporated.

**Comment Summary #19:** The commenter recommended adding considerations regarding plunger rib design and quantity, as this has a significant influence on forces.

**Response:** Comment incorporated.

**Comment Summary #20:** The commenter recommended including additional information regarding two typical root causes of lubricant breakdown.

**Response:** Comment incorporated.

***General Chapter <382> Background and Guidance—Tip Cap and Needle Shield Functional Suitability Tests***

**Comment Summary #21:** The commenter suggested providing additional information regarding the actual attachment metrics to be carefully considered as part of the tip cap/needle shield attachment force evaluation as they are very important to the overall assessment.

**Response:** Comment not incorporated. The EC determined that the addition would not provide clarification for users.

**General Chapter/Sections:** <1430.3> Analytical Methodologies Based on Scattering Phenomena—Dynamic Light Scattering  
**Expert Committee:** General Chapters—Chemical Analysis  
**No. of Commenters:** 3

### **General**

**Comment Summary #1:** The commenter noted that the chapter does not discuss validation and that the expectation for size measurement is very different from any other analytical method. The commenter recommended that the chapter should clearly communicate that for dynamic light scattering (DLS) or any other scattering based method, ensuring precision is more important than accuracy and that it may be helpful to include reference to ICH Q2R1 for what may or may not be needed for validation purposes (e.g., accuracy, linearity, range, specificity, detection, or quantitation limit are not needed), while validation on precision such as repeatability, reproducibility, and robustness should be emphasized.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable for the scope of this chapter. The recommended aspects are addressed in the proposed harmonized Chapter <430> published in *PF* 46(3).

### **Introduction**

**Comment Summary #2:** The commenter suggested revising the first sentence and provided a recommended text.

**Response:** Comment partially incorporated. The EC revised the text to add a sentence which addresses the commenter's concern and to add clarity to the paragraph.

**Comment Summary #3:** The commenter recommended revising the third sentence to state "DLS can provide size information in the several micron range."

**Response:** Comment not incorporated. The EC determined that the existing text was suitable. The text does not exclude the proposed range but denotes the range that DLS can perform, whereas the other light scattering techniques cannot.

**Comment Summary #4:** The commenter, referring to the penultimate sentence, recommended that the EC consider the overall value of its statement since it may become untrue over time.

**Response:** Comment incorporated. The sentence was deleted.

### **Applications**

**EC-Initiated Change #1:** The EC replaced the entry "Micronization of water insoluble active pharmaceutical ingredients" in the first bullet of the section with "Measuring micronized water insoluble active pharmaceutical ingredients".

### **Theory**

**Comment Summary #5:** The commenter, referring to the discussion associated with Equation 6, recommended expanding the section and including a reference to ISO 22412:2017 Annex B.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable, and the ISO Standard is already referenced in the chapter.

**Comment Summary #6:** The commenter, referring to the first paragraph of subsection *Correlation Functional Analysis*, stated that the scenario did not accurately capture the autocorrelation and recommended the ISO standard to define autocorrelation.

**Response:** Comment partially incorporated. The EC revised the text to replace the "Intensity correlation functions are usually normalized..." with "Intensity correlation functions are commonly normalized...".

**Comment Summary #7:** The commenter, referring to the third paragraph of subsection *Correlation Functional Analysis*, recommended abbreviating the term "polydispersity index" as

“Pdl” or “PDI” instead of “PI” reasoning that those terms are used in some instrument manufacturers manuals.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable, and the “PI” abbreviation as defined in the chapter is well established and recognized in many standards including ISO referenced in the document.

**Comment Summary #8:** The commenter, referring to the first sentence of the penultimate paragraph of subsection *Correlation Functional Analysis*, stated that the aggregation stage (early vs. late) was not relevant to the DLS technique and recommended revising the entry.

**Response:** Comment partially incorporated. The EC removed mentions of aggregates and clarified the paragraph.

**Comment Summary #9:** The commenter, referring to the second sentence of the penultimate paragraph of subsection *Correlation Functional Analysis*, recommended revising the text to replace “from a greater presence of aggregates” with “resulting from the presence of non-specific protein-protein interactions.”

**Response:** Comment partially incorporated. See response to Comment Summary #8.

**Comment Summary #10:** The commenter, referring to the sentence starting with “In addition, sample concentration, relative RI of the particle...” of the final paragraph of subsection *Correlation Functional Analysis*, recommended adding the optical transparency of the cuvette to this list.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable. The cuvettes must be suitable for the intended use as part of the system.

**Comment Summary #11:** The commenter, referring to the penultimate paragraph of subsection *Correlation Functional Analysis*, stating that it discusses the factors that can affect the accuracy of the results determined by DLS, noted that the measurements obtained by DLS are sensitive to temperature and viscosity and recommended including language to indicate the same. Further, the commenter recommended that Temperature and Viscosity be added to the list of factors in section 5.1.

**Response:** Comment partially incorporated. The EC, noting that the influence of temperature and viscosity are inherent in equation 5 and are discussed there, added Temperature and Viscosity to the list of factors in subsection *Factors that Affect the Measurement*.

### **Measurement**

**EC-Initiated Change #2:** The EC revised the second sentence of the Size Range entry under Subsection 5.1 *Factors that Affect the Measurement* from “The laser power determines the lower size limit, while....” to “The instrument optics and engineering determine the lower size limit, while...”.

**EC-Initiated Change #3:** The EC revised the sentence “However, converting to number distribution is not recommended” under subsection *Data Interpretation* to “However, converting to number distribution should be done with caution”.

**Comment Summary #12:** The commenter, referring to the subsection *Factors that Affect the Measurement*, stated this section is of great value to the user and regulator, and recommended expanding the section to include more parameters that are known to change the measurement results.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable. The recommended revisions are instrument setting parameters which are instrument brand specific and are included in an instrument’s user manuals.

**Comment Summary #13:** The commenter, referring to the “avoid large particles” entry under the Sample Preparation item in subsection *Factors that Affect the Measurement*, recommended adding a typical size to better define what constitutes a “large particle”.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable. This need to be determined by the user on a case-by-case basis.



**Comment Summary #14:** The commenter, referring to the first paragraph of the subsection *Sample Preparation*, objected to using the entry “it is best to consider DLS as suspension/emulsion analyzer rather than a particle size analyzer”.

**Response:** Comment incorporated. The EC deleted the first sentence.

**Comment Summary #15:** The commenter, referring to the second paragraph of subsection *Sample Preparation*, suggested revising it and provided revision text. The commenter also noted that the section does not discuss filtration and recommended including some discussion on filtration.

**Response:** Comment partially incorporated. The EC revised the text using part of the recommended text and added an entry on filtration.

**Comment Summary #16:** The commenter, referring to item 6 Sample Ionic Strength Optimization of the listed items in subsection *Test Procedures*, recommended deleting the first sentence and provided a suggested replacement text.

**Response:** Comment partially incorporated. The EC revised the entire paragraph, which addresses the commenter’s concerns.

**Comment Summary #17:** The commenter, referring to item 7 Number of Repetitions in subsection *Test Procedures* recommended adding further explanation to the text.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable noting that this section is mainly about selection of parameters in the instrument’s software and may be interpreted differently in different systems.

**Comment Summary #18:** The commenter, referring to item 7 Number of Repetitions in subsection *Test Procedures*, suggested adding a recommendation for the number of repetitions, e.g., typically triplicate (n=3) or hexaplicate (n=6).

**Response:** Comment not incorporated. The EC determined that the existing text was suitable for this chapter. It is included in the proposed harmonized Chapter <430> published in *PF* 46(3).

**Comment Summary #19:** The commenter, referring to the last paragraph of subsection *Test Procedures*, suggested revising the entry “... the values of  $D_{10}$ ,  $D_{50}$ , and  $D_{90}$  should not be used to describe the distribution” to “...reporting distribution results in  $D_{10}$ ,  $D_{50}$ , and  $D_{90}$  is not recommended”.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable noting that the only reportable values of a DLS measurement are a) average particle size,  $\bar{x}_{DLS}$  and b) Polydispersity index, PI.

### ***Advantages and Limitations***

**Comment Summary #20:** The commenter, referring to the first paragraph, stated that it was not clear why the laser diffraction was specifically highlighted and suggested rewording the sentence and recommended revised text.

**Response:** Comment incorporated.

**Comment Summary #21:** The commenter, noting that this section briefly discusses size ranges, stability, resolution, viscosity, etc., suggested expanding this section and provide a list of items to be included and defined for clarity.

**Response:** Comment not incorporated. The EC determined that the existing text was suitable. The suggestion is outside the scope of the section.

<b>General Chapter/Sections:</b>	<1430.6> Analytical Methodologies Based on Scattering Phenomena—Particle Counting via Light Scattering
<b>Expert Committee:</b>	General Chapters—Chemical Analysis
<b>No. of Commenters:</b>	2

### ***Introduction***

**Comment Summary #1:** The commenter suggested reorganizing the entire section to group media information (i.e., have the paragraphs regarding liquids grouped together and those regarding gases grouped together) for ease of readability.

**Response:** Comment not incorporated. The EC determined that the reorganization did not provide additional clarity.

**Comment Summary #2:** The commenter, stating that the commercially available LSAPC can measure particles as small as 0.05  $\mu\text{m}$ , suggested changing the typical size range in the final paragraph from 0.1–10  $\mu\text{m}$  to 0.1–0.05  $\mu\text{m}$ .

**Response:** Comment incorporated.

### ***Theory***

**Comment Summary #3:** The commenter, referring to the second sentence of the first paragraph, suggested adding “or counted” so that it reads “Particles may be sized or counted...”.

**Response:** Comment partially incorporated. The EC revised the first sentence of the paragraph deleting “or sized,” thus clarifying the content of the second sentence.

**Comment Summary #4:** Referring to the second paragraph entry that “Different models cover different scattering regimes, e.g., the Rayleigh regime, Mie regime, or Fraunhofer regime...”, the commenter stated that the term “regime” to describe these theories is not used consistently throughout the <1430> series of chapter and recommended harmonizing these terms.

**Response:** Comment not incorporated. The EC determined that the current text is suitable. The use of “regime” or “theory” depends on the context of the content being discussed. The EC will review all these chapters in the future as part of the regular review.

### ***Instrumentation***

**Comment Summary #5:** The commenter suggested revising the first sentence for clarity and specificity and provided a recommended text.

**Response:** Comment incorporated. The EC revised the text as recommended.

### ***Factors that Affect the Testing***

**Comment Summary #6:** The commenter suggested revising the first sentence of the first paragraph for clarity and provided recommended text.

**Response:** Comment partially incorporated. The EC revised the text to change the “deviations in the physical properties” to “differences in the physical properties.” The additional recommended text was a matter of style.

**Comment Summary #7:** The commenter, referring to the second sentence of the first paragraph, recommended revising the text to add that “if silicone is suspected, this methodology should not be used”.

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

### ***Qualification of Light Scattering Particle Counting Instruments***

**Comment Summary #8:** The commenter suggested an editorial change in the second sentence of the second paragraph of subsection *Size Calibration* replacing “and” with “where” to read “The particles will produce a distribution of voltages and where the median voltage...”.

**Response:** Comment incorporated.

**Comment Summary #9:** The commenter suggested revising the second sentence of the third paragraph of subsection *Size Calibration* to replace “irregular” with “nonspherical” to read “Due to the influence of optical properties of the particle material, particle shape (spherical or nonspherical) ...”.

**Response:** Comment partially incorporated. The EC removed the content of the parenthesis.

**Comment Summary #10:** The commenter, referring to the subsection *Sensor Resolution*, suggested revising the section and provided a recommended outline for the revised content.

**Response:** Comment incorporated. The EC revised the text as recommended.

**Comment Summary #11:** The commenter, referring to the subsection *Calibration Interval*, suggested revising the sentence to add “or LSAS” to it.

**Response:** Comment incorporated.

**General Chapter/Sections:** <1430.7> Analytical Methodologies Based on Scattering Phenomena—Nephelometry and Turbidimetry  
**Expert Committee:** General Chapters—Chemical Analysis  
**No. of Commenters:** 1

### **Theory**

**Comment Summary #1:** The commenter referring to section *Rate Nephelometry* entry “Formation of light scattering complexes is dependent on optimal concentration of antibodies and antigen molecules” stated that the antibody-antigen complexes are not the only kind of the complexes that this technology can be used with and suggested revising the section to make a clear distinction that antibody-antigen complexes are an example.

**Response:** Comment partially incorporated. The EC, noting that the previous paragraph clearly uses the antibody-antigen complex as an example of the complexes, revised the paragraph for clarity to state “The extent of formation of light scattering complexes depends on concentrations of complex formation entities, e.g., antibodies and antigen molecules for immunonephelometry.”

### **Instrumentation**

**Comment Summary #2:** The commenter, referring to section *Calibration of Rate Nephelometric Instruments*, recommended including more comprehensive content regarding instrument calibration and system suitability testing for intended use and suggested including a reference to <1058>.

**Response:** Comment partially incorporated. The EC noted that the “Performance Qualification” is addressed in sub-1000 chapters and the “Calibration” entered here was intended to emphasize the specificity of this instrument type. The EC revised the text by deleting the entry “select panels of commercial, certified” text to state “The user-defined component relies on protein controls.”

### **Method Development**

**Comment Summary #3:** The commenter, referring to section *Robustness*, suggested including a bullet point for “Reagent Stability” reasoning that it is part of the robustness assessment.

**Response:** Comment incorporated. The EC revised the text adding a bullet for “Reagent use/hold times”.

**General Chapter/Section:** <1603> Good Cascade Impactor Practices  
**Expert Committee(s):** General Chapters—Dosage Forms  
**No. of Commenters:** 4

### **General**

**Comment Summary #1:** The commenter indicated that although this chapter is very well written, part of this chapter is too detailed and out of scope for <1603>.

**Response:** Comment not incorporated. The chapter is informational and is intended to provide detailed information for users.

**Comment Summary #2:** The commenter suggested clarifying whether this chapter covers newer types of impactors (ELPI, ELPI+, automated systems, etc.).

**Response:** Comment not incorporated. This chapter does not cover newer impactors, only the impactors covered in <601>.

**Comment Summary #3:** The commenter suggested removing references to Tables and Figures in <601> and <1601> as these referenced chapters may undergo revisions, resulting in changes to Figures and Tables references, therefore making the references in <1603> redundant.

**Response:** Comment not incorporated. The EC noted that the references will be updated according to existing dependency processes if changes are made in the referenced chapters in the future.

**Comment Summary #4:** The commenter suggested removing any examples of specific equipment names to avoid any unintentional commercial bias/preference, for example, page 10, 'TSI Model 4040'.

**Response:** Comment incorporated.

### ***Introduction***

**Comment Summary #5:** The commenter suggested presenting the introduction in a single section (without subsections) as done for most of the other USP general chapters.

**Response:** Comment not incorporated. Format used provides clarity for the reader.

**Comment Summary #6:** The commenter suggested noting that the FDA guidance was updated in 2018.

**Response:** Comment incorporated.

**Comment Summary #7:** The commenter requested clarifying what “adequate resolution of the fine particle mass component of the delivered dose” means in the second paragraph under the *Introduction* section.

**Response:** Comment not incorporated. “Adequate resolution” is product specific, and therefore it is not possible to include a general criterion in this informational chapter.

**Comment Summary #8:** The commenter requested removing the entire second paragraph from the section *Background and Rationale* except for the portion about regulatory guidance as extensive history of the need for this chapter is not necessary and detracts from the information presented in the chapter. The commenter suggested removing the historical information in this paragraph.

**Response:** Comment not incorporated. Existing text provides the rationale for the chapter.

**Comment summary #9:** The commenter suggested revising the following sentence in section 1.1. from “GCIP has the following purposes from a regulatory perspective:” to “The purpose of GCIP is to:”.

**Response:** Comment incorporated.

**Comment Summary #10:** The commenter proposed modifying the following sentence because impactors are used for clinical and commercial drug products only if qualified and placed in a Good Manufacturing Practices (GMP) state and the analytical method is performed only if validated for release and stability testing. Therefore, there are many factors at play for the generation of discriminatory aerodynamic particle size distribution (APSD) results. The commenter suggested changing the following sentence from “The ultimate goal is to establish and maintain the capability to distinguish between acceptable and unacceptable drug product batches” to “The ultimate goal is to establish and maintain the capability to determine the APSD and quality consistency of drug product batches.”

**Response:** Comment incorporated.

**Comment Summary #11:** The commenter recommended aligning *Figure 2* with any currently planned update of <601> to avoid duplication.

**Response:** Comment incorporated.

**Comment summary #12:** The commenter requested referencing the current FDA draft guidance published in April 2018 [Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products – Quality Considerations] and indicating that it has replaced the 1998 guidance.

**Response:** Comment incorporated.

**Comment summary #13:** The commenter recommended replacing “material (mass)” with “mass” in the second paragraph and second sentence of section *Background and Rationale* for consistency with <601>.

**Response:** Comment incorporated.

**Comment summary #14:** In section *Purpose and Scope*, the commenter suggested indicating that the chapter presents “current thinking” on cascade impactor practices.

**Response:** Comment incorporated.

### ***Definitions of Key Terms Related to this Chapter***

**Comment Summary #15:** The commenter requested adding further explanation of “dynamic shape factor” or an appropriate reference in this section.

**Response:** Comment incorporated. The EC added a reference to, “Hinds W.C. 1999 ‘Properties, behavior and measurement of Airborne Particles’ Wiley Interscience, NY 1999.”

### ***Cascade Impactor Operating Principles***

**Comment Summary #16:** The commenter suggested replacing the term, “collection surface” with “impaction surface” as this is the term used in *Figure 1*.

**Response:** Comment partially incorporated. The term “collection surface” has been replaced with “impaction plate/cup” for clarity.

**Comment Summary #17:** The commenter suggests defining  $W_{eff}$  in this section as “effective nozzle diameter – as defined in Section 2—most stages will contain n nozzles machined to be as close to identical as possible” and not as “nozzle diameter—most stages will contain n nozzles machined to be as close as possible to identical”.

**Response:** Comment incorporated.

**Comment summary #18:** The commenter requested replacing “a jet or nozzle plate” with “a nozzle plate” in section 3, for consistency with <601>.

**Response:** Comment incorporated.

**Comment summary #19:** The commenter suggested revising *Figure 1* for clarity by replacing “particle too small to impact” with “particle with too small inertia to impact” and “particle too large to remain airborne” with “particle with too large inertia to remain airborne.”

**Response:** Comment incorporated.

**Comment summary #20:** The commenter indicated that the Stokes number has already been defined in Section 2 of the chapter (*Definitions of Key Terms Relating to this Chapter*) therefore, suggest moving the fourth paragraph of Section 3 and equation [3] to Section 2.

**Response:** Comment not incorporated. Section 2 is the definitions section and the equation is correctly placed for the discussion in this section.

**Comment Summary #21:** The commenter suggested revising “The ratio, S/W, can vary widely in the range 1–10 for effective size fractionation ...” to read “The ratio, S/W, can vary widely in the range 1–10 for effective size fractionation to occur, and therefore changes in service are unlikely to influence stage performance, given typical mass loadings associated with inhaler APSD measurements, even on the stages where most of the particulate deposits” for clarity.

**Response:** Comment incorporated.

**Comment Summary #22:** The commenter suggested revising the definition of  $C_{ae}$  in this section to read “...designated as unity from this point onwards”.

**Response:** Comment incorporated.

**Comment Summary #23:** The commenter suggested revising the second to the last sentence of this section as follows: “More importantly, however, any leakage of ambient air into the

impactor at locations other than via the induction port, will increase the local value of Q after the leakage point, and in consequence result in an uncontrolled decrease in  $d_{50}$  for stages downstream.”

**Response:** Comment incorporated.

**Comment Summary #24:** The commenter suggested adding text to clarify the applicability of the restriction of total flow volume to dry powder devices and not to inhalation aerosols or nasal sprays.

**Response:** Comment not incorporated. The language is consistent with <601>.

**Comment Summary #25:** The commenter indicated that one should not ignore the flow start up duration, and therefore suggested revising the instructions to read “In practice, this finite start-up time is ignored in such assessments on the basis that it represents a small fraction of the total time during which the 4-L volume is sampled.”

**Response:** Comment not incorporated. In practice, the process stated in the existing text is understood as accepted practice, i.e., the small but finite start-up time for the flow rate of the apparatus to reach stability in DPI testing for aerosol APSD is ignored.

**Comment Summary #26:** The commenter suggested clarifying the first sentence below *Figure 3*.

**Response:** Comment incorporated.

### ***Apparatus Maintenance***

**Comment Summary #27:** The commenter recommended replacing “material balance” with “mass balance” throughout the second paragraph for consistency with <601>.

**Response:** Comment incorporated.

**Comment Summary #28:** The commenter suggested replacing “be washed separately” with “be washed separately from both each other and from the collection surfaces.” This change will clarify that the wall deposits must be kept separate from the deposits on the collection surfaces.

**Response:** Comment incorporated.

**Comment Summary #29:** The commenter suggested replacing “the minimum volume” with “the minimum necessary volume” for clarity in the second paragraph, third sentence.

**Response:** Comment incorporated.

**Comment Summary #30:** The commenter recommended replacing “particulate” with “deposits” for clarity in the first paragraph, first sentence of section *Inspection of Damaged/Deformed Collection Surfaces*.

**Response:** Comment incorporated

**Comment Summary #31:** The commenter suggested replacing “if damage/deformation is apparent” with “if the measured dimensions or surface condition are not within tolerances” in the first paragraph, last sentence of the section *Inspection of Damaged/Deformed Collection Surfaces*.

**Response:** Comment not incorporated. This is an informational chapter and text provides for judgement by the individual; there are no specifications for the impactor components (other than the stage nozzles) that can be referred to.

**Comment Summary #32:** The commenter recommended replacing “damaged” with “damaged or marginally functional” for clarity in the second paragraph, fourth sentence of the section *Inspection of Damaged/Deformed Collection Surfaces*.

**Response:** Comment incorporated. This language was moved to section *Inspection of Cascade Impactor Components Susceptible to Deterioration* in response to comments received.

**Comment Summary #33:** The commenter suggested moving the “Stage Mensuration” definition from *Definitions of Key Terms Related to this Chapter* (Section 2) to *Apparatus Maintenance*.

**Response:** Comment not incorporated. The EC kept the definition in Section 2 since this section includes definitions for all relevant terms.

**Comment Summary #34:** The commenter requested changing from “up to 100 ms” to “up to 400 ms” in the following sentences “This process can take up to 100 ms for impactors having large internal volume, in particular, the Next Generation Impactor (NGI).”

**Response:** Comment incorporated.

**Comment summary #35:** The commenter suggested removing the word “performance” from the sentence “The calculated value of W is compared with the tolerance range established for that stage for either the Andersen Cascade Impactor or the NGI in <601> to establish if the stage performance is within specification” as performance is not what is actually measured.

**Response:** Comment incorporated.

**Comment summary #36:** The commenter suggested revising the following “Note” under *Figure 4* because the material from which the impactor is made as well as formulation excipients may influence wear on nozzle plates and thus the required frequency for mensuration. The sentence would read “The frequency of the ‘In-use mensuration’ check is determined by the amount of impactor use, the material from which the impactor is constructed, the product ingredients, and the recovery solvent characteristics.”

**Response:** Comment incorporated.

**Comment Summary #37:** The commenter suggested revising the following sentence above *Figure 4* in *Stage Mensuration, Measurement, Traceability, and Mensuration Interval* and questioned whether there are manufacturers that provide impactors compliant with the NGI design that have removable stages. The sentence would read “However, in the case of the NGI, the entire unit will need to be returned to the supplier for remedial action to provide stage(s) whose W values are within specification. Once values of W for each stage are ascertained to be within specification, the entire cascade impactor can be accepted for use.”

**Response:** Comment not incorporated. Text in the chapter refers to NGIs as defined in <601>.

**Comment summary #38:** The commenter suggested revising point 1 in *Stage Mensuration, Measurement Traceability, and Mensuration Interval* titled “Stage by Stage installation mensuration” because this is completed by the manufacturer before dispatch and not after receipt.

**Response:** Comment not incorporated. Users are not expected to redo the mensuration, they can check the certificate from the manufacturer.

**Comment Summary #39:** The commenter suggested aligning the APSD profile statement in *Internal Losses* (last 2 sentences) with the current <601> method as this is common practice.

**Response:** Comment not incorporated. The statement in <1603> is consistent with the current proposed version of <601>.

**Comment Summary #40:** The commenter suggested revising section *Stage Mensuration, Measurement Traceability, and Mensuration Interval* to add the phrase “as well as the end user established cleaning procedures” to the end of point 4.

**Response:** Comment incorporated.

**Comment Summary #41:** The commenter suggested revising point 6 in *Stage Mensuration, Measurement Traceability, and Mensuration Interval* to recommend that an impact assessment is conducted on how/if the results of previous analyses may/may not have been affected since the last “good” mensuration and what this may or may not mean regarding product quality.

**Response:** Comment not incorporated. Information is included in <601> in the NGI section.

**Comment summary #42:** The commenter suggested revising the last sentence of the first paragraph under *Internal Losses* as follows “Chapter <601> therefore sets an upper limit of 5% of the total delivered drug mass per actuation from the inhaler as a ~~system suitability~~ validation requirement to limit the impact of such internal losses on measurement.”

**Response:** Comment incorporated.

**Comment summary #43:** The commenter suggested revising the first sentence of the first paragraph under section 4.3 as follows “Cascade impactors are ~~nowadays~~ typically manufactured from durable materials...”.

**Response:** Comment incorporated.

**Comment summary #44:** The commenter suggested revising the last sentence of section 4.3 to read “The component should be taken out of use and replaced if damage/deformation is apparent and is likely to affect performance.”

**Response:** Comment incorporated.

**Comment Summary #45:** The commenter suggested moving the following text under *Inspection of Damaged/Deformed Collection Surfaces* to section 6.2 *Inspection of Cascade Impactor Components Susceptible to Deterioration*. The moved text would read “The frequency of such inspections will depend upon the amount of use the components receive, as well as experience gained with time in service, however, as a start an annual inspection is recommended. Inspected components that are deemed damaged should be identified as such and removed from service. Visual inspection of the seal body and inter-stage passageways of the Next Generation Impactor can be difficult and may therefore best be undertaken by the supplier/manufacture.”

**Response:** Comment incorporated.

**Comment Summary #46:** The commenter suggested deleting *Apparatus Maintenance and Cascade Impactor Method Development*.

**Response:** Comment not incorporated. The purpose of this chapter is to discuss measures to ensure cascade impactors are system suitable in the context of inhaler product quality control (QC) and provide the necessary guidance.

#### ***Cascade Impactor Method Development***

**Comment summary #47:** The commenter suggested revising the first sentence under *Initial Considerations* to replace “should always be” with “is typically”.

**Response:** Comment incorporated.

**Comment Summary #48:** The commenter suggested modifying the following sentence in *Number of Inhaler Actuations/Inhalations per Determination* from “may disguise underlying shifts in APSD that occur from one operation of the inhaler to the next” to “may disguise any underlying variability in APSD that occur from one actuation of the inhaler to the next.”

**Response:** Comment incorporated.

**Comment Summary #49:** The commenter proposed to delete the following from *Number of Inhaler Actuations/Inhalations per Determination* as any apparent variability (changes) in APSD during APSD testing will be within the specifications of the product and phrases such as “shift” should not be used. The deleted text would be “. . .repeated actuations/inhalations may disguise underlying shifts in APSD that occur from one operation of inhaler to the next, and therefore. . .”.

**Response:** Comment not incorporated. The EC determined that the language is necessary.

**Comment Summary #50:** The commenter requested deleting the following sentence from *Number of Replicate APSD Determinations* or if the sentence is retained, then change the phrase “labor-intensive” with “relatively time-consuming.” The sentence suggests that replicates are always or routinely performed. Additionally, the phrase “labor-intensive” may be misconstrued that such tests are not scientific or technologically advanced. Various full or partial automation equipment are also commercially available to assist cascade impaction testing. The sentence reads “The cascade impactor-based method for determining inhaler APSD performance is both a labor-intensive and exacting procedure, so that there is an incentive to reduce the number of replicate determinations to the minimum to provide assurance of the intrinsic variability of the metrics used to assess the size properties.”

**Response:** Comment not incorporated. There are existing laboratories that are doing this test manually.

**Comment Summary #51:** The commenter proposed deleting the sentence “It is common to undertake at least five replicate measurements at each condition being assessed” in *Number of*



*Replicate APSD Determinations* unless there is a public reference or statistical justification for this statement.

**Response:** Comment not incorporated. This procedure is consistent with current FDA guidance and <601>.

**Comment Summary #52:** The commenter suggested revising the second sentence under *Number of Replicate APSD Determinations*, stating that minimum number should not be specified. The number of replicates should be justified based on the specific product being tested and will depend on the variability of the method and the intrinsic variability of the product and the acceptance criteria being applied.

**Response:** Comment not incorporated. Information provided in the chapter is consistent with the FDA guidance.

**Comment Summary #53:** The commenter requested revising the third sentence under *Number of Replicate APSD Determinations* to remove the word “backup.”

**Response:** Comment incorporated.

**Comment Summary #54:** The commenter requested revising the sentence in third paragraph under *Number of Replicate APSD Determinations*, as care must be taken that any plate coating material used does not interfere with recovery of drug from the plates nor with the subsequent analysis procedure. The commenter provided proposed text.

**Response:** Comment partially incorporated. The proposed text was modified. Revised text reads “The choice of coating material will depend upon the physicochemical properties of the drug product being sampled as well as the subsequent recovery and analytical procedure.”

**Comment Summary #55:** The commenter suggested revising the first sentence of second paragraph under *Mitigation of Electrostatic Charge Accumulation* to simplify the instructions regarding grounding the measurement equipment and operator.

**Response:** Comment not incorporated. Existing text denotes that precautions are necessary depending on the local conditions.

**Comment summary #56:** The commenter suggested replacing “more than one actuation/inhalation will likely be needed” with “more than one actuation or dose unit may be needed” and “the minimum number of actuations” with “the minimum number of actuations or dose units” in *Number of Inhaler Actuations/Inhalations per Determination*.

**Response:** Comment incorporated.

**Comment summary #57:** The commenter suggested the following changes in *Number of Replicate APSD Determinations*:

- The first sentence mentions that APSD determination is labor-intensive. Indicate that automated or semi-automated systems are becoming available on the market.
- Replace “incentive to reduce the number of replicate determinations to the minimum to provide assurance” with “incentive to minimize the number of replicate determinations to provide assurance.”
- Editorial correction for the last sentence to replace “the number of conditions” with “the number of actuations.”

**Response:** Comments incorporated.

**Comment Summary #58:** The commenter suggested including some instruction about the mouthpiece adapter design/fitting and impact on the impaction data.

**Response:** Comment not incorporated. This is outside of the scope.

**Comment summary #59:** The commenter indicated that an inhalation is not applicable to APSD testing and therefore recommended replacing “actuation or inhalation” with “one actuation or dose unit” in the first sentence.

**Response:** Comment incorporated.

**Comment Summary #60:** In *Number of Inhaler Actuations/Inhalations per Determination*, the commenter suggested replacing “may disguise underlying shifts in APSD that occur from one

operation of the inhaler to the next” to “may disguise any underlying variability in APSD that occur from one actuation of the inhaler to the next.”

**Response:** Comment incorporated.

**Comment Summary #61:** The commenter proposed deleting “repeated actuations/inhalations may disguise underlying shifts in APSD that occur from one operation of inhaler to the next, and therefore...” from *Number of Inhaler Actuations/Inhalations per Determination* as any apparent variability (changes) in APSD during APSD testing will be within the specifications of the product and phrases such as “shift” should not be used.

**Response:** Comment not incorporated. The EC determined that this information is necessary.

**Comment summary #62:** The commenter requested following edits in *Mitigation of Particle Bounce and Re-Entrainment*:

- a. First paragraph, third sentence: replace “will almost certainly be necessary” with “will usually be necessary.”

**Response:** Comment not incorporated as the EC determined that stronger language is needed here.

- b. First paragraph, fourth sentence: For clarity, replace “pre-coating is a prerequisite for inhalation powders” with “pre-coating is normally used for inhalation powders.”

**Response:** Comment incorporated.

- c. Third paragraph, second sentence: For clarity, replace “dispersed” with “deposited.”

**Response:** Comment incorporated.

- d. Third paragraph, third sentence: For clarity, replace “drug product being sampled” with “drug product being sampled and the lack of interference with subsequent quantitation.”

**Response:** Comment incorporated.

- e. Third paragraph, last sentence: For clarity, replace “visibly inspected for non-uniformities in the coating” with “visually inspected for coating uniformity.”

**Response:** Comment partially accepted. The EC changed “visibly” to “visually,” but retained language for non-uniformities because the inspection is for non-uniformities.

- f. Delete the last sentence of the last paragraph (“alternatively, it may be appropriate...”) because it is unnecessary.

**Response:** Comment not incorporated. This describes an alternative procedure. The EC also changed “tacky” to “viscous.”

**Comment summary #63:** In *Mitigation of Electrostatic Charge Accumulation*, the commenter suggested replacing “modifying the size properties” with “modifying the particle size properties” and replacing “increase of variability” with “increase in variability.”

**Response:** Comment incorporated.

### ***In-Use Aspects***

**Comment Summary #64:** The commenter requested clarification regarding whether the purpose of *Initial Considerations* is operational or performance.

**Response:** Comment not incorporated. The text in this section states the purpose.

**Comment Summary #65:** The commenter requested revising the second to last sentence in *Initial Considerations* to read as follows because typically stage groupings or interpolated results such as specific mass fractions are reported, rarely stage-by-stage for QC. The sentence would read “From a regulatory science perspective, *the mass of active pharmaceutical ingredient deposited on a stage-by-stage basis is generally initially reported to establish the APSD profile of the drug product. At the appropriate time, stage groupings may be proposed based agreement with the regulatory agency.*”

**Response:** Comment incorporated.

**Comment Summary #66:** The commenter requested revising the last paragraph under *Inspection of Cascade Impactor Components Susceptible to Deterioration* because not all damage will be detected by the visual inspection.

**Response:** Comment not incorporated. A user can check for and visually identify cracks in the O-ring seals.

**Comment Summary #67:** The commenter requested revising the second to last sentence before *Table 1* in section 6.4.1, by adding, “unless justified” since some inhalation powders do not require the use of the pre-separator, but this needs to be justified by data.

**Response:** Comment incorporated.

**Comment Summary #68:** The commenter requested removing reference to the specific model of flowmeter from *Setting the Flow Rate* as it has a wide bore flow tube which is inconsistent with tubing diameters (typically 10 mm) referred to in <601>.

**Response:** Comment not incorporated. The reference to the specific model of flowmeter is provided as an example and not a requirement.

**Comment Summary #69:** The commenter suggested revising *Figure 5* because the set-up must be changed after the leak test in order to perform dose withdrawal. It is better to recommend a set-up so that dose withdrawal can be performed directly after removal of the elastomer plug.

**Response:** Comment incorporated. Text added in procedure to address the issue.

**Comment Summary #70:** The commenter suggested showing the NGI in *Figure 5*, since it is the “next generation impactor”.

**Response:** Comment incorporated. A “Note” included with *Figure 5* covers the topic.

**Comment Summary #71:** The commenter requested clearly defining “accuracy” and “precision” in different measurements.

**Response:** Comment not incorporated. “Accuracy” and “precision” have already been defined as terms in ICH and the definitions apply here.

**Comment summary #72:** The commenter suggested the following changes in “Assertion of Correct Assembly – Andersen Cascade Impactor”:

- a. The flow rate of 30 L/min is not discussed in <601>. *Table 3* in <601> includes 28.3 L/min. Therefore, replace “30 L/min” with “28.3 L/min” in the second paragraph of this section and in *Table 1* (title and column A). If 30 L/min is used for powders, then both <601> and <1604> need to be updated to include the cut off diameter table with 30 L/min.

**Response:** Comment incorporated. Andersen is operated at a nominal flow rate of 28.3 L/min at the lowest flow rate.

- b. Editorial correction for the third paragraph, last sentence to change “plate” to “plates.”

**Response:** Comment not incorporated. The plural is reflected in the language “two types.”

- c. Editorial correction for the fourth paragraph, fifth sentence to change “following by” to “followed by.”

**Response:** Comment incorporated.

**Comment summary #73:** The commenter suggested the following changes in “Assertion of Correct Assembly – Next Generation Impactor”:

- a. Second paragraph, third sentence: For clarity, replace “entity” with “unit.”

**Response:** Comment incorporated.

- b. Delete the last three sentences of the second paragraph (“Multiple cup-sets may be used...so they are identified as a single set”) because they are unnecessary.

**Response:** Comment not incorporated. Text describes an alternative, so the word “alternatively” was added.

**Comment summary #74:** The commenter suggested the following changes in *Mitigation of Air Leakage in the Apparatus*:

- a. First paragraph, first sentence: replace “Equation 4” with “Equation 4 of Section 3” because the reference is unclear.

**Response:** Comment incorporated.

- b. Third paragraph, list item (1.): The initial position of the flow control valve should be specified. Therefore, revise item (1.) to read as follows: “1. With the flow control valve closed, the gate valves, G1 and G2, are opened, and the vacuum source is activated.”

**Response:** Comment incorporated.

- c. Third paragraph, list item (2.): There is no needle valve identified in the referenced drawing. Therefore, change “adjusting the needle valve” to “adjusting the flow control valve.”

**Response:** Comment incorporated.

- d. Third paragraph, list item (3.): For clarity, replace “to isolate the test apparatus” with “to isolate the test apparatus from the vacuum pump.”

**Response:** Comment incorporated.

- e. Third paragraph, list item (4.): There needs to be an air bleed valve open to the atmosphere into the evaluated system between G1 and the vacuum pump to prevent oil backing up from the pump into the system. Either the diagram and instructions need to be modified to include this bleed valve and instructions to vent to air prior to shutting off the pump, or the pump needs to be left on until the system is open to the atmosphere. Therefore, either deleting item (4.), modifying it as described in this comment, or moving the instruction to after item (7.) in the list.

**Response:** Comment incorporated. The instructions were moved as suggested.

- f. Last paragraph, first sentence: For clarity, replace “if L exceeds this limit, carry out an” with “if L exceeds this limit, disassemble the.”

**Response:** Comment incorporated. Replaced “disassemble” with “examine.” This section was also reworded for clarity.

**Comment summary #75:** The commenter suggested following changes in *Setting of Flow Rate*:

- a. Replace “air volumetric flow rate flowing” with “air volumetric flow rate.”

**Response:** Comment incorporated.

- b. Figure 6: For clarity, separate A and B into two illustrations instead of using the dashed line.

**Response:** Comment not incorporated. The EC determined that the illustration is clear as presented.

- c. Figure 6, Part A: For clarity, replace “Andersen cascade impactor” with “Andersen cascade impactor with PS.”

**Response:** Comment incorporated.

**Comment summary #76:** The commenter suggested replacing “the impactors may be treated as interchangeable” with “the impactors may be interchangeable, but it is advisable to perform comparative testing to validate their equivalence” in *Assertion that Individual Cascade Impactor Assemblies of the Same Type (i.e., Andersen Cascade Impactor or Next Generation Impactor) are Interchangeable*.

**Response:** Comment partially incorporated. A modified version of the proposed text is included.

**Comment Summary #77:** The commenter suggested deleting *Mitigation of Air Leakage into the Apparatus*, as the title of this Section gives the impression that air leakage is an issue when

determining APSD. For APSD determinations, leak rate testing is routinely performed, and the APSD test is performed only when any leak rate limit has been met and assured.

**Response:** Comment not incorporated. The EC determined that this is a critical issue to cover and it would be inappropriate to remove this advice.

**Comment Summary #78:** The commenter suggested re-wording the title of Section 6.5 (if it is retained) from *Mitigation of Air Leakage into the Apparatus* to *Air Leak Testing*.

**Response:** Comment not incorporated. This title is consistent with structure of In-Use Aspects.

**Comment Summary #79:** The commenter suggested deleting *Assertion that Individual Cascade Impactor Assemblies of the Same Type (i.e., Andersen Cascade Impactor or Next Generation Impactor) are Interchangeable*, as the aspects regarding “inter-changeability” represent the authors’ opinions. The use of components of an impactor and any “inter-changeability” is governed by cGMP.

**Response:** Comment not incorporated. The EC determined that the content of this section is consistent with the structure of the section/chapter.

**General Chapter/Sections:** <1671> Application of Moisture Vapor Transmission Rates for Solid Oral Dosage Forms in Plastic Packaging Systems  
**Expert Committee(s):** General Chapters—Packaging and Distribution  
**No. of Commenters:** 4

#### **General Comments**

**Comment Summary #1:** The commenter suggested revising all instances of longer-than-typical sentences.

**Response:** Comment incorporated.

#### **Use of Desiccants for MVTR Determination**

**Comment Summary #2:** The commenter recommended clarifying what is meant by “preconditioning.”

**Response:** Comment incorporated.

#### **Comparison of MVTR Results for Water and Desiccant Method**

**Comment Summary #3:** The commenter suggested adding guidelines on the range of insignificant difference required for two packaging systems to be equivalent for Solid Oral Dosage Forms (SODF) when comparing Moisture Vapor Transmission Rates (MVTRs) without the need to provide stability data.

**Response:** Comment incorporated.

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### **Monographs**

**Monograph/Section(s):** Bitter Orange Fruit Flavonoids Dry Extract /Multiple Sections  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines  
**No. of Commenters:** 2

#### **Definition**

**EC-Initiated Change #1.** Because the compounds poncirin and hesperitin coelute, the wording in the *Definition* and throughout the monograph has been changed to “hesperitin/poncritin”.

### Identification

**Comment Summary #1.** The commenter proposed that the acceptance criteria in HPLC Identification be revised to state that every substance identified “may be” present, rather than that all “must be” present.

**Response:** Comment incorporated.

### Composition

**EC-Initiated Change #2.** In *Table 1*, the following compounds in Column 1 (*Analyte*) have been excluded: Unspecified flavonoid 2, unspecified flavonoid 4, unspecified flavonoid 6, and unspecified flavonoid 7.

**Comment Summary #2.** The commenter suggested that taking into account the analytical results obtained for batches of this product, they propose a synephrine content limit of NMT 1%.

**Response:** Comment incorporated. A *Limit for Synephrine* of NMT 1% will be incorporated in the *Specific tests* section of the monograph in a revision that will be published in *PF 46(4)* [Jul.-Aug. 2020].

**Comment Summary #3.** The commenter recommended that a limit of NMT 2% for synephrine be added.

**Response:** Comment partially incorporated. A *Limit for Synephrine* of NMT 1% will be incorporated in the *Specific tests* section of the monograph in a revision that will be published in *PF 46(4)* [Jul.-Aug. 2020].

**Monograph/Section:** Budesonide Nasal Spray/Multiple  
**Expert Committee:** Chemical Medicines Monographs 6  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the budesonide drug substance is defined as a mixture of two epimers, A and B, and requested clarification regarding the two epimers not being referred or resolved in the proposed *Assay* procedure.

**Response:** Comment not incorporated. The EC determined that the proposed *Assay* procedure is consistent with the FDA-approved application and is suitable for the intended use.

**Comment Summary #2:** The commenter indicated that the budesonide related compound E and the budesonide pyruvic acid analog are listed as separate entries in the *Organic Impurities, Table 3*, unlike the drug substance monograph where only the budesonide related compound E is mentioned.

**Response:** Comment not incorporated. The EC determined that the proposed impurity profile and the corresponding acceptance criteria are consistent with the FDA-approved application and can adequately monitor the quality of the drug product.

**Comment Summary #3:** The commenter recommended that the chemical name for Budesonide 21-acetate (epimers) be made consistent with the chemical name in the budesonide drug substance monograph.

**Response:** Comment not incorporated. The proposed chemical name for Budesonide 21-acetate (epimers), 16 $\alpha$ ,17-[Butylidenebis(oxy)]-11 $\beta$ -hydroxypregna-1,4-diene-3,20-dione-21-yl acetate, is consistent with the current USP naming convention. Steps have been taken to update the budesonide drug substance monograph.

**Monograph/Section:** Ciprofloxacin Ophthalmic Solution/Multiple  
**Expert Committee:** Chemical Medicines Monographs 1  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the acceptance criteria for Ciprofloxacin ethylenediamine analog is not consistent with the FDA-approved limits in the test for organic impurities.

**Response:** Comment incorporated. The limit for Ciprofloxacin ethylenediamine analog is widened from NMT 0.2% to NMT 0.5%.

**Comment Summary #2:** The commenter noted that some degradation products of ciprofloxacin are not included in the acceptance criteria in the test for organic impurities.

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

**Comment Summary #3:** The commenter recommended inclusion of appropriate tests from <771> such as *Particulate and Foreign Matter* and *Container Content*.

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

**Monograph/Section(s):** Cod Liver Oil/Labeling  
**Expert Committee:** Non-Botanical Dietary Supplements  
**No. of Commenters:** 1

**Comment Summary #1:** In addition to  $\mu\text{g}$ , the *Labeling* requirement should also include the Retinol Activity Equivalent (RAE) in order to align with recent FDA labeling requirements.

**Response:** Comment incorporated.

**Monograph/Section(s):** Cod Liver Oil Capsules/Labeling  
**Expert Committee(s):** Non-Botanical Dietary Supplements

**EC-initiated Change #1:** The *Labeling* section was revised to indicate that the content of vitamin A must be labeled in  $\mu\text{g}$  RAE (Retinol Activity Equivalent) and that expression of the amounts of vitamin A and vitamin D in terms of units may be added in parentheses after the mass units.

**EC-initiated Change #2:** Footnotes were added to clarify RAE measurements and the relationship of USP or International Units (IU) to mass.

**Monograph/Section(s):** D-*chiro*-Inositol/Multiple  
**Expert Committee:** Non-Botanical Dietary Supplements  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended adding a limit for chloride peak as a specified impurity to the Related Compounds procedure and recommended adding a test for *Chloride and Sulfate* with a limit of chloride at NMT 0.5%.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended adding a test for *Residue on Ignition* with acceptance criteria of NMT 0.5%.

**Response:** Comment incorporated.

**Monograph/Section:** Dicyclomine Hydrochloride/Multiple  
**Expert Committee:** Chemical Medicines Monographs 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the acceptance criteria for dicyclomine related compound A is not consistent with the FDA-approved limits in the test for Organic Impurities.

**Response:** Comment incorporated. The limit for dicyclomine related compound A is widened from 0.15% to 0.2%.

**Comment Summary #2:** The commenter indicated that the acceptance criterion for total impurities is not consistent with the FDA-approved limits in the test for Organic Impurities.

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

**Comment Summary #3:** The commenter requested not to widen the limit from 99.0%–102.0% to 98.0%–102.0% in the Assay.

**Response:** Comment not incorporated. The liquid chromatography method replaces the nonspecific titration method for Assay. The EC determined that the proposed limit is consistent with the chromatographic procedure.

**Comment Summary #4:** The commenter requested the addition of a temperature requirement in the *Packaging and Storage* section.

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

**Monograph/Section:** Dicyclomine Hydrochloride Injection/Impurities

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the acceptance criteria for *Limit of Dicyclomine Related Compound A* is different from what has been approved by the FDA in the test for Organic Impurities.

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

**Monograph/Section:** Dicyclomine Hydrochloride Oral Solution/Multiple

**Expert Committee:** Chemical Medicines Monographs 3

**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended adding limits for “Any individual unspecified degradation products” and “Total impurities” to be consistent with ICH Q3B guidelines in the test for Organic Impurities.

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

**Comment Summary #2:** The commenter recommended inclusion of *Deliverable Volume* and *Microbial Limit* tests with appropriate acceptance criteria.

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

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

**Expert Committee(s):** Chemical Medicines Monographs 2

**No. of Commenters:** 1

**Comment Summary #1:** The commenter indicated that the acceptance criteria for doxazosin related compound D and total impurities are different from what has been approved by the FDA.

**Response:** Comment not incorporated. The proposed impurities acceptance criteria are consistent with the sponsor’s FDA-approved application and the EC will consider a future revision upon receipt of supporting data.

**EC-Initiated Change #1:** The chemical name of doxazosin related compound G in the footnote b under *Table 2* was revised from 4-Amino-6,7-dimethoxyquinazolin-2-ol to 4-Amino-6,7-dimethoxyquinazolin-2(1*H*)-one to be consistent with the current USP naming convention.

**Monograph/Section(s):** Fish Oil Omega-3 Acid Ethyl Esters Concentrate/Multiple Sections

**Expert Committee:** Non-Botanical Dietary Supplements

**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended adding a note stating that manufacturers should be aware that fish oil is susceptible to oxidation and they need to implement necessary controls for air exposure.

**Response:** Comment incorporated.



**Comment Summary #2:** The commenter proposed that the criteria for the *Oligomers and Partial Glycerides* test should not include the partial glycerides since the formula indicates the calculation is for oligomers only.

**Response:** Comment partially incorporated. The test procedure and the formula definition were updated and clarified to include partial glycerides.

**Comment Summary #3:** The commenter proposed replacing “0.60” with “0.6” in the acceptance criteria for the *Specific Tests/Absorbance*.

**Response:** Comment incorporated.

**Comment Summary #4:** The commenter proposed removing the concentration of antioxidants added from the *Additional Requirements/Labeling* section because it is not required in the Supplement Facts panel.

**Response:** Comment not incorporated. The *General Notices and Requirements* section of *USP–NF* requires the listing of substances and their concentrations.

**Monograph/Section:** Hydroxychloroquine Sulfate/Multiple  
**Expert Committee:** Chemical Medicines Monographs 1  
**No. of Commenters:** 4

**Comment Summary #1:** The commenters requested widening the following limits in the test for Organic Impurities to be consistent with their FDA-approved specifications: for the hydroxychloroquine acetate impurity from 0.15% to 0.5%, for the sulfohydroxychloroquine impurity from 0.15% to 0.5%, for the desethyl hydroxychloroquine impurity from 0.50% to 0.5%, and for total impurities from 0.8% to 1.0%.

**Response:** Comment incorporated.

**Comment Summary #2:** The commenter recommended including a resolution requirement to the *System Suitability* section in the test for Organic Impurities.

**Response:** Comment not incorporated. The EC will consider developing additional reference standards for impurities and will consider establishing additional system suitability requirements when the reference standards become available

**Comment Summary #3:** The commenter indicated that the column efficiency is reduced after a number of injections in the Assay and test for Organic Impurities, and there is a possibility of the peak for the desethyl hydroxychloroquine impurity merging with the principal peak in the test for Organic Impurities.

**Response:** Comment not incorporated. The EC determined that the validation data support these concerns and will consider future revisions to the monograph upon receipt of the necessary supporting data.

**Comment Summary #4:** The commenter requested a correction to the Sample solution concentration in the test for Organic Impurities from 0.01 mg/mL to 0.1 mg/mL to be consistent with the validation data.

**Response:** Comment incorporated.

**Comment Summary #5:** The commenter indicated that two impurities reported in *Ph Eur* monograph, Impurity D and Impurity A, are not listed in the *PF* proposal. The commenter indicated that Impurity D (monoethyl chloroquine) may be co-eluting with the principal peak, and Impurity A (hydroxychloroquine N-oxide) eluted closely to the commenter’s unspecified impurity.

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

**EC-initiated Change #1:** In the test for Organic Impurities, a note was added that the Hydroxychloroquine Acetate impurity should be controlled “if present,” and the footnote is updated to indicate that this process impurity may be specific to the synthetic route where acetic acid or acetates are used.

**EC-initiated Change #2:** The official date for this monograph was extended from December 1, 2020 to June 1, 2021 because of the situation related to COVID-19 and to allow manufacturers time to adapt to the changes.

**Monograph/Section(s):** Indian Barberry Stem/Multiple  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**EC- Initiated Change #1:** In *Composition*, the suitability requirement for Resolution was changed from “2.0” to “1.7” in the *System suitability* section.

**EC- Initiated Change #2:** In Standard Solution B in *Composition*, the statement “equivalent to 10 mg of berberine” was changed to “equivalent to 5 mg of berberine”.

**EC- Initiated Change #3:** The following label caution is included in the monograph: Dosage forms prepared with this article should bear the following statement: “Indian Barberry Stem contain berberine which may interact with medications. Consult your health care practitioner before using.”

**Monograph/Section(s):** Indian Barberry Stem Dry Extract/Multiple Sections  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**EC- Initiated Change #1:** In *Composition*, the suitability requirement for Resolution was changed from “2.0” to “1.7” in the *System suitability* section.

**EC- Initiated Change #2:** In Standard Solution B in *Composition*, the statement “equivalent to 10 mg of berberine” was changed to “equivalent to 5 mg of berberine”.

**EC- Initiated Change #3:** The following label caution is included in the monograph: Dosage forms prepared with this article should bear the following statement: “Indian Barberry Stem contain berberine which may interact with medications. Consult your health care practitioner before using.”

**Monograph/Section(s):** Indian Barberry Stem Powder/Multiple Sections  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines

**EC- Initiated Change #1:** In *Composition*, the suitability requirement for Resolution was changed from “2.0” to “1.7” in the *System suitability* section.

**EC- Initiated Change #2:** In Standard Solution B in *Composition*, the statement “equivalent to 10 mg of berberine” was changed to “equivalent to 5 mg of berberine”.

**EC- Initiated Change #3:** The following label caution is included in the monograph: Dosage forms prepared with this article should bear the following statement: “Indian Barberry Stem contain berberine which may interact with medications. Consult your health care practitioner before using.”

**Monograph/Sections:** Magnesia Tablets  
**Expert Committee(s):** Chemical Medicines Monographs 6

**EC-Initiated Change #1:** The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Magnesium Carbonate  
**Expert Committee(s):** Chemical Medicines Monographs 6

**EC-Initiated Change #1:** The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Magnesium Hydroxide/Multiple  
**Expert Committee(s):** Chemical Medicines Monographs 6  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended using quadrupole ICP–MS or ICP–OES in the tests for *Assay* and the *Limit of Calcium*.

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

**EC-Initiated Change #1:** The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Magnesium Hydroxide Paste  
**Expert Committee(s):** Chemical Medicines Monographs 6  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended extending the implementation time for the proposed revision to allow manufacturers additional time to prepare for compliance.

**Response:** Comment incorporated. The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Magnesium Oxide/Multiple  
**Expert Committee(s):** Chemical Medicines Monographs 6  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended retaining the currently official procedures for the *Assay* and the *Limit of Calcium* test as the monograph procedures are suitable for testing and the proposed methods would require large expenditure associated with the required instrumentation and implementation of the new procedures.

**Response:** Comment not incorporated. The EC determined that the proposed ion chromatography-based procedures are specific compared to the current titration-based procedure.

**Comment Summary #2:** The commenter indicated that there may be robustness issues with the ion chromatographic procedures as was previously reported in the case of the ion chromatographic procedure listed under the *Limit of NH<sub>3</sub>* test in the *USP–NF* monograph for *Sodium Bicarbonate*.

**Response:** Comment not incorporated. The EC determined that the proposed procedure was robust and suitable for the intended use.

**Comment Summary #3:** The commenter recommended providing an option to use the currently official methods or the newly proposed test procedures.

**Response:** Comment not incorporated. The EC determined that under *USP* General Notices 6.30, *Alternative and Harmonized Methods and Procedures* manufacturers can use alternate procedures.

**Comment Summary #4:** The commenter recommended including a temperature requirement in the *Packaging and Storage* section.

**Response:** Comment not incorporated. The EC will consider a future revision upon receipt of the supporting information.

**EC-Initiated Change #1:** The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Magnesium Oxide Capsules  
**Expert Committee(s):** Chemical Medicines Monographs 6

**EC-Initiated Change #1:** The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Magnesium Oxide Tablets  
**Expert Committee(s):** Chemical Medicines Monographs 6

**EC-Initiated Change #1:** The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Magnesium Trisilicate  
**Expert Committee(s):** Chemical Medicines Monographs 6

**EC-Initiated Change #1:** The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Sections:** Milk of Magnesia/Multiple  
**Expert Committee(s):** Chemical Medicines Monographs 6  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended extending the implementation time for the proposed revision to allow manufacturers additional time to prepare for compliance.

**Response:** Comment incorporated. The official date for the proposed revision is extended from December 1, 2020 to June 1, 2021, providing additional time to prepare for compliance.

**Monograph/Section:** Piroxicam/Multiple  
**Expert Committee:** Chemical Medicines Monographs 2  
**No. of Commenters:** 2

**Comment Summary #1:** The commenter recommended revising the acceptance criteria in the *Definition* and the *Assay* by including the phrase “calculated on the dried basis.”

**Response:** Comment not incorporated. The proposed acceptance criteria for the *Definition* and the *Assay* are consistent with the sponsor’s FDA-approved application. The EC will consider a future revision to the monograph upon receipt of the supporting data.

**Comment Summary #2:** The commenter recommended including the number of injections for the %RSD requirements under *System suitability*, in the tests for *Assay*, *Limit of Piroxicam Related Compound B*, and *Organic Impurities*.

**Response:** Comment not incorporated. The numbers of repeated injections are described under <621>, *System suitability*, which is referenced under the *Chromatographic system* in each of these tests.

**EC-Initiated change #1:** The EC canceled the proposed change to *Identification A* based on the comments received, indicating that the use of 197K and 197A are not be suitable for Piroxicam in some polymorphic forms.

**Monograph/Sections:** Potassium Carbonate/Assay  
**Expert Committee(s):** Chemical Medicines Monographs 6  
**No. of Commenters:** 1

**Comment summary #1:** The commenter recommended considering the sample weight of 0.5 g as described in the *European Pharmacopoeia* monograph instead of the proposed 0.7 g.

**Response:** Comment incorporated.

**Monograph/Section:** Pseudoephedrine Hydrochloride Oral Solution/Multiple  
**Expert Committee:** Chemical Medicines Monographs 6  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the injection volumes in the tests for *Assay* and *Organic Impurities* from “10 µL” to “7 µL” to be consistent with the validation data.  
**Response:** Comment incorporated.

**Monograph/Section(s):** Pummelo Peel/Multiple  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines  
**No. of Commenters:** 5

#### **Identification A**

**Comment Summary #1:** The commenter suggested using “PEG 400” instead of “PEG 4000” in *Derivatization reagent B* without any parameter changes because “PEG 400” is less cumbersome to use and more easily dissolved in ethanol.

**Response:** Comment incorporated.

#### **Identification B**

**Comment Summary #2:** The commenter suggested noting that meranzin hydrate mentioned in the *Acceptance criteria* is not a flavonoid but a coumarin.

**Response:** Comment incorporated. The phrase “which is a coumarin” was added after meranzin hydrate.

#### **Composition**

**Comment Summary #3:** The commenter indicated that 2.5 mg hesperidin could not be fully dissolved in *Standard solution A*.

**Response:** Comment incorporated. The amount of hesperidin was reduced from 2.5 mg to 1.0 mg.

**Comment Summary #4:** The commenter suggested sharpening the HPLC peaks and shortening the retention times by modifying HPLC conditions.

**Response:** Comment not incorporated. The EC will consider a future revision to this monograph using a modified HPLC method.

#### **Specific Tests, Botanical Characteristics**

**Comment Summary #5:** The commenter suggested adding a diameter for an opened peel of unripe fruit to avoid using very young fruits that have not been differentiated with very thick mesocarp.

**Response:** Comment incorporated. The statement “The whole peel has a diameter of 15 cm to 28 cm in flat open” was added under *Macroscopic*.

**Monograph/Section(s):** Pummelo Peel Flavonoids Dry Extract/Multiple  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines  
**No. of Commenters:** 5

#### **Identification A**

**Comment Summary #1:** The commenter suggested using “PEG 400” instead of “PEG 4000” in *Derivatization reagent B* without any parameter changes because “PEG 400” is less cumbersome to use and more easily dissolved in ethanol.

**Response:** Comment incorporated.

#### **Identification B**

**Comment Summary #2:** The commenter suggested noting that meranzin hydrate mentioned in the *Acceptance criteria* is not a flavonoid but a coumarin.

**Response:** Comment incorporated. The phrase “which is a coumarin” was added after meranzin hydrate.

#### **Composition**

**Comment Summary #3:** The commenter indicated that 2.5 mg hesperidin could not be fully dissolved in *Standard solution A*.

**Response:** Comment incorporated. The amount of hesperidin was reduced from 2.5 mg to 1.0 mg.

**Comment Summary #4:** The commenter suggested sharpening the HPLC peaks and shortening the retention times by modifying HPLC conditions.

**Response:** Comment not incorporated. The EC may consider a future revision to this monograph using a modified HPLC method.

#### **Contaminants**

**Comment Summary #5:** The commenter suggested adding *Limits of Elemental Impurities* which are the same as those provided in the plant monograph.

**Response:** Comment not incorporated. The EC explained that “Since the compendial monographs for botanical extracts require the use of plant materials or powdered plant materials that meet the specifications for elemental impurities, the limits in the botanical extracts are addressed by limiting their levels in the plant materials and powdered plant materials.”

**Monograph/Section(s):** Pummelo Peel Powder/Multiple  
**Expert Committee:** Botanical Dietary Supplements and Herbal Medicines  
**No. of Commenters:** 4

#### **Identification A**

**Comment Summary #1:** The commenter suggested using “PEG 400” instead of “PEG 4000” in *Derivatization reagent B* without any parameter changes because “PEG 400” is less cumbersome to use and more easily dissolved in ethanol.

**Response:** Comment incorporated.

#### **Identification B**

**Comment Summary #2:** The commenter suggested noting that meranzin hydrate mentioned in the *Acceptance criteria* is not a flavonoid but a coumarin.

**Response:** Comment incorporated. The phrase “which is a coumarin” was added after meranzin hydrate.

#### **Composition**

**Comment Summary #3:** The commenter indicated that 2.5 mg hesperidin could not be fully dissolved in *Standard solution A*.

**Response:** Comment incorporated. The amount of hesperidin was reduced from 2.5 mg to 1.0 mg.

**Comment Summary #4:** The commenter suggested sharpening the HPLC peaks and shortening the retention times by modifying HPLC conditions.

**Response:** Comment not incorporated. The EC may consider a future revision to this monograph using a modified HPLC method.

**Monograph/Section:** Thalidomide  
**Expert Committee:** Chemical Medicines Monographs 3

**EC-Initiated Change #1:** Section title was changed from *Ordinary Impurities <466>* to *Limit of glutamine (See Ordinary Impurities <466>)* to clarify the procedure to determine the glutamine impurity.

**Monograph/Section:** Triamcinolone Acetonide Nasal Spray/Specific Tests-Absence of Specified Microorganisms  
**Expert Committee:** Chemical Medicines Monographs 4  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter requested revising the currently official microbial requirements to be consistent with <1111> and adding a requirement to have an absence of *Burkholderia cepacia* complex.

**Response:** Comment not incorporated. The currently official microbial limits are consistent with the FDA-approved application. The EC will consider future revisions to the monograph upon receipt of supporting data.

**Monograph/Section:** Vincristine Sulfate Injection/Multiple  
**Expert Committee:** Chemical Medicines Monographs 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended clarifying the usage of USP Vincristine Sulfate RS for quantification in the monograph and on the reference standard product label.

**Response:** Comment not incorporated. The requirements for use of the reference standard are specified on the reference standard product label and in the *Labeling* and *Packaging and Storage* sections of the proposal.

**Monograph/Section:** Vincristine Sulfate for Injection/Multiple  
**Expert Committee:** Chemical Medicines Monographs 3  
**No. of Commenters:** 1

**Comment Summary #1:** The commenter recommended clarifying the usage of USP Vincristine Sulfate RS for quantification in the monograph and on the reference standard product label.

**Response:** Comment not incorporated. The requirements for use of the reference standard are specified on the reference standard product label and in the *Labeling* and *Packaging and Storage* sections of the proposal.