Commentary

First Supplement to USP 37–NF 32

February 3, 2013

In accordance with USP's Rules and Procedures of the 2010-2015 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 republication in *PF*, a summary of comments received and the appropriate Expert Committee's responses are published in the Revisions and Commentary section of the USP Web site 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.

For further information, contact:

USP Executive Secretariat
United States Pharmacopeia
12601 Twinbrook Parkway
Rockville, MD 20852-1790 USA
execsec@usp.org

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

General Chapters:

<121.1> Physicochemical Analytical Procedures for Insulins
<601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Tests
<603> Topical Aerosols
<604> Leak Rate
<621> Chromatography
<551> Alpha Tocopherol Assay
<726> Electrophoresis
<787> Sub-visible Particulate Matter in Therapeutic Protein Injection
<790> Visible Particulates in Injections
<1094> Capsules—Dissolution Testing and Related Quality Attributes
<1044> Cryopreservation of Cells
<1229.4> Sterilizing Filtration of Liquids
<1229.7> Gaseous Sterilization
<1229.8> Dry Heat Sterilization
<1229.10> Radiation Sterilization
<1285> Preparation of Biological Specimens for Histologic and Immunohistochemical Analysis
<1285.1> Hematoxylin and Eosin Staining of Sectioned Tissue for Microscopic Examination
<2040> Disintegration and Dissolution of Dietary Supplements

Monographs:

Albuterol Extended-Release Tablets
Aripiprazole
Atrophine Sulfate
Aztec Marigold Zeazanthin Extract
Aztreonam for Injection
Aztreonam Injection
Calcium Gluconate
Calcium L-5-Methyltetrahydrofolate Capsules
Calcium L-5-Methyltetrahydrofolate Tablets
Cefadroxil Capsules
Cefadroxil
Ceftriaxone for Injection
Ceftriaxone Sodium
Chloroquine Phosphate
Chondroitin Sulfate Sodium
Clindamycin Phosphate
Dioxybenzone
Dipyridamole
Efavirenz Tablets
Extended Phenytoin Sodium Capsules
Fluorouracil
Fluorouracil Injection
Fluorouracil Topical Solution
Insulin Aspart Injection
Insulin Aspart
Lecithin
Metoclopramide Injection
Metoclopramide Oral Solution
Metoclopramide Tablets
Olanzapine Orally Disintegrating Tablets
Padimate O
Piperacillin and Tazobactam for Injection
Piperacillin for Injection
Piperacillin Sodium
Piperacillin
Propafenone Hydrochloride Tablets
Sumatriptan Tablets
Thiotepa for Injection
Thiotepa
Trazodone Hydrochloride
Warfarin Sodium
Warfarin Sodium Tablets

No comments received for the following, when they were proposed in Pharmacopeial Forum

<123> Glucagon Bioidentity Tests
<602> Propellants
<2040> Disintegration and Dissolution of Dietary Supplements
Apomorphine Hydrochloride
Atovaquone
Benzalkonium Chloride Solution
Bisacodyl Delayed-Release Tablets
Butorphanol Tartrate Nasal Solution
Calcium Stearate
Chlorpheniramine Maleate
Cladribine Injection
Corticotropin Zinc Hydroxide Injectable Suspension
Dexbrompheniramine Maleate
Dexchlorpheniramine Maleate
Dimenhydrinate
Erythromycin Delayed-Release Tablets
Estazolam
Fish Oil Containing Omega-3 Acids
Fluorouracil Cream
Ketoprofen Capsules
Levetiracetam Tablets
Lithium Carbonate Capsules
Lithium Carbonate Tablets
Lithium Carbonate Extended-Release Tablets
Magnesium Carbonate and Citric Acid for Oral Solution
Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution
Magnesium Citrate for Oral Solution
Meradimate
Methsuximide
Methysergide Maleate Tablets
Naftifine Hydrochloride
Oxytocin Nasal Solution
Perphenazine
Phenytoin Chewable Tablets
Phenytoin Sodium Injection
Pimozide
Pimozide Tablets
Polyoxyl 40 Stearate
Sodium Stearate
Sufentanil Citrate
Terbinafine Hydrochloride
Tricitrates Oral Solution
Vinpocetine
Warfarin Sodium for Injection

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: 3

Comment Summary #1: A commenter indicated that testing for residual solvents and volatile and semivolatile leachables should not be routine, because testing for residual solvents is not needed if no solvents are used during manufacturing, or if these solvents are already controlled in individual components.

Response: Comment not incorporated. General Chapter <5> presents the critical quality parameters for inhalation products. The standards contained within this General Chapter are not required for drug products that have a monograph in the *USP–NF*. This General Chapter describes the information that should be known and controlled in products that do not have a compendial quality standard. The Expert Committee believes that the knowledge of potential leachables for a product is a critical attribute that should be understood. The frequency and extent of testing are not discussed in this General Chapter and are within the purview of the manufacturer and regulators as a component of good manufacturing practices.

Section II: General Quality Tests for Inhalation Drug Products--Inhalation Solutions

Comment Summary #2: The commenter requested that the text specify that the test for Leachables should be performed on stability and not on release.

Response: Comment not incorporated. General Chapter <5> presents the critical quality parameters for inhalation products. The standards contained within this General Chapter are not required for drug products that have a monograph in the *USP–NF*. This General Chapter describes the information that should be known and controlled in products that do not have compendial quality standards. The Expert Committee believes that the knowledge of potential leachables for a product is a critical attribute that should be understood. The frequency and extent of testing are not discussed in this General Chapter and are within the purview of the manufacturer and regulators as a component of good manufacturing practices.

Comment Summary #3: The commenter requested that the text clearly state that the requirement for Net Fill Weight is best determined through an in-process test versus a quality control release test.

Response: Comment not incorporated. General Chapter <5> presents the critical quality parameters for inhalation products. The standards contained in this General Chapter are not required for drug products that have a monograph in the *USP–NF*. The General Chapter describes the information that should be known and controlled in products that do not have a compendial quality standard. The frequency and extent of testing are not discussed in this General Chapter and if a manufacturer is able to assure compliance with the standard, then an in-process test may be used in accordance with General Notices 6.20 and 6.30.

Comment Summary #4: The commenter requested the text specify that the test for Weight Loss be performed during development. It is not appropriate as a routine quality

control test or as an in-process test. Weight loss is a function of the container/closure system and product characteristics.
Response: Comment not incorporated. General Chapter <5> presents the critical quality parameters for inhalation products. The standards contained in this General Chapter are not required for drug products that have a monograph in the *USP-NF*. This General Chapter describes the information that should be known and controlled in products that do not have a compendial quality standard. The frequency and extent of testing are not discussed in this General Chapter and are within the purview of the manufacturer and the regulators as a component of good manufacturing practices.

Comment Summary #5: The commenter requested that the text specify that the performance tests referenced in General Chapter <1601> be performed during development, because it is not appropriate as a routine quality control test or an in-process test.
Response: Comment not incorporated. General Chapter <5> presents the critical quality parameters for inhalation products. The standards contained in this General Chapter are not required for drug products that have a monograph in the *USP–NF*. This General Chapter describes the information that should be known and controlled in products that do not have a compendial quality standard. The frequency and extent of testing are not discussed in this General Chapter and are within the purview of the manufacturer and the regulators as a component of good manufacturing practices.

Section II: General Quality Tests for Inhalation Drug Products--Inhalation Powder
Comment Summary #6: The commenter requested revising the first sentence as follows: "Inhalation powder drug products, commonly known as dry powder inhalers (DPIs), dispense powders for inhalation with the use of a device that aerosolizes and delivers an accurately metered dose ~~amount~~ ~~and~~ of active ingredient(s) with consistent ~~quality~~ physical characteristics alone, or with a suitable excipient(s)…"
Response: Comment partially incorporated. The term **"**metered amount" was not changed, because when the dose is more than one metered activation, the definition was intended to indicate each activation, rather than the mean of multiple activations.
Comment Summary #7: The commenter suggested expanding the definition of inhalation powder drug products to include excipient-only products.
Response: Comment not incorporated. The scope of this General Chapter was not intended to address placebo products.
Comment Summary #8: The commenter suggested revising the definition for "metered DPIs" to include "drug-only products and excipients-only products"
Response: Comment not incorporated. The Expert Committee found the wording of this statement to be sufficiently clear
Comment Summary #9: The commenter suggested revising the description for premetered DPIs as:"Premetered DPIs contain ~~previously~~ pre-dispensed ~~measured~~ amounts of drug or formulation in individual containers."
Response: Comment not incorporated. The Expert Committee found the wording of this statement to be sufficiently clear and the scope of this General Chapter is not intended to address placebos.
Comment Summary #10: The commenter requested revising the description for "Device metered DPIs" as follows" "Device-metered DPIs have an internal reservoir

that contains a sufficient quantity of drug or formulation for multiple doses that are metered by the device ~~itself~~ during actuation by the patient."
Response: Comment not incorporated. The Expert Committee found the wording of this statement to be sufficiently clear and the scope of this General Chapter is not intended to address placebos.

Section III. General Quality Tests for Nasal Drug Products
Comment Summary #11: The commenter suggested revising the sentence under *Nasal Spray* as follows: "They may contain drug substance(s) dissolved in solution with, or without ~~or mixtures of~~ excipient(s), in a nonpressurized compact container."
Response: Comment not incorporated. The Expert Committee found the wording of this statement to be sufficiently clear.

Section IV. Description of Product Quality Tests
Comment Summary #12: The commenter suggested revising the sentence of this section as follows: "Product quality tests are listed as follows, and should be applied to inhalation and nasal drug products and to products for nebulization. Specific product ~~general~~ quality tests are addressed in product."
Response: Comment incorporated.
Comment Summary #13: The commenter suggested revising the sentence under the *Assay* section as follows: "The Assay test should be capable of quantifying measure the available medicament drug substance and stability issues such as its stability, including adherence of the medicament drug substance to the container and any closure components."
Response: Comment not incorporated. The Expert Committee found the wording of this sentence to be sufficiently clear
Comment Summary #14: The commenter suggested revising the ICH reference under *Assay for preservative and Stabilizing Excipients* so that it does not make reference to a specific revision number.
Response: Comment incorporated. The reference was removed.
Comment Summary #15: The commenter suggested revising the ICH reference under *Impurities and Degradation Products* so that it does not make reference to a specific revision number.
Response: Comment incorporated. The reference was removed.
Comment Summary #16: The commenter indicated that the reference to General Chapter <1601> –an informational general chapter– could make the tests indicated in <1601> requirements. The following wording was suggested to avoid this situation: "— We recommend stating that performance tests in chapter <1601> can be used to provide further information, but are not considered a requirement for compliance with chapter <5>."
Response: Comment partially incorporated. A general footnote was added to the General Chapter that states: "All references to chapters above 1000 are for information only, for use as a helpful resource. These chapters are not mandatory unless explicitly called out for application."
Comment Summary #17: The commenter suggested deleting sentence: "Moreover, if the drug substance is a salt, an appropriate identification test also should be included for the counterion," in the *Identification* section, because it is not always necessary to identify the counterion in the specific drug product. Assay methods based on HPLC are

purity tests for the drug and any salt form is compensated for in calculations of purity.
Response: Comment not incorporated. The *Identification* section includes information on the chemical entity and may not necessarily be limited to the active moiety portion of the chemical entity. General Chapter <5> presents the critical quality parameters. The standards contained within this General Chapter are not required for drug products that have a monograph in the *USP–NF*. This General Chapter describes the information that should be known and controlled in products that do not have a compendial quality standard. The frequency and extent of testing are not discussed in this General Chapter and are within the purview of the manufacturer and the regulators as a component of good manufacturing practices.
Comment Summary #18: The commenter suggested revising the sentence under *Foreign Particulate Matter* as follows: "Foreign particulate matter in inhalation and nasal ~~these~~ drug products may originate…."
Response: Comment incorporated.
Comment Summary #19: The commenter requested revising the sentence under the *Leachables* section as follows: "Thus, throughout the ~~expiration dating period the~~ proposed life time of the drug product, up until its expiry date, the drug product should be evaluated for compounds that can migrate into the formulation from a variety of sources
Response: Comment not incorporated. The Expert Committee found the wording of this statement to be sufficiently clear.
Comment Summary #20: The commenter suggested adding titles and the general chapter numbers for the references in the *Microbial Limits section.*
Response: Comment incorporated
Comment Summary #21: The commenter suggested revising the sentence under *Microbial Limits* as follows: "The microbial quality of dosage forms where indicated under *General ~~Product~~ Quality Tests for Inhalation Drug Products* and *~~Product~~ General Quality Tests for Nasal Drug Products* normally."
Response: Comment incorporated.
Comment Summary #22: The commenter suggested using the term "water content" instead of "Residual water content "when referencing General Chapter <921> Water Determination to avoid confusion.
Response: Comment incorporated.
Comment Summary #23: The commenter requested revising the *Weight Loss* section to accommodate all types of products as follows: **"**Where appropriate, drug products should be evaluated for weight loss, e.g., drug products packaged in semipermeable containers, to assess the moisture-loss protective properties of the overall container–closure system."
Response: Comment not incorporated. The Expert Committee found the wording of this section to be sufficiently clear.
Comment Summary #24: The commenter requested clarification on whether the monographs will be updated to specify limits for tests, such as osmolality and viscosity.
Response: Comment not incorporated. The Expert Committee will consider further revisions to the monographs upon the receipt of the necessary supporting data

General Chapter/Section(s): <121.1> Physicochemical Analytical Procedures for Insulins/Multiple Sections
Expert Committee: Monographs—Biologics and Biotechnology 1
No. of Commenters: 2

Peptide Mapping
Comment Summary #1: The commenter indicated that the weight ratio of enzyme to insulin is very high (20:50). Although *Staphylococcus aureus* V8 protease is stable at 40º, autolysis may occur and the by-products may interfere with detection of insulin fragments. It was recommended that additional information be provided to assist the user in demonstrating no interference from autolysis by-products.
Response: Comment incorporated. The following was added to the note in the *Insulin Digestion* section: "If interfering autolysis by-products are observed in the chromatogram when the enzyme alone is run, the enzyme insulin ratio must be decreased and digestion time must be increased."

Limit of High Molecular Weight Proteins
Comment Summary #2: The commenter indicated that the current proposed text specifies the *Resolution solution* be prepared over a period of 5-10 days. Since different insulins produce polymers at different rates, the following more generalized statement was suggested: "*Resolution solution*: Store a suitable amount of insulin drug substance at room temperature for a sufficient period of time (5–10 days, or as needed) to obtain insulin with more than 0.4% high molecular weight proteins."
Response: Comment incorporated.

Expert Committee-initiated Change #1: The following section was added because a USP Reference Standard is cited in the text as an alternative to preparing the *Resolution solution* from the insulin drug substance in the *Limit of High Molecular Weight Proteins* method: "Additional Requirements; USP Reference Standards <11>; USP High Molecular Weight Insulin Human RS (alternative, optional)."

General Chapter/Section(s): <551> Alpha Tocopherol Assay
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 1
Comment Summary #1: The commenter requested that the test procedure for active pharmaceutical ingredients be separated from the test procedures for dosage forms.
Response: Comment not incorporated. The chromatographic procedures in the General Chapter are arranged according to the types of chromatographic systems employed for the assay, and not according to the types of test materials that are analyzed using the assay.
Expert Committee Initiated Change #1: Applicability of each procedure in the General Chapter was clarified using bullet points.

General Chapter/Section: <601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests
Expert Committee(s): General Chapters—Dosage Forms
No. of Commenters: 3

Comment Summary #1: The commenter suggested clarification of the term "rate" in the following sentence in section A.2."Note that for inhalation aerosols the rate of discharges to waste should not cause excessive canister cooling."
Response: Comment Incorporated.

Comment Summary # 2: The commenter suggested revision of the sentence in section C.1.as follows for clarity. "Cascade impaction devices classify aerosol particles and droplets on the basis of ~~those particles'~~ aerodynamic diameters."
Response: Comment incorporated.

Comment Summary # 3: The commenter requested revision of the sentence in section A2.1.as follows for clarity."A dose in this test is defined as the minimum recommended number of sprays specified in the product labeling or instructions for use ~~but not more than two sprays~~.
Response: Comment not incorporated. A fewer number of actuations for a given drug product is a better reflection of the quality and performance of such drug products. The higher the number of actuations, the quality and the performance behavior of the product could be averaged out and the true performance be masked and thus be misrepresented. Therefore, the phrase "not to exceed two actuations" was incorporated to better reflect the quality of the drug product.

Comment Summary # 4: The commenter requested clarification of the new requirement (for the DDU of inhalation aerosols and sprays (formerly MDIs) not allowing the volume of air sampled to exceed 2 L. At 28.3 L/min. This means that the flow duration will be approx. 4 seconds. In order to achieve sufficient steady-state flow through the impactor for this duration (and ensure that 2 L is not exceeded), it may be necessary to use the type of flow controller (simplified TPK) used for DPI testing.
Response: Comment not incorporated. The revised General Chapter does not require cascade impactor studies to be conducted with a volume not exceeding 2L; therefore, there are no concerns over inability to reach steady state.

General Chapter/Section: <603> Topical Aerosols
Expert Committee(s): General Chapters—Dosage Forms
No. of Commenters: 1

Comment Summary #1: The commenter requested removal of the *Pressure Test* from the General Chapter, because the *Pressure Test* is duplicative when *Delivery Rate and Delivered Amount* and *Leak Rate* are all taken into account. If there is no pressure, *Delivery Rate and Delivered Amount* will be impacted, thus it is redundant to test for both.
Response: Comment not incorporated. This content is taken as is from the existing official General Chapter <601>. The Expert Committee was not in favor of making any changes at this time, because the pressure of a product may depend on various factors (e.g., manufacture, composition, CCS, etc) and data is not available to relate a quantitative change in pressure to corresponding quantitative changes in Delivery Rate and Delivered Amount. It would be premature to formalize such a change in absence of data from its original and current source, i.e., General Chapter <601>.

General Chapter/Section: <604> Leak Rate
Expert Committee(s): General Chapters—Dosage Forms
No. of Commenters: 1
Comment Summary #1: The commenter suggested using the term 'predicted leak rate per year' when determining a predicted or anticipated leak rate per year.
Response: Comment not incorporated. Leak rate is product specific rather than calculated (Predicted) at the time of testing.

General Chapter/Section(s): <621> Chromatography/Multiple Sections
Expert Committee(s): General Chapters—Chemical Analysis
No. of Commenters: 12

Liquid Chromatography (LC)
Comment Summary #1: A commenter suggested that the guard column should have the same particle size as the analytical column under the Chromatographic column section.
Response: Comment not incorporated. As long as the particle and bonded phase are the same and the volume is not too large, the guard column should have little or no influence on the separation.
Comment Summary #2: A commenter indicated that the inner diameter of the guard column should be restricted to the same or smaller than the analytical column under the Guard column section.
Response: Comment incorporated.
Comment Summary #3: Several commenters indicated that the adjustments in gradient conditions should be allowed as long as all gradient segments are adjusted using equivalent column volumes.
Response: Comment not incorporated. The Expert Committee believes that adjusting the conditions in gradients may introduce unexpected changes in the chromatography, so validation under the new conditions is necessary.

System Suitability
Comment Summary #4: Several commenters requested that the General Chapter specifically discuss core shell columns, as these columns do not follow the same relationship L/dp as the fully-porous particles.
Response: Comment incorporated.
Comment Summary #5: Several commenters indicated that text should be added to the *Injection Volume (HPLC)* section, to caution against exceeding the validated linear range of the monograph, by increasing the injection volume.
Response: Comment incorporated.
Comment Summary #6: A commenter suggested that the sequence of the introductory paragraphs for chromatographic parameter adjustment could be more logically arranged.
Response: Comment incorporated.
Comment Summary #7: A commenter suggested adding references for the new formula for flow rate adjustment under Flow Rate (HPLC).
Response: Comment not incorporated. The references were indicated in the briefing of the proposal in *PF* 37(3) [May–Jun. 2011]. The formula and concepts are based on the Stimuli article titled *Transfer of HPLC Procedures to Suitable Columns of Reduced*

Dimensions and Particle Sizes by Neue et al., published in *PF* 35(6) [Nov.–Dec. 2009], pages 1622–1626.
Expert Committee-initiated Change #1: The meaning of the *K* factor in the formula for the maximum permitted %RSD was corrected.

Quantitation, Calibration procedure
Expert Committee-initiated Change #2: A reference was added to the parenthetical expression in the second paragraph that refers to the relative response factor.
Additional comments were received that affect sections of this General Chapter not revised in this revision cycle. The Expert Committee will consider these comments in a future revision.

General Chapter/Section(s): <726> Electrophoresis
Expert Committee: General Chapters—Biological Analysis
No. of Commenters: 1
Comment Summary #1: The commenter s suggested changing the <726> reference in monographs to General Chapters <1054>, <1056>, or <1057> rather than omitting each link as proposed in the briefing.
Response: Comment not incorporated. There are currently four official *USP* monographs (*Alteplase, Chromium Cr51 Edetate Injection, Anthrax Vaccine Adsorbed*, and *Technetium Tc 99m Pentetate Injection*), three official *NF* monographs (*Chitosan, rAlbumin Human*, and *Zein*), and four Dietary Supplement monographs (*Chondroitin Sulfate Sodium, Chondroitin Sulfate Sodium Tablets, Glucosamine, Chondroitin Sulfate Sodium, and Methylsulfonylmethane Tablets*, and *Glucosamine and Chrondroitin Sulfate Sodium Tablets*) with a reference to <726>, but the General Chapter does not contain a validated procedure. Each monograph contains its own procedure and no General Chapter reference is needed to complete the monograph test therefore the links will be removed.

General Chapter: <1094> Capsules—Dissolution Testing and Related Quality Attributes
Expert Committee: General Chapters—Dosage Forms
No. of Commenters: 1
Comment Summary #1: The commenter indicated that it is not clear how buoyancy will help release of the fill from the capsule.
Response: Comment not incorporated. This will be addressed in future revisions to General Chapters <711>, <1092>, and <1094>.
Comment Summary #2: The commenter indicated that the text that recommends taking into account the swelling of the capsule when selecting the appropriate size of the sinker is confusing and noted that General Chapter <1092> The Dissolution Procedure: Development and Validation does not consider capsule swelling when selecting the size of the sinker.
Response: Comment not incorporated. This will be addressed in future revisions to General Chapters <711>, <1092>, and <1094>.

Comment Summary #3: The commenter indicated that the pre-treatment of the capsule with the proteolytic enzyme followed by a later addition of the surfactant to the medium is not mentioned in General Chapter <711> Dissolution.
Response: Comment not incorporated. This will be addressed in future revisions to General Chapters <711>, <1092>, and <1094>.
Comment Summary #4: The commenter recommends revising section 6.1. Gelatin, subsection Chemistry of Gelatin to address all types of capsules.
Response: Comment not incorporated. This will be addressed in future revisions to General Chapters <711>, <1092>, and <1094>.
Comment Summary #5: The commenter suggested revising section 6.3 Formulation Development and Manufacturing for Liquid-filled Capsules to address all types of capsules.
Response: Comment not incorporated. This will be addressed in future revisions to General Chapters <711>, <1092>, and <1094>.

General Chapter/Sections: <787> Subvisible Particulate Matter in Therapeutic Protein Injections
Expert Committee(s): General Chapters—Dosage Form
No. of Commenters: 5

Introduction
Comment Summary #1: The commenter suggested clarifying whether General Chapters <787> and <788> can be used for biopharmaceutical products.
Response: Comment incorporated
Comment Summary #2: The commenter suggested removing the particle type definitions from the General Chapter.
Response: Comment not incorporated. The definitions are necessary for stakeholders to understand the various sources of contamination.
Comment Summary #3: The commenter requested additional text clarifying the requirements for method verification, the number of units tested, and the sample handling procedures.
Response: Comment not incorporated. The topic is outside the scope of this General Chapter.
Comment Summary #4: The commenter recommended adding text that discusses the expectation for products that use a final filter.
Response: Comment incorporated.

Light Obscuration Particle Count Test
Comment Summary #5: The commenter suggested mentioning other organizations that develop metrological particle size standards.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested adding instructions for lyophilized products.
Response: Comment incorporated.

Light Obscuration Particle Count Test—Test Method
Comment Summary #7: The commenter suggested an exemption for the testing of solvent in a dual chamber cartridge.
Response: Comment not incorporated. Further clarification was added that subtraction of the solvent particle count from the total count is not allowed.
Comment Summary #8: The commenter suggested defining whether the mean result or results from single units should comply with the specification.
Response: Comment incorporated.
Comment Summary #9: The commenter recommended adding guidance on what volume should be used for testing.
Response: Comment not incorporated. This topic is outside the scope of the General Chapter.
Comment Summary #10: The commenter requested an exemption for testing USP quality diluents.
Response: Comment not incorporated. Contamination of USP quality diluents can occur, and thus they need to be tested for particle load.
Comment Summary #11: The commenter requested the addition of language stating that other methods can be used to determine suitability.
Response: Comment incorporated.

Light Obscuration Particle Count Test—General Considerations
Comment Summary #12: The commenter requested inclusion of guidance on what orthogonal methods are appropriate.
Response: Comment not incorporated. The topic is addressed in General Chapter <1787>, which was proposed in *PF* 39(6) [Nov.–Dec. 2013].
Comment Summary #13: The commenter suggested clarification on whether the General Chapter applies to the evaluation of all parenterals: intravenous, subcutaneous, intraophtalmic, and intrathecal.

Response: Comment not incorporated. This topic is outside the scope of the General Chapter and is addressed in General Chapter <1>.

Light Obscuration Particle Count Test—Test Evaluation
Comment Summary #11: The commenter requested guidance on how limits should be set to replace the historical <788> limits.

Response: Comment not incorporated. The topic is addressed in General Chapter <1787>, which was proposed in *PF* 39(6) [Nov.–Dec. 2013].

General Chapter/Sections: <790> Visible Particulates in Injections
Expert Committee(s): General Chapters—Dosage Form
No. of Commenters: 6

Introduction
Comment Summary #1: The commenter suggested adding text exempting radiopharmaceutical from the requirements of the General Chapter.

Response: Comment not incorporated. More information was needed to address this comment. The Expert Committee will consider further revisions to the monograph upon the receipt of the necessary supporting data.
Comment Summary #2: The commenter suggested adding text clarifying what products are included within the scope of the General Chapter.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested adding text clarifying that inspection of constituted (e.g., dried) or withdrawn (e.g., dark amber container, suspensions, highly-colored liquids) powders and lyophilized products requires reduced sample size.
Response: Comment Incorporated.
Comment Summary #4: The commenter suggested replacing the word “inherent” with “intrinsic.”
Response: Comment not incorporated. The Expert Committee agreed that the appropriate term is “inherent” and not “intrinsic.”

Inspection Procedure
Comment Summary #5: The commenter suggested adding greater flexibility for a higher illumination depending on the container size.
Response: Comment incorporated
Comment Summary #6: The commenter suggested that the reference to batch-release tests in relation to 100% inspection be deleted and reworded as “not sufficient” or “not in itself sufficient.”
Response: Comment incorporated. The sentence was clarified.

Batch Release
Comment Summary #7: The commenter recommended revising the section heading, because batch release is not the appropriate term.
Response: Comment incorporated.

Product in Distribution
Comment Summary #8: The commenter suggested that the text “Inspect a sample size that provides sufficient statistical confidence in the quality of the product batch in question” should be used instead of “inspect 20 units.”
Response: Comment not incorporated. The testing of 20 units is based on statistical confidence.
Comment Summary #9: The commenter suggested stating where the retention sample should come from.
Response: Comment not incorporated. The Expert Committee determined that this topic is outside the scope of the General Chapter.

General Chapter/Sections: <1044> Cryopreservation of Cells
Expert Committee: General Chapters—Biological Analysis
No. of Commenters: 6

General Comments

Comment Summary #1: The commenter indicated that cell banks are tested to meet acceptance criteria and evaluated over time to assure stability. Each individual process step need not be validated. It would be a burdensome requirement with little benefit, because many years of cryopreservation of many different cell types have demonstrated that a generic approach is successful.
Response: Comment not incorporated. Some cryopreservation process steps should be validated, but not all, and this is noted in the suitable location in the General Chapter.
Comment Summary #2: The commenter indicated that, where relevant, this General Chapter should defer to ICH Q5D for cell banks.
Response: Comment incorporated.
Comment Summary #3: The commenter stated that the General Chapter is very long and could be reduced.
Response: Comment not incorporated. The General Chapter covers multiple cell types and purposes, and thus the length and scope are appropriate.
Comment Summary #4: The commenter requested additional sections on *Container Closure Integrity Testing for Cryopreserved Cell Therapy Products* and *Stability Testing* and offered suggestions for content in each section.
Response: Comment partially incorporated. References to *ICH Q5D* were added where appropriate; however, some of the additional suggestions were very product-and purpose-specific and were beyond the intended scope of the General Chapter.

Introduction

Comment Summary #5: The commenter indicated that the General Chapter's definition of cryopreservation was not common and suggested a revision.
Response: Comment incorporated. The definition was changed to, "Cryopreservation is the process of cooling and storing cells, tissues, or organs at very low temperatures to maintain their viability."
Comment Summary #6: The commenter indicated that cryopreservation of cells can be used for purposes other than therapeutic purposes and suggested a revision.
Response: Comment incorporated by stating, "Cryopreserved cells provide a ready source of viable cells that can be used, either directly or indirectly, for the purposes of diagnostic tests, therapy, manufacture of drug products and vaccines, and for bioassays used to evaluate the potency of therapeutic drugs and vaccines."
Comment Summary #7: Two commenters requested clarification regarding the scope of the General Chapter and whether it was intended for cells used for potency bioassays.
Response: Comment incorporated. The General Chapter scope statement was revised (see Comment #6) and an additional statement was added to the *Cell Substrates Used in Production and Characterization of Biotechnology-Derived and Biologic Therapeutic Products* section to clarify this point.
Expert Committee-initiated Change #1: Added a sentence to cite an additional benefit: "Cryopreservation also minimizes the risk of genetic mutation or development of subpopulations due to cell replication."

Expert Committee-initiated Change #2: Revised a sentence to add a vaccine example: “In some cases the cells themselves, after cryopreservation and thaw, constitute the patient therapy, and in other cases the cells are propagated or otherwise manipulated ex vivo in order to generate the product (e.g., a culture-expanded cellular therapy, a therapeutic protein, a monoclonal antibody, or a vaccine).”

Principles of Cryopreservation

Comment Summary #8: The commenter indicated that it is detrimental to remove water from cells as indicated in the sentence, “Understanding the role of water and the need to adequately remove it from cells…”

Response: Comment not incorporated. Removal of sufficient water is crucial to successful cryopreservation and the original sentence is appropriate.

Comment Summary #9: The commenter indicated that additional tests should be performed and suggested several additions to this section in the sentence, “Therefore, during development.....or alteration of functionality.”

Response: Comment not incorporated. The suggested additions are already included later in the General Chapter.

Comment Summary #10: The commenter requested including additional clarity regarding which processes in this section related to different types of cells and suggested introducing the terms “research cell bank” or “development cell bank.”

Response: Comment not incorporated. This is a fundamental principles section which applies broadly and independent of application.

Comment Summary #11: The commenter indicated that "Precryopreservation characteristics and identity should be established during development, because testing for identity before cryopreservation is not feasible in routine testing. The commenter suggested a modification of this sentence to clarify this point.

Response: Comment incorporated. The section was modified to state: "Precryopreservation characteristics and identity should be established during early process development.”

Comment Summary #12: The commenter requested clarification of the statement: "For cell banks in particular, the cell status and optimal growth conditions, as well as validated history, characteristics,..." because it is not clear what method of history validation will be acceptable and how far back such history needs to go.

Response: Comment incorporated. The sentence was modified to state: “For cell banks in particular, the cell status and optimal growth conditions, as well as documented history (with traceability to a qualified cell bank or acceptable source), characteristics, and authenticity should be documented.”

Comment Summary #13: The commenter suggested adding that cell banks should be established from a single expanded cell culture and not be derived from pooled cultures.

Response: Comment incorporated. The sentence was modified to state “Cell status and history typically are described in terms of the nature and number of manipulations and culture passages from the primary cells or original isolate.” The statement, “It is recommended to prepare cell banks from a single preparation or expanded population of cells since it is often necessary to pool cells for freezing from multiple culture vessels. Cells from cultures with different passage histories and certainly from different donors should not be pooled” also was added.

Comment Summary #14: The commenter suggested adding typical cell densities for cryopreservation.

Response: Comment incorporated. The section was modified to state "The optimal concentration of cells will depend on the cell type, purpose and best recovery. Typically this lies between 10^6 and 10^7/mL for manufacturing cell banks but may be different for other purposes."
Comment Summary #15: Two commenters indicated that the assertion that "log growth" was better than "rapid growth" may not be appropriate because it may depend on the cell type.
Response: Comment incorporated. The section was modified to state, "To prepare for cryopreservation of cultured cells, cells should be harvested during exponential or the most rapid phase of growth and before the culture enters stationary phase."
Comment Summary #16: The commenter suggested an editorial change to the cell washing statement.
Response: Comment incorporated. The sentence was shortened to state the essential point: "Additionally, most cell suspensions benefit from washing by centrifugation and resuspension in an isotonic medium to a specific cell concentration."
Comment Summary #17: The commenter requested deletion of the sentence, "The cell concentration range for harvesting is determined by use of growth curve."
Response: Comment incorporated.
Comment Summary #18: The commenter suggested adding that non-animal reagents are preferred.
Response: Comment incorporated. The first sentence was modified and a second sentence was added that states: "The culture medium should be optimized and the same medium should be used throughout all experiments, and each batch of animal-derived raw materials (e.g., serum) and other culture reagents should be qualified (e.g., see the 2010 WHO guidance and the FDA 2010 guidance referenced in the *Appendix*). If possible, it is recommended to not use animal-derived components in the culture medium particularly for cells used for therapy or as manufacturing substrates."
Comment Summary #19: Three commenters suggested changes to the sentence, "Ideally, cells should be tested for adventitious agents before freezing."
Response: Comment incorporated. The sentence was modified to state, "Per the WHO 2010 guidance and based on a risk assessment, either the Master Cell Bank (MCB) or the Working Cell Bank (WCB) must be tested for adventitious agents. Ideally, samples of cells should be tested for adventitious agents before freezing. The specific testing regimen for potential microbial or viral contamination of cells depend on the donor source, the culture history, and the intended use."
Comment Summary #20: The commenter indicated that in addition to citing General Chapter <1046>, appropriate ICH and FDA Points to Consider documents should also be cited.
Response: Comment incorporated.
Comment Summary #21: Two commenters suggested adding information regarding reagent quality (e.g., DMSO), containers, and cryovials, including that containers for clinical/commercial use should be tested for leachables and extractables according to relevant guidances.
Response: Comment incorporated. The section was modified to state: "All cryoprotectants, containers, etc. should be fit for purpose as indicated in relevant regulatory guidances. Sterile, single-use, disposable plastic bags, cryovials, ampules, or straws are customarily used for cryopreservation. Manufacturers' specifications should be carefully reviewed to ensure that the material used to manufacture the cryocontainer

is appropriate for use at the storage temperature, is chemically compatible with the contents, minimizes the potential for leachables and extractables, and assures container closure integrity. If straws are used, then primary or secondary containment during storage is important to prevent direct contact of the preserved cells with liquid nitrogen. Cryovials should be selected based on their ability to provide adequate cell bank integrity."

Comment Summary #22: The commenters suggested that the section discourage the use of human- and animal-derived materials in the culture medium.

Response: Comments incorporated. The statement, "If possible, it is recommended to not use animal-dervied components in the culture medium particularly for cells used for therapy or as manufacturing substrates," was added.

Comment Summary #23: The commenter requested the addition of conditioned medium to the list of proteins in the sentence, "Preservation of cells typically requires the use of specialized solutions that contain a base (typically an isotonic saline–based solution) with CPAs (most commonly DMSO but sometimes glycerol) and sometimes proteins (fetal bovine serum, human serum or plasma, or human albumin)."

Response: Comment Incorporated.

Comment Summary #24: Three commenters requested clarification regarding the minimum labeling information statements.

Response: Comments incorporated. The section was revised to state: "The minimum information on the label should include name or description of cell population, date of cryopreservation, lot number, and passage number if needed. Since most cryolabels are very small, additional information can be included on associated documentation. In certain applications it may also be necessary to sequentially number vials within a single lot as part of the minimum information on the label, to enable better control over movement of vials from a single bank, and to identify sectors of the bank which may have received different cryopreservation conditions."

Comment Summary #25: The commenter asked that "Osm" be corrected to "Osm/L" if truly osmolarity.

Response: Comment incorporated.

Comment Summary #26: The commenter indicated that this section's subsection *Addition of Cryoprotectant Solutions* is excessively detailed.

Response: Comment not incorporated. The Expert Committee determined that the information is important and suitable.

Comment Summary #27: The commenter suggested edits regarding the cryoprotectant solution addition statements.

Response: Comment incorporated. The sentence was modified to state: "Therefore, cryopreservation solutions commonly are added to a cell suspension in stepwise additions or gradually (e.g., using a syringe pump) or slowly dispensing down the side of the container to prevent cell losses resulting from osmotic stress."

Comment Summary #28: Two commenters suggested edits regarding "validation" of the cryopreservation solution addition steps.

Response: Comment incorporated. The sentence was modified to state: "The method for introducing or removing a cryopreservation solution should be developed and evaluated for its impact on cell viability and functionality."

Comment Summary #29: The commenter suggested addition of the following sentence to the end of the *Addition of Cryoprotectant Solution* subsection: "The time that cells are exposed to the cryoprotectant, prior to freezing, should be limited and the maximum

time allowable, without deleterious effects, should be determined during development work for routine use."
Response: Comment incorporated.
Comment Summary #30: One commenter suggested a modification to the sentence regarding controlled and uncontrolled rate freezers.
Response: Comment incorporated. The sentence was modified to state: "Two different types of freezing typically are used for cells: controlled-rate cooling (using programmable freezers) and passive cooling (including use of insulated containers)."
Comment Summary #31: Two commenters questioned the sentence discussing validation of the controlled-rate freezing protocol.
Response: Comments incorporated. The sentence was modified to state, "Controlled-rate freezing protocols typically involve several steps, each of which should be evaluated and qualified for a specific cell type."
Comment Summary #32: Two commenters asked for clarification regarding temperatures (i.e., specify if Celsius or Fahrenheit).
Response: Comments not incorporated. Per *USP–NF General Notices* all temperatures are Celsius unless defined otherwise.
Comment Summary #33: A commenter requested a sentence modification so that controlled rate freezers are not required.
Response: Comment incorporated. Two sentences were modified as follows to add clarity: "Controlled-rate freezing protocols typically involve several steps, each of which should be evaluated and qualified for a specific cell type. The use of controlled-rate freezing provides more precise control of the freezing environment and therefore may provide more consistent (and higher) post-thaw recovery…"
Comment Summary #34: Two commenters requested modification of the sentence, "The average cooling rate achieved for the majority of the process and the consistency of freezing curves should be validated."
Response: Comments incorporated. The sentence was modified as follows: "The average cooling rate achieved for the majority of the process and the consistency of freezing curves should be evaluated and qualified for purpose."
Comment Summary #35: The commenter requested introducing transient warming and uncontrolled storage early in the Cryogenic Storage subsection.
Response: Comment not incorporated. The topics are sufficiently covered later in the General Chapter.
Comment Summary #36: The commenter requested adding that the shipping containers that are used during transfer of the cell product from the freezing device to storage should be validated and that samples should be shipped with temperature monitors to detect any excursions.
Response: Comment not incorporated. These issues are sufficiently covered later in the General Chapter.
Comment Summary #37: The commenter requested that "liquid nitrogen pans" be added to the suitable transfer device list.
Response: Comment not incorporated. These pans have significant safety risks and the Expert Committee will not recommend their use in the chapter.
Comment Summary #38: The commenter requested consistent use of the words "Dewar" and "cryogenic storage units."
Response: Comment incorporated.

Comment Summary #39: The commenter stated that minimizing disturbance of the Master Cell Bank (MCB) is not unique to MCBs and that this statement should be modified to include any cell bank.
Response: Comment incorporated. The sentence was modified to add clarity: "Cell banks (e.g., MCBs) or other cell cultures that are accessed infrequently should be stored separately from WCBs or other cell cultures that are accessed more often. Frequent retrieval from the cell bank/culture may cause shifts in temperature. This activity must not compromise the long-term stability and performance of the infrequently used cell bank/culture. It is also valuable to divide a bank and store it in multiple locations to decrease risks due to a catastrophic event at a particular site."
Comment Summary #40: The commenter requested an editorial change of "specimens" to "cells."
Response: Comment incorporated.
Comment Summary #41: Two commenters requested clarification of storage temperatures in this section.
Response: Comment incorporated. The sentence was modified to state: "For long-term storage of fastidious specimens such as cell lines and primary cell cultures, this critical temperature is not warmer than -130° for nonclinical specimens or not warmer than -150° for clinical material (to give an adequate margin of error) in the vapor phase of the liquid-nitrogen freezer."
Comment Summary #42: The commenter requested modification of the sentence regarding hazardous cryocontainers.
Response: Comment incorporated. The sentence was modified to state: "Although storing cryopreserved cells in liquid nitrogen prolongs longevity, hazards associated with unsuitable containers or container use (e.g., exploding vials and rupturing bags) have prompted greater use of nitrogen vapor phase storage."
Comment Summary #43: A commenter indicated that the vapor phase of a liquid nitrogen freezer is usually -150^{o} or colder, not -170^{o} and another commenter asked for clarification of these points.
Response: Comments incorporated. The following sentences were revised as follows: "If the liquid-nitrogen freezer is suitably configured, the working temperature in the vapor phase is commonly -150° or colder. The liquid-nitrogen freezer should be qualified, and the temperature of the vapor phase should be routinely checked to ensure that the temperature does not become warmer than -130° for cell lines or other frozen material or warmer than -150° for material used for clinical applications (e.g., cell therapies)."
Comment Summary #44: Two commenters indicated that a backup of dry ice was not a good recommendation for all cell types and should not be required.
Response: Comments incorporated. The following sentences were revised as follows: "In the event of equipment or power failure, backup refrigeration should be available. Proper operation of a repository requires monitoring of temperature and liquid-nitrogen levels and automatic filling. In addition, it is recommended to have a backup for emergency cooling (e.g., empty back-up cryogenic storage) in case of freezer failure."
Comment Summary #45: The commenter suggested recommending the use of log books next to the freezer for real-time documentation of the contents stored in each cane and box number (in addition to an electronic inventory database).

Response: Comment incorporated. A sentence was added: “In addition, it is recommended that all changes to cryostorage inventories be recorded in log books near the storage unit.”
Comment Summary #46: The commenter requested clarification of the shipping temperatures.
Response: Comment incorporated. The following sentences was revised to state: “Cryopreserved cells typically are shipped in liquid-nitrogen vapor shippers with temperature-monitoring systems to ensure that the unit does not become warmer than -130° for cell lines and -150° for clinical material during the shipping process.”
Comment Summary #47: The commenter indicated that the General Chapter should state that shipping validation studies should include worst case scenarios and include temperature monitors.
Response: Comment incorporated.
Comment Summary #48: Several commenters requested clarification regarding the shipping validation studies and suggested caution using dry ice.
Response: Comments incorporated. The following statements were revised as follows: “For most cryopreserved cells, shipping in dry ice for short duration may be adequate but the shipping process should be validated, shown to have no adverse impact on the cells, and temperature monitors should be included. However, some cells may require shipping in liquid-nitrogen vapor phase (Dewars). Prevalidation of the shipping methods may be required to determine the best option and prevalidation risk assessment should be performed even if only one option for transport is being considered.”
Comment Summary #49: The commenter indicated that prevalidation risk assessment should be performed independent of the number of shipping options.
Response: Comment incorporated.
Comment Summary #50: The commenter requested that the impact of X-rays during transportation be discussed.
Response: Comment not incorporated. Air travel studies have not demonstrated any significant impact from these levels of X-rays.
Comment Summary #51: Two commenters suggested broadening thawing options that are appropriate for each cell type and purpose.
Response: Comments incorporated. The following sentences were revised as follows: “For each cell therapy product and cell line the most appropriate thawing procedure (temperature, gradient, and time) needs to be developed. These products and cell lines typically are thawed in a warm-water bath or for therapeutic cell preparations in a bead bath or thermoblock.”
Comment Summary #52: The commenter requested removing the validation requirement for thawing rates.
Response: Comment incorporated.
Comment Summary #53: The commenter requested additional explanation regarding the caution that CPA removal or dilution protocols must be optimized.
Response: Comment not incorporated. The Expert Committee stated that the issue is sufficiently covered by the current text in the chapter.
Comment Summary #54: The commenter requested that minimum viability limits be based on experience.

Response: Comment incorporated. The sentence was added: “Minimum viability limits should be set based on experience, and thawed products with viabilities below the set limits should be discarded.”
Comment Summary #55: The commenter requested additional clarification of the trypan blue use for specific cell types.
Response: Comment incorporated. The following sentence was added: “The method to test viability needs to be carefully selected and qualified for the particular cell type being measured with a protocol that specifies diluents and time.”
Comment Summary #56: Two commenters suggested that post-thaw assessment should be conducted over time due to freezing losses.
Response: Comments incorporated. The following sentence was added: “Stability of cryopreserved cells can be assured by periodically thawing and testing a vial of the cells (also see ICH Q5D)."
Comment Summary #57: The commenter indicated that some evaluation procedures may take longer than the time of intended use and so these data may have to be extrapolated from historical data from "mock test" vials.
Response: Comment not incorporated. The use of such an approach is beyond the scope of this General Chapter.
Comment Summary #58: Two commenters requested additional guidance for adventitious agent testing.
Response: Comment not incorporated. General Chapter <1050> is harmonized with ICH Q5A and additional testing guidance is beyond its scope.
Expert Committee-initiated Change #3: Changed “must” to “should” in the sentence: “Prefreeze processing should not result in cells that are stressed before...”
Expert Committee-initiated Change #4: Changed “developed and validated” to “prepared” in the sentence: “Protocols for handling disruption of the freezing process and backup plans should be prepared.”
Expert Committee-initiated Change #5: Removed the word “mechanical” before “freezer” in the sentence: “Passive freezing involves placing a product in a freezer...”
Expert Committee-initiated Change #6: Added the sentence: “Some microbial cell cultures can be suitably maintained in mechanical freezers but this should be demonstrated.”
Expert Committee-initiated Change #7: Changed “units” to “containers” in the sentence: “Shipping containers are subjected to significant vibrations...”
Expert Committee-initiated Change #8: Changed “physical” to “membrane” in the sentence: “Membrane integrity is used most often.”
Expert Committee-initiated Change #9: Made editorial changes to clarify the sentence: “The batch record should be detailed, including the history of the cells and all activities starting from their receipt to release of the cell banks or products for use.”

Cryopreservation of Human Cell Therapy Products
Comment Summary #59: Two commenters asked for more DMSO guidance.
Response: Comment incorporated. The following sentence was added: “A DMSO limit of 1 g/kg recipient weight/day is commonly used in clinical cell therapy practice.”
Comment Summary #60: The commenter requested that “must” be changed to “should” in the sentence “Prefreeze processing must not result in cells that are stressed…”
Response: Comment incorporated.

Comment Summary #60: Two commenters requested caution and qualification of human- and animal-derived protein additives.
Response: Comments incorporated. The following sentences were revised to state: "The use of human-derived protein additives such as human serum albumin, serum, or plasma is common, but they may need extensive qualification so should be avoided if possible and alternatives should be evaluated. Additives such as animal derived heparin, citrate-based anticoagulants, and DNase sometimes are used."
Comment Summary #61: A commenter stated that validation of cryopreservative introduction and removal is not required.
Response: Comment incorporated. The following sentence was revised: "Procedures for introduction or removal of a cryopreservation solution should be assessed before freezing to ensure that cell losses resulting from this step are minimized."
Expert Committee-initiated Change #10: Made editorial changes to clarify the sentence: "Cryopreserved cell therapy products typically are stored and transported at temperatures of -150° or colder."
Expert Committee-initiated Change #11: Deleted the sentence: "Emergency salvage procedures, which typically include use of hemostats to…"

Preservation of Human Pluripotent Stem Cell Lines
Comment Summary #62: A commenter requested clarification of the vitrification temperatures.
Response: Comment incorporated. An example temperature was added to the sentence: "All cryopreserved or vitrified samples must be stored at temperatures below the glass transition temperature of the sample, and for vitrified samples this is much lower (e.g., -150^{o}) than for traditionally cryopreserved cell samples."

Cell Substrates Used In Production and Characterization of Biotechnology-Derived and Biologic Therapeutic Products
Comment Summary #63: A commenter asked for more guidance between the differences between cryopreservation of microbes and eukaryotic cells in the introduction of this section.
Response: Comment not incorporated. Microbes are sufficiently covered in later subsections of the General Chapter.
Comment Summary #64: A commenter suggested adding that it is advisable to characterize the parental cell bank prior to its use in cloning.
Response: Comment incorporated.
Comment Summary #65: A commenter indicated that the WCB should be prepared from a single expanded culture, due to concerns about pooling a number of vials together, as it could introduce heterogeneity.
Response: Comment incorporated. See response to Comment #13.
Comment Summary #66: Two commenters requested consolidating this section because it was repetitive to earlier content.
Response: Comments not incorporated. The subsection content is suitable for the specific issues regarding these cell types and purposes.
Comment Summary #67: A commenter suggested adding BHK-21 and MDCK cells to the list of common vaccine substrate examples.

Response: Comment incorporated.
Comment Summary #68: A commenter indicated that it is most important to ensure that cells are not contaminated and that they are viable and suggested that the General Chapter should not expand the possible approaches in this section.
Response: Comment incorporated.
Comment Summary #69: A commenter indicated that cell cultures should not be pooled to make a cell bank.
Response: Comment incorporated. See response to Comment #13. Also, as cultures can be flasks of cells, the current sentence is sufficient with the clarification.
Comment Summary #70: A commenter indicated that describing DMSO as "endotoxin free" is not accurate.
Response: Comment incorporated.
Comment Summary #71: A commenter indicated that it would be useful to add hermetically sealed glass ampoules as another cryocontainer example.
Response: Comment not incorporated. The example given is suitable, and cryocontainers is sufficiently covered in earlier sections of the General Chapter.
Comment Summary #72: Two commenters indicated that the labeling recommendation in this section is excessive and not entirely consistent with the labeling general section earlier in the General Chapter.
Response: Comment incorporated. The sentence was deleted from this section.
Comment Summary #73: Two commenters requested edits to the sentence regarding introduction of cryopreservation medium.
Response: Comment incorporated. The following sentence was revised to state: "Immediately following centrifugation of cells, growth medium is removed from cell pellets, and cells are gently resuspended by slow addition of cryopreservation medium that is often precooled for many cell types."
Comment Summary #74: Two commenters suggested edits to the cryovial filling recommendations.
Response: Comment incorporated. The following sentences were revised to state: "Vials can be filled manually by using a hand-held pipetting device or by using an automated vial-filling machine. In either case, vials are usually refrigerated as the filling progresses in order to minimize potential toxic effects of DMSO at higher temperatures. Time limits should be established for the entire filling process and recorded in the batch record."
Comment Summary #75: A commenter indicated cooling rates of up to 5^{o}/minute may be too fast for some cell types and recommended that a target of 1^{o}/minute may be more appropriate.
Response: Comment not incorporated. The sentence already recommends testing a range that includes both these values, so no change is required.
Comment Summary #76: A commenter indicated that warm water baths pose a contamination risk for thawing and asked that other warming options be included.
Response: Comment incorporated.
Comment Summary #77: A commenter indicated that sometimes centrifugation during post-thaw processing can be suitable and suggested a modification of the sentence to add flexibility.
Response: Comment incorporated.
Comment Summary #78: A commenter requested if DMSO could be added to the CPA discussion.

Response: Comment incorporated.
Expert Committee-initiated Change #12: Broadened the testing options by editing the end of the sentence: “The MCB or MCS is extensively tested to confirm purity, phenotype, genotype, protein expression, or other important attributes.”
Expert Committee-initiated Change #13: Made editorial changes to clarify the sentence: Production of recombinant proteins in these insect cells employs recombinant baculovirus infection...”
Expert Committee-initiated Change #14: Edited this sentence to add caution: “If a liquid-nitrogen Dewar is not available, then vials can sometimes be packed in dry ice but this process should be demonstrated as suitable since it can result in detrimental pH changes.”
Expert Committee-initiated Change #15: Changed “glycerin” to “glycerol” throughout for consistency.
Expert Committee-initiated Change #16: Clarified the sentence: “The final cell suspension is transferred to a vessel in which the cells can be mixed during filling of final containers to facilitate uniformity of the cell bank.”
Expert Committee-initiated Change #17: Clarified the sentence: “Alternatively, microbial cell banks may not use liquid nitrogen storage but can be stored at approximately -80°.”
Expert Committee-initiated Change #18: Changed “vial” to “container” in the subsection header “WARMING AND CONTAINER THAWING.”

Appendix
Comment Summary #79: A commenter suggested adding ICH Q5D to the list of references.
Response: Comment incorporated.
Comment Summary #80: A commenter indicated that the WHO reference was incorrect and should be changed.
Response: Comment incorporated.

General Chapter/Sections: General Chapter <1229.4> Sterilizing Filtration of Liquids
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6

Comment Summary #1: The commenter requested including information on the sterilizing filtration of gases such as nitrogen and compressed air, because this is also often a critical function within aseptic filling (due to the similarities of accomplishing the creation of sterile gases) or creating a separate General Chapter on this topic.
Response: Comment not incorporated. A separate General Chapter, Sterilizing Filtration of Gases, may be developed in the future.
Comment Summary #2: The commenter requested harmonizing the proposed draft with other available sources of information on sterilizing filtration such as *PDA TR #26*.
Response: Comment not incorporated. General Chapter <1229.4> is currently harmonized with *PDA TR #26* and other available sources, insofar as possible.
Comment Summary #3: The commenter suggested clearly stating the scope of this General Chapter, because there are microorganisms other than viruses (for example mycoplasmas and prions) that are not included in sterile filtration.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested revising the text to indicate that filter qualification and validation studies can be conducted by (or for) the filter user to demonstrate that the chosen sterilizing filtration process achieves a sterile filtrate.
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that in this document, filter, equipment, and pharmaceutical manufacturers are noted and suggested they must be defined relative to the comment or section.
Response: Comment incorporated.
Comment Summary #6: The commenter suggested replacing the ASTM definition for a sterilizing grade filter with the one from *PDA Technical Report 26*: "A filter that reproducibly removes all test microorganisms from the process stream, producing a sterile filtrate."
Response: Comment not incorporated. ASTM International is a recognized standards-setting organization, similar to ISO.
Comment Summary #7: The commenter suggested replacing the term "available filter area" with “Effective Filter Area (EFA).”
Response: Comment incorporated.
Comment Summary #8: The commenter indicated the filter end user does not set the integrity test specifications. That is done only by the filter manufacturer. The end user only validates the aseptic process according to FDA requirements; therefore, the text should be clarified.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested replacing “nominal" pore size with "absolute” pore size.
Response: Comment not incorporated. Membrane filters do not have absolute pore-size ratings. For example, 0.2 micron-rated filters from different filter manufacturers have substantially different pore-size ranges and distributions.
Comment Summary #10: The commenter indicated that use of 0.45 µm is uncharacteristic for modern processes and recommended deletion of the text that refers to its use.

Response: Comment not incorporated. While the use of 0.45 micron-rated filters may be uncharacteristic, the use of these filters should not be precluded.
Comment Summary #11: The commenter suggested adding "entrapment" as the third mechanism of filtration.
Response: Comment not incorporated. The two “primary” mechanisms are sieve retention and adsorption. Entrapment is not a primary mechanism.
Comment Summary #12: The commenter suggested indicating that Filter users should consider both mechanisms when they develop, qualify, and validate sterilizing filtration processes.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested that it is a misconception that high pressures and flow rates can squeeze microorganisms through the filter’s pores.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested that only some microorganisms are deformable and it is not a general observation.
Response: Comment incorporated.
Comment Summary #14: The commenter indicated that Grow through phenomenon has yet to be conclusively demonstrated and recommended deletion of the text referencing it.
Response: Comment not incorporated. There is evidence of this phenomenon in the scientific literature.
Comment Summary #15: The commenter indicated that filter membranes are not multilayer as manufactured.
Response: Comment incorporated.
Comment Summary #16: The commenter requested providing a reference for the observation that thicker membranes generally are more retentive than thinner membranes of the same type and pore-size rating.
Response: Comment incorporated.
Comment Summary #17: The commenter indicated that Bacterial retention is never entirely due to sieve retention. Therefore, the presence of surfactants and pH are always important.
Response: Comment incorporated.
Comment Summary #18: The commenter indicated that while temperature effects are not significant, the explanation regarding temperature and effect on viscosity is contradicting this and should be clarified.
Response: Comment incorporated.
Comment Summary #19: The commenter suggested clarifying that the log reduction value of sterilizing-grade filters is described as greater than or equal to the log of the challenge population.
Response: Comment incorporated.
Comment Summary #20: The commenter suggested clarification of the number of lots required for validation.
Response: Comment not incorporated. It is not possible to generally specify the number of lots required for validation.
Comment Summary #21: The commenter requested adding the factor "volume" to the factors that should be considered when developing a sterilizing-filtration validation protocol.
Response: Comment incorporated.

Comment Summary #22: The commenter suggested clarifying the sentence: “The filters should have pre-use integrity test values….”
Response: Comment incorporated.
Comment Summary #23: The commenter suggested clarifying the sentence: “The assembled filtration apparatus…..”
Response: Comment incorporated.
Comment Summary #24: The commenter suggested clarifying “the “exact” bubble point” and “is difficult to detect in high-surface-area filters . . ."
Response: Comment incorporated.
Comment Summary #25: The commenter suggested modification of the text to read: "filter does not contain objectionable levels" to “filter does not release objectionable levels " and that the text also indicate that the filter manufacturer conducts cleanliness tests to assure that the filter does not adversely affect the USP particle cleanliness requirements of the product.
Response: Comment incorporated.

General Chapter/Sections: General Chapter <1229.7> Gaseous Sterilization
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6
Comment Summary #1: The commenter suggested changing the abbreviation for Ethylene Oxide from EtO, to EO, because it is commonly abbreviated as EO in other standards, such as ISO.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested deleting the sentence, “Efficiency of gas sterilization is reduced if the agent condenses during the process.”
Response: Comment not incorporated. The Expert Committee finds that it is critically important to distinguish between gases and vapor sterilization processes.
Comment Summary #3: The commenter requested that more categories of items, such as plastic containers (as used for topical and ophthalmic preparations) and drug substances/ingredients, be defined as candidates for sterilization with ethylene oxide to give the user a greater understanding of the options when using ethylene oxide as a sterilant.
Response: Comment not incorporated. The first sentence in the section gives sufficient indication of the type of materials to be used for sterilization with ethylene oxide.
Comment Summary #4: The commenter requested deleting the sentence, "Because these are true gases, single-point monitoring during operation can be used to determine process lethality,” because even though these are “true gases,” stratification can occur without recirculation and single point monitoring may not be appropriate in chambers without recirculation.
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that the sentence, “Ethylene oxide has been approved for parametric release…” could be interpreted to mean that parametric release is allowed for all items subject to ethylene oxide sterilization and recommended clarification regarding the use of parametric release.
Response: Comment incorporated.

Comment Summary #6: The commenter indicated that materials do not need to be unaffected by the process because beneficial changes are acceptable and suggested changing the word “unaffected” to “not adversely affected.”
Response: Comment incorporated.
Comment Summary #7: The commenter requested that the items listed in the text as process “parameters” be changed to “considerations.”
Response: Comment incorporated.
Comment Summary #8: The commenter requested that the process sequence reflect most routine ethylene oxide sterilization processes.
Response: Comment incorporated.
Comment Summary #9: The commenter requested deleting the phrase “Unlike heat sterilization processes” and clarifying the text to indicate the minimum addition of gas to maintain pressure within the processing vessel during sterilization.
Response: Comment incorporated.
Comment Summary #10: The commenter requested changing the concentration of ethylene oxide used from 3% to 2.6%, because this is the lower flammability limit. In addition, ethylene oxide is explosive in concentrations of greater than 2.6% by volume in air; therefore, inert gases are often used to minimize flammability.
Response: Comment incorporated.
Comment Summary #11: The commenter suggested adding a new section for Nitrogen Dioxide to complete the listing of "other gaseous sterilants."
Response: Comment incorporated.
Comment Summary #12: The commenter suggested revising the introductory text on the validation of gaseous sterilization to indicate that it generally begins with the establishing of a "minimum lethal process dwell time” through the use of fractional exposure studies.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested adding references to other validation approaches for sterilization.
Response: Comment incorporated.
Comment Summary #13: The commenter suggested explanation or deletion of the term "passive biological indicator.”
Response: Comment incorporated.
Comment Summary #14: The commenter requested changing the term “process control devices” to “process challenge devices.” Process control implies use of analytical methods for process monitoring and the paragraph is discussing use of a biological system for process monitoring, which currently is more often referred to as process challenge device.
Response: Comment incorporated.
Comment Summary #15: The commenter suggested clarifying the text to indicate that evaluation of lethal conditions within and across the load items by placing BI’s / or process challenge devices within the load during the process confirmation and microbiological challenge study.
Response: Comment incorporated.
Comment Summary #16: The commenter suggested adding a section for chemical indicators.
Response: Comment not incorporated. Chemical indicators will be described separately in General Chapter <1229.9>.

Comment Summary #17: The commenter indicated that parametric release is not routinely used for gas sterilization of finished drug products and recommended that statements regarding the use of parametric release for finished product commercial release be clarified.
Response: Comment not incorporated. This document does not supersede any requirement for a firm to conform to the applicable regulations, nor does it suggest that terminal sterilization of a drug product using a gaseous sterilization process is acceptable practice.
Comment Summary #18: The commenter requested correcting the reference *ISO 11135:2007* to *ISO 11135-1:2007*, and adding a reference to *ISO 11135-2:2008.*
Response: Comment incorporated.

General Chapter/Sections: General Chapter <1229.8> Dry Heat Sterilization
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6
Comment Summary #1: The commenter suggested clarifying the use of the terms "items" and "materials" and clearly addressing in the introduction the categories or types of materials/substances/items that can be subject to dry heat sterilization.
Response: Comment incorporated.
Comment Summary #2: The commenter indicated that the minimum temperature of 170°C conflicts with the *Ph.Eur*. temperature of 160° for 2h and suggested aligning the text with the existing *Ph.Eur.* text.
Response: Comment not incorporated. USP recommends, and most US firms have always used, a base temperature of 170°.
Comment Summary #3: The commenter suggested revising the definition of F_H and considering inclusion of equivalent time for 170°, which the load received at other temperature conditions and time frame.
Response: Comment incorporated.
Comment Summary #4: The commenter suggested revising the text that describes the cycle to be defined more by a targeted lethality than by a time at a defined minimum temperature.
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that containers and wrapping of items has a positive effect in dry heat sterilization and Bioburden-based processes may be necessary in some instances.
Response: Comment not incorporated. The suggestion that containers and wrapping of items has a positive effect in dry heat sterilization is not proven. Bioburden-based processes, while technically possible, are rarely used in dry heat sterilization.
Comment Summary #6: The commenter suggested clarifying that a major use of qualification of the sterilizing equipment is to assure that the sterile process is constantly and accurately performed.
Response: Comment incorporated.

Comment Summary #7: The commenter requested revising the paragraph:

> "Fixed loading patterns for dry heat sterilization are essential because the limited heat capacity of the air allows substantial temperature differences across the load...It may be possible to validate maximum and minimum loads as determined by either the number of items or their mass."

The commenter noted that these two statements conflict with each other. The term "essential" implies almost absolute, but the last sentence states that validation using minimum and maximum loads is possible. The commenter recommended that the statements be revised to clearly explain the possibility of using minimum and maximum loads for validation.
Response: Comment incorporated.
Comment Summary #8: The commenter suggested revising the phrase "typically are present." This implies that the statement is referring to bioburden present on items; therefore, the statement should be revised to clarify that it is a biological indicator that is either inoculated onto a surface or inoculated (or placed) within an item/material.
Response: Comment incorporated.
Comment Summary #9: The commenter indicated that the reference to "identical items" is not clear and recommended revising the sentence for improved clarity.
Response: Comment incorporated.
Comment Summary #10: The commenter suggested clarifying the sentence: "This study customarily is performed using worst case conditions where the exposure time or temperature is reduced slightly from the routine set points."
Response: Comment incorporated. The sentence was changed to: "This study is customarily is performed using slightly sub-minimal to the lower specification limits for time, temperature, and/or cumulative lethality."

General Chapter/Sections: General Chapter <1229.10> Radiation Sterilization
Expert Committee: General Chapters—Microbiology
No. of Commenters: 6
Comment Summary #1: The commenter suggested clarifying that UV sterilization has a restricted application and X-ray is an example of ionizing radiation.
Response: Comment incorporated.
Comment Summary #2: The commenter suggested adding additional references for methods used to establish appropriate radiation doses to achieve the desired sterility assurance level.
Response: Comment incorporated.
Comment Summary #3: The commenter suggested clarifying that an additional reason why the use of a biological indicator is inappropriate during radiation sterilization validation or routine sterilization is that all of the commonly used dose establishment methods are based on the product's bioburden in its natural state.
Response: Comment incorporated.

Comment Summary #4: The commenter suggested changing ‘mRads’ to 'Mrads'
Response: Comment incorporated.
Comment Summary #5: The commenter indicated that dose mapping inside the Product package is not always necessary.
Response: Comment not incorporated. Drug usage would require internal dose measurement, because the contents are what are being sterilized.
Comment Summary #6: The commenter suggested correcting the half life of cobalt-60 to 5.271 years.
Response: Comment incorporated.
Comment Summary #7: The commenter indicated that the statement that e-beam systems are smaller and can be installed and operated by the end user needs to be revised.
Response: Comment incorporated.
Comment Summary #8: The commenter indicated that Method 1 does not compare a dose and the radiation resistance of a population, rather it substantiates based on an assumption of a standard distribution of resistances.
Response: Comment incorporated.
Comment Summary #9: The commenter suggested deleting the sentence, "After verification, analysts read the appropriate radiation sterilization dose from a table."
Response: Comment incorporated.
Comment Summary #10: The commenter indicated that per *AAMI TIR33*, Method VDmax can be used for bioburden levels that are higher than 1000 CFU.
Response: Comment incorporated.
Comment Summary #11: The commenter indicated that the series of incremental doses is used to estimate the dose at which the SAL would be 10-2; bioburden is still required for routine monitoring and control.
Response: Comment incorporated.
Comment Summary #12: The commenter requested adding the following statement at the end of Material Compatibility section: “Product stability, safety, and functionality should be confirmed over the product's shelf life.”
Response: Comment incorporated.
Comment Summary #13: The commenter indicated that Figure 1 is unclear regarding which method is being used to determine the validation dose. The figure should be annotated to refer to the method.
Response: Comment incorporated.
Comment Summary #14: The commenter suggested changing the sub-section title from “Load Mapping” to "Load Dose Mapping."
Response: Comment incorporated.
Comment Summary #15: The commenter indicated that the section on Load Mapping refers to PQ, and suggested this needs to be expanded to cover both OQ and PQ validation exercises.

Response: Comment incorporated.

Comment Summary #16: The commenter suggested addition of a reference to ASTM guidance documents and standards on the use and calibration of dosimetry systems.

Response: Comment incorporated.

Comment Summary #17: The commenter suggested clarifying the text that states dosimetry results for sterilization cycle efficacies correspond to the required minimum value for sterility assurance and demonstrate that the maximum value has not been exceeded.

Response: Comment incorporated.

General Chapter/Section(s): <1285> Preparation of Biological Specimens for Histologic and Immunohistochemical Analysis
Expert Committee: Monographs—Biologics and Biotechnology 2
No. of Commenters: 1

General Comments

Comment Summary #1: The commenter indicated that histology (methods and diagnostic) should not be included in the *USP–NF,* because laboratories have their own knowledge, experiences, equipment, and procedures.

Response: Comment not incorporated. General Chapter <1285> is an informational general chapter providing best practices for preparation of tissues for histological analysis. The General Chapter contains a useful method example that laboratories could choose to adopt if suitable for their purpose.

Comment Summary #2: The commenter requested clarification of why only formaldehyde is mentioned for fixation.

Response: Comment not incorporated. Multiple fixation techniques are already discussed in the *Procedures–Points to Consider* section regarding fixation, as well as in *Table 1*.

Comment Summary #3: The commenter indicated that the procedures were written from histology methods used for mice and asked for more guidance for other types of tissues.

Response: Comment not incorporated. The General Chapter contains best practices for a variety of tissues prepared from human samples as well as other species. The General Chapter contains an example protocol that is suitable for many tissue sources that are prepared for therapeutic purposes and may be in a *USP–NF* product monograph.

Comment Summary #4: The commenter indicated that nontoxic alternatives to the organic solvents discussed in the General Chapter exist.

Response: Comment not incorporated. The General Chapter already includes nontoxic alternatives, but since some solvents are still commonly used for histological methods (e.g., xylene), with appropriate precautions these solvents are still suitable and so were not excluded from the General Chapter.

Comment Summary #5: The commenter indicated that immunohistology also is a histological method and would require very different tissue preparation from that presented in this General Chapter.

Response: Comment not incorporated. In the future, USP plans to propose a new general chapter for immunohistological methods. The scope of the current General Chapter includes the principle that fixation techniques that preserve morphology can also be used to stabilize tissues for immunohistological analysis.

General Chapter/Section(s): <1285.1> Hematoxylin and Eosin Staining of Sectioned Tissue for Microscopic Examination
Expert Committee: Monographs—Biologics and Biotechnology 2
No. of Commenters: 1

General Comments
Comment Summary #1: The commenter indicated that histology (methods and diagnostic) should not be included in the *USP–NF,* because laboratories have their own knowledge, experiences, equipment, and procedures.
Response: Comment not incorporated. <1285.1> is an informational general chapter providing best practices for hematoxylin and eosin (H&E) staining of tissues for histological analysis. The General Chapter contains a useful example method that laboratories could choose to adopt if suitable for their purpose.
Comment Summary #2: The commenter asked why only one H&E protocol is included, because multiple tissue preparation methods could be used prior to staining.
Response: Comment not incorporated. The General Chapter contains an example protocol that is very common for H&E staining of many tissue sources that are prepared for therapeutic purposes and may be in a *USP–NF* product monograph.

General Chapter/Section(s): <2040> Disintegration and Dissolution of Dietary Supplements/Rupture Test for Soft Shell Capsules.
Expert Committee(s): General Chapters—Dosage Forms
No. of Commenters: 1
Comment Summary: The commenter requested that the current Rupture Test for Soft Shell Capsules be replaced with a disintegration method “equivalent to USP General Chapter <701>” with NMT 45 minutes acceptance criteria.
Response: Comment not incorporated. The comment was beyond the scope of the proposed revision and the Expert Committee concluded that there was not adequate justification to consider the replacement of the existing Rupture Test for Soft Shell Capsules. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/ Sections: Albuterol Extended-Release Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
Expert Committee-initiated Change #1: In *Organic impurities, Procedure 1*, the preparation of the *Standard solution* and the equation used to calculate the amount of levalbuterol related compound D were changed to reflect the use of the sulfate salt instead of the benzenesulfonic acid salt of levalbuterol related compound D.
Expert Committee-initiated Change #2: In *Organic Impurities Procedure 2*, the *Peak identification solution* was changed to reflect that it is prepared with the sulfate salt instead of the benzenesulfonic acid salt of levalbuterol related compound D.

Expert Committee-initiated Change #3: The chemical information for USP Levalbuterol Related Compound D was changed in the *USP Reference Standards* <11> section to reflect the use of the sulfate salt instead of the benzenesulfonic acid salt of the standard.

Monograph/Section: Aripiprazole/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested calculating each impurity using the external standard approach rather than using the area normalization approach.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section: Atropine Sulfate/Assay
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested changing the name of the reagent used in the *Buffer* from sodium 1-pentanesulfonate monohydrate to sodium 1-pentanesulfonate to match the *Reagents* section of the *USP–NF*.
Response: Comment incorporated.

Monograph/Section(s): Aztec Marigold Zeaxanthin Extract/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter requested removing (3S,3'S)-zeaxanthin from the test for *Stereoisomeric composition*, because it is not a component of zeaxanthin extract.
Response: Comment incorporated.

Monograph/Sections: Aztreonam for Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the *Assay* to include column particle size.
Response: Comment incorporated.
Comment Summary #2: The commenter requested adding a test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Aztreonam Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the *Assay* to include column particle size.
Response: Comment incorporated.
Comment Summary #2: The commenter requested adding a test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section(s): Calcium Gluconate/ Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 2
Comment Summary #1: The commenter requested removing the cross reference <197K> in the test for *Infrared Absorption* because it is not applicable to the article.
Response: Comment incorporated.
Comment Summary #2: The commenter requested expanding *Table 1* with additional information for clarity.
Response: Comment incorporated.

Monograph/Section(s): Calcium L-5-Methyltetrahydrofolate Tablets/Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 1
Comment Summary #1: The commenter indicated that the reproducibility of the calcium content in the Identification test A was poor.
Response: Comment incorporated. The Expert Committee eliminated Identification test A.
Comment Summary #2: The commenter indicated that the Standard solution in the test for Strength was not stable.
Response: Comment incorporated. A note was added to indicate that Standard and Sample solutions must be injected immediately after preparation and injected only once. In addition, the concentration of both the Standard solution and Sample solution was changed from 0.05 mg/mL to 0.1 mg/mL to increase the peak response.
Comment Summary #3: The commenter indicated that the D-isomer peak response was low for the System suitability solution in the test for Enantiomeric Purity.
Response: Comment incorporated. The concentration of Standard solution and Sample solution was changed from 0.1 mg/ml to 0.4 mg/ml and preparation of System suitability solution was revised accordingly.

Monograph/Section(s): Calcium L-5-Methyltetrahydrofolate Capsules/ Multiple Sections
Expert Committee: Monographs—Dietary Supplements
Expert Committee-initiated Change #1: The Expert Committee proposed to incorporate the comments # 1-3 that were received for the Calcium L-5-Methyltetrahydrofolate Tablets monograph. (See commentary above)
Response: Comments incorporated.

Monograph/Sections: Cefadroxil/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 3
Comment Summary #1: The commenter requested replacing the *Assay* and *Organic Impurities* procedures with the commenter's methods.

Response: Comment not incorporated. The Expert Committee determined that the *Assay* procedure is suitable for its intended use and a revision is not necessary.
Comment Summary #2: The commenter requested widening the limits in the test for *Organic Impurities* based on FDA-approved limits as follows: cefadroxil R-sulfoxide, cefadroxil S-sulfoxide, cefadroxil related compound I, cefadroxil ethyl homolog, N-Ethoxycarbonyl 7-aminodesacetoxycephalosporanic acid, and cefadroxil dimer from 0.1% to 0.15%; and the limit for unspecified impurities from 0.05% to 0.10%.
Response: Comment incorporated.

Monograph/Section: Cefadroxil Capsules/Organic Impurities
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 2
Comment Summary #1: The commenter requested widening the limits in the test for *Organic Impurities* based on FDA-approved limits as follows: amoxicillin related compound I, cefadroxil related compound B, diketopiperazine derivative and 3-hydroxy-4-methylthiophenone from 0.50% to 0.5%; N-phenylglycyl delta-3 cefadroxil from 0.10% to 0.15% and unspecified impurities from 0.10% to 0.2%.
Response: Comment incorporated.
Comment Summary #3: The commenter requested correcting the calculation formula in the test for *Organic Impurities* to add a unit conversion factor.
Response: Comment incorporated.

Monograph/Sections: Ceftriaxone for Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested widening the limits in the test for *Organic Impurities* based on FDA-approved limits as follows: deacyl ceftriaxone and ceftriaxone E-isomer from 0.5% to 1.0% and the limit for total impurities from 2.0% to 2.5%.
Response: Comment incorporated.
Comment Summary #2: The commenter requested adding an *Identification* test for sodium.
Response: Comment not incorporated. The Expert Committee considers the proposed tests for Identification to be adequate for the monograph.

Monograph/Section: Ceftriaxone Sodium/Organic Impurities
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the limits in the test for *Organic Impurities* based on FDA-approved limits as follows: add a limit for 7-aminocephalosporanic acid to be controlled at 0.5% if this impurity is part of a manufacturer's impurity profile; widen the limit for total impurities from 2.0% to 2.5%.
Response: Comment incorporated.

Monograph/Sections: Chloroquine Phosphate/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 2

Comment Summary #1: The commenter requested correcting the chemical name of Chloroquine Phosphate.
Response: Comment incorporated.
Comment Summary #2: The commenter requested widening the limit of chloroquine related compound D from NMT 0.1% to NMT 0.50% in the test for *Organic Impurities*, to be consistent with FDA approved specifications.
Response: Comment incorporated.
Comment Summary #3: The commenter requested including the chemical names of impurities.
Response: Comment incorporated.

Monograph/Section(s): Chondroitin Sulfate Sodium/ Multiple Sections
Expert Committee: Monographs—Dietary Supplements
No. of Commenters: 3
Comment Summary #1: The commenter requested changing the ratio of ΔDi-4S to ΔDi-6S in the test for *Disaccharide Composition* from NLT 1.5 to NLT 1.0 to accommodate material originated from land animals.
Response: Comment incorporated.
Comment Summary #2: The commenter requested changing the name of the test for *Specific Disaccharides* to *Limit of Non-Specific Disaccharides* and changing the acceptance criteria for the test accordingly, from NLT 90.0% to NMT 10.0%.
Response: Comment incorporated.
Comment Summary #3: The commenter requested changing the water content from NMT 10.0% to NMT 12.0%.
Response: Comment incorporated.

Monograph/Sections: Clindamycin Phosphate/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 4
Comment Summary #1: The commenter requested tightening the limits for individual unspecified impurities in the test for *Organic Impurities*.
Response: Comment not incorporated. The Expert Committee concluded that the acceptance criteria in the monograph are consistent with FDA's regulatory authority.
Comment Summary #2: The commenter requested widening the acceptance criteria for lincomycin phosphate in the test for *Organic Impurities* from 0.40% to 1.0% and correcting the limit for lincomycin.
Response: Comment incorporated.
Comment Summary #3: The commenter requested revising the test for *Organic Impurities* to include a limit for clindamycin 2, 4-diphosphate.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #4: The commenter requested revising the calculation formula in the *Assay* to remove the unit conversion factor, which is unnecessary.
Response: Comment incorporated.

Monograph/Section: Dioxybenzone /Assay
Expert Committee: Monographs—Small Molecules 3

Expert Committee-initiated Change #1: Based on supporting validation data, the solvent used to prepare the *Standard solution* and *Sample solution* in the *Assay* was revised from methanol to the *Mobile phase*.
Expert Committee-initiated Change #2: Based on supporting validation data and commercially available column dimensions, the HPLC column inner diameter was corrected from 4.7 mm to 4.6 mm.

Monograph/Section: Dipyridamole/Assay
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter requested including a run time for the proposed procedure.
Response: Comment incorporated.
Comment Summary #2: The commenter requested including column efficiency as a system suitability requirement.
Response: Comment not incorporated. The Expert Committee determined that the proposed suitability parameters are adequate to evaluate system suitability.
Comment Summary #3: The commenter requested revising the *Assay* to use the same mobile phase and column dimensions as in the test for *Organic Impurities***.**
Response: Comment not incorporated. The parameters in the *Assay* reflect the validated procedure. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Sections: Efavirenz Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 0
Expert Committee initiated Change #1: The names of *Standard solution 1* and *Standard solution 2* in the *Assay* were revised to *Standard stock solution 1* and *Standard stock solution 2*, respectively, for clarity.
Expert Committee initiated Change #2: A note was added to *System suitability* in the *Assay* to provide relative retention times.
Expert Committee initiated Change #3: *Table 2* in the test for *Organic Impurities* was revised to indicate that efavirenz ethane analog is also called efavirenz related compound B.

Monograph/Section: Extended Phenytoin Sodium Capsules/Organic Impurities
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the limits for phenytoin related compound A from NMT 0.5% to 0.9% to align the limits with those in the drug substance monographs.
Response: Comment not incorporated. The drug substance monographs will be revised to tighten the limit for related compound A in future revisions.

Monograph/Sections: Fluorouracil/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1

Comment Summary #1: Commenter requested revising the *Assay* procedure to be the same as *Organic impurities* procedure.
Response: Comment not incorporated. The Expert Committee determined that the *Assay* procedure is suitable for its intended use and a revision is not necessary.
Expert Committee-initiated Change #1: For consistency across the monograph family, the test for *Identification C* was revised to use retention time agreement based on the *Assay* instead of on the test for *Organic Impurities*. The *Identification* solution is deleted from the test for *Organic impurities*.
Expert Committee-initiated Change #2: USP Fluorouracil Related Compound D RS is deleted from *USP Reference Standards* <11> due to lack of availability of a suitable reference material. The reference standard name is deleted from the *Standard solution* in the test for *Organic impurities*. The impurity name of fluorouracil related compound D in the test for *Organic impurities* is revised to 5-Methoxyuracil according to current USP style.

Monograph/Section: Fluorouracil Injection/Assay
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: Commenter requested revising the *Assay* procedure to be the same as *Organic impurities* procedure in the *Fluorouracil* monograph.
Response: Comment not incorporated. The Expert Committee determined that the *Assay* procedure is suitable for its intended use and a revision is not necessary.

Monograph/Section: Fluorouracil Topical Solution/Identification
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the *Assay* to indicate the use of a diode array detector to accommodate the proposed *Identification B*.
Response: Comment incorporated.

Monograph/Sections: Insulin Aspart/Multiple sections
Expert Committee(s): Monographs – Biologics and Biotechnology 1
No. of Commenter: 1

Identification/Peptide Mapping
Expert Committee-initiated Change #1: The title and text of the section were revised to make reference to the new General Chapter <121.1> *Physical Analytical Procedures for Insulins*, *Peptide Mapping*. The descriptions of *Mobile phase*, *Chromatographic system*, and *Acceptance criteria* were not changed.

Assay
Comment Summary #1: The commenter requested using the term **“**Solutions:” instead of “Samples:” in System suitability and Analysis sections.
Response: Comment not incorporated. Using the term "Samples" is specified in the current USP style.

Impurities/Limit of High Molecular Weight Proteins

Comment Summary #2: The commenter requested referencing General Chapter <121.1> *Physical Analytical Procedures for Insulins*, *Limit of High Molecular Weight Proteins* instead of using full text, but to keep the description of *Sample solution*.
Response: Comment incorporated with a modification. The description of *Sample solution* was removed, because it is identical to the one described in General Chapter <121.1>.

Monograph/Sections: Insulin Aspart Injection/Multiple sections
Expert Committee(s): Monographs–Biologics and Biotechnology 1
No. of Commenter: 1

Assay
Comment Summary #1: The commenter suggested using the term **"**Solutions:" instead of "Samples in System suitability and Analysis sections.
Response: Comment not incorporated. Using the term of "Samples" is specified in the current USP style.

Impurities/Limit of High Molecular Weight Proteins
Comment Summary #2: The commenter suggested referencing General Chapter *Physical Analytical Procedures for Insulins*, *Limit of High Molecular Weight Proteins* <121.1> instead of using full text, but to keep description of *Sample solution*.
Response: Comment incorporated.

Monograph/Section: Lecithin/Multiple Sections
Expert Committee(s): Monographs—Excipients
No. of Commenters: 1
Comment Summary #1: The commenter requested adding an allowance for adjustment of detector temperature and flow rate to the section on Chromatographic system for the *Content of Phospholipids* test, because of the different settings of the detector.
Response: Comment Incorporated.
Expert Committee-initiated Change #1: In the *Identification*, the Expert Committee changed the test A title from "*Thin-Layer Chromatography* <201>" to "*Identification of Phospholipids by Thin-Layer Chromatography*."

Monograph/Sections: Metoclopramide Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 2
Comment Summary #1: The commenter requested revising the *Assay* to indicate the use of a diode array detector to accommodate the proposed *Identification B*.
Response: Comment incorporated.
Comment summary #2: The commenter indicated that changing the detector from variable wavelength UV to a diode array detector cannot be done without qualification or validation.
Response: Comment not incorporated. USP monograph procedures employing detection at a single wavelength do not specify the type of detector (variable wavelength or diode array) that must be used. Both types of detectors are applicable for monitoring

a single wavelength. Manufacturers should perform method verification and evaluate system suitability during routine use to ensure suitability under actual conditions of use.
Comment summary #3: The commenter indicated that diode-array detectors are not as common in industry as variable wavelength UV detectors and that additional training and qualification are needed to switch to this type of detector.
Response: Comment not incorporated. The Expert Committee determined that the proposed *Identification* test is appropriate for this monograph and the use of diode-array detectors should not present a significant challenge to manufacturers.
Comment summary #4: The commenter indicated that identification tests based on retention time coupled with UV spectral evaluation of an HPLC peak are not orthogonal procedures.
Response: Comment not incorporated. The use of chromatographic and spectroscopic identification tests for drug products is consistent with USP efforts to modernize monographs and with current regulatory expectations. The proposed procedure is consistent with *ICH Q6A 3.2.2.b* guidelines.

Monograph/Sections: Metoclopramide Oral Solution/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
Expert Committee-initiated change: A note was added to the *Chromatographic system* in the *Assay* to indicate that the diode array detector should be used to perform the test for *Identification B*.

Monograph/Sections: Metoclopramide Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 3
Expert Committee-initiated change: A note was added to the *Chromatographic system* under *Assay* to indicate that the diode array detector should be used to perform the test for *Identification B*.

Monograph/Sections: Olanzapine Orally Disintegrating Tablets/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 3
Comment Summary #1: The commenter requested clarifying the *Sample solution* preparation in the test for *Organic Impurities*.
Response: Comment incorporated.
Comment Summary #2: The commenter requested including the test for *Water determination*.
Response: Comment not incorporated. The Expert Committee determined that water content requirements for drug products should remain as agreements between individual manufacturers and the FDA. These should not be included in the public standard due to inherent variability arising from differences in formulations.
Comment Summary #3: The commenter requested revising the analytical wavelength in *Dissolution Test 1* from 344 nm to 258 nm.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #4: The commenter requested revising the sample preparation procedure in *Identification A* to include extraction with an organic solvent to minimize the interference from water-soluble formulation components.

Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.

Monograph/Section: Padimate O/Organic Impurities
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 0
Expert Committee-initiated Change #1: The calculation was revised to be consistent with USP style.

Monograph/Sections: Piperacillin/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 0
Expert Committee Initiated Change #1: The mobile phase pH in the *Assay* and test for *Piperacillinylampicillin* was revised to remove the requirement to control the pH within ± 0.02 units. Validation data does not support the need for a restrictive requirement. General Chapter <621> allows the mobile phase pH to be adjusted to within ± 0.2 units of the required value.
Expert Committee Initiated Change #2: The calculation formulas and the relative response factors in the test for *Ampicillin, Piperacillin Penicilloic Acid, Piperacillin Related Compound E and Acetylated Penicilloic Acid of piperacillin*, and in the test for *Piperacillinylampicillin* were updated to reflect current USP style.

Monograph/Sections: Piperacillin and Tazobactam for Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the mobile phase pH in the *Assay* and *Organic Impurities Procedure 1* from 5.5 to 5.50 ± 0.02 for consistency with the other monographs in the family.
Response: Comment not incorporated. The requested change is not supported by validation data. The other monographs in the family were revised to make the pH range less restrictive.
Comment Summary #2: The commenter requested revising the test for *Organic Impurities Procedure 1* to include limits for the individual penicilloic acids.
Response: Comment not incorporated. The Expert Committee concluded that the acceptance criteria in the monograph are consistent with FDA's regulatory authority.
Comment Summary #3: The commenter requested revising the *Organic Impurities Procedures 1* through *4* to tighten the limit for individual unspecified impurities.
Response: Comment not incorporated. The Expert Committee concluded that the acceptance criteria in the monograph are consistent with FDA's regulatory authority.
Expert Committee Initiated Change #1: The calculation for piperacillin in the *Assay* was revised to correct the definition for potency of the reference standard.
Expert Committee Initiated Change #2: The storage conditions for the *System suitability solution*, the *Standard solution,* and the *Sample solution* in *Organic Impurities Procedure 4* were revised based on the sponsor's validated procedure.

Monograph/Sections: Piperacillin for Injection/Multiple Sections
Expert Committee: Monographs—Small Molecules 1

Expert Committee Initiated Change #1: The mobile phase pH in the *Assay* was revised to remove the requirement to control the pH within ± 0.02 units. Validation data does not support the need for such a restrictive requirement. General Chapter <621> allows the mobile phase pH to be adjusted to within ± 0.2 units of the required value.

Monograph/Sections: Piperacillin Sodium/Multiple Sections
Expert Committee: Monographs—Small Molecules 1
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the calculation formula in the test for *Piperacillin Penicilloic Acid and Acetylated Penicilloic Acid of Piperacillin* to reflect current USP style.
Response: Comment incorporated.
Expert Committee Initiated Change #1: The mobile phase pH in the *Assay* was revised to remove the requirement to control the pH within ± 0.02 units. Validation data does not support the need for a restrictive requirement. General Chapter <621> allows the mobile phase pH to be adjusted to within ± 0.2 units of the required value.
Expert Committee Initiated Change #2: The *Assay* was revised to indicate that the *System Suitability* evaluation and the *Analysis* are performed using Standard solution 1.

Monograph/Section: Propafenone Hydrochloride Tablets/Organic Impurities
Expert Committee(s): Monographs—Small Molecules 2
No. of Commenters: 2
Comment Summary #1: The commenter requested replacing the name of the specified impurity, N-DPP (dealkyl propafenone), with a more descriptive name.
Response: Comment incorporated.
Comment Summary #2: The commenter requested deleting the acceptance criterion for the specified impurity, N-DPP, as it is not a degradation product.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.
Comment Summary #2: The commenter requested including run time for the proposed method.
Response: Comment not incorporated. The Expert Committee concluded that the gradient program determines the run time.

Monograph/Section: Sumatriptan Tablets/Assay
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the number of tablets used to prepare the *Sample solution* from NLT 10 to NLT 5.
Response: Comment incorporated.

Monograph/Section: Thiotepa/Organic Impurities
Expert Committee: Monographs—Small Molecules 3
Expert Committee-initiated Change #1: The name of the chloro-adduct impurity was changed to thiotepa chloroethyl analog in the *Peak identification solution* to be consistent with the impurity name in *Table 1*.

Monograph/Section: Thiotepa for Injection/Organic Impurities
Expert Committee: Monographs—Small Molecules 3
Expert Committee-initiated Change #1: The name of the chloro-adduct impurity was changed to thiotepa chloroethyl analog in the *Peak identification solution* to be consistent with the impurity name in *Table 1*.

Monograph/Section: Trazodone Hydrochloride/Multiple Sections
Expert Committee: Monographs—Small Molecules 4
No. of Commenters: 3
Comment Summary #1: The commenter indicated that the retention time of trazodone related compound D in the *Assay* and the test for *Organic impurities* is not reproducible and requested the inclusion of the commenter's validated procedure.
Response: Comment not incorporated. Evaluation of the proposed procedure in the USP laboratories indicated that the retention time is reproducible.
Comment summary #2: The commenter requested revising the *Assay* and the test for *Organic impurities* to change the resolution between trazodone related compound C and trazodone from NLT 2.0 to NLT 1.5.
Response: Comment incorporated.
Comment summary #3: Two commenters requested widening the relative standard deviation requirement in the test for *Organic impurities* from NMT 2.0% to NMT 5.0% based on supporting validation data.
Response: Comment incorporated.
Comment summary #3: The commenter requested replacing the proposed LC-MS test for *Trazodone Related Compound F and Cyclophosphamide Related Compound A* with two separate HPLC procedures.
Response: Comment not incorporated. The HPLC procedures do not offer significant advantages over the proposed LC-MS procedure.

Monograph/Section: Warfarin Sodium/Isopropyl Alcohol Content
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested revising the tailing factor in the *System suitability* requirements from NMT 1.5 to NMT 2.0.
Response: Comment incorporated.

Monograph/Section: Warfarin Sodium Tablets/Organic Impurities
Expert Committee: Monographs—Small Molecules 3
No. of Commenters: 1
Comment Summary #1: The commenter requested tightening the limit of Alice's ketone to be consistent with the limit in the drug substance monograph.
Response: Comment not incorporated. Alice's ketone is a degradation product and its limit of NMT 0.5% is consistent with ICH guidelines.
Comment Summary #2: The commenter requested including acceptance criteria for unidentified and total impurities.
Response: Comment not incorporated. The Expert Committee will consider a future revision upon receipt of supporting data.